Mathematical modelling of the population impact of screening for Chlamydia trachomatis and Neisseria gonorrhoeae in South Africa

By Rachel Esra
ESRRAC001

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Supervisor: Dr Leigh Johnson
School of Public Health and Family Medicine

University of Cape Town

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Abstract

A large proportion of chlamydial and gonococcal infections are asymptomatic. In lower- and middle-income countries like South Africa, where syndromic management is practiced, it is likely that a large proportion of curable sexually transmitted diseases (STIs) go untreated, as screening for asymptomatic STIs is rarely conducted. Due to the lack of empirical data on the effectiveness of STI screening programs, dynamic mathematical modelling has been used to assess the impact of screening, although most previous modelling studies have focused on high-income settings. Here we utilize dynamic mathematical modelling to evaluate the potential impact of opportunistic STI screening programs on the incidence and prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoea* in South Africa. We extended an existing agent-based model of heterosexual HIV and STI transmission in South Africa to investigate the impact of targeted screening strategies directed at high risk groups including youth, female sex workers, pregnant women and patients in HIV care. All four screening strategies resulted in reductions in general and key population STI transmission. Opportunistic STI screening of youth and ART patients were shown to be most effective and represent viable interventions for reducing STI transmission in the South African population. Additionally, we compared the modelled impact of a standardized screening program to results obtained from other published mathematical models of chlamydia screening. Differences between models could be attributed to differences in the modelled heterogeneity in sexual behaviour as well as differences in assumptions about immunity following chlamydia recovery.

List of abbreviations

ANC	Antenatal Care
ART	Anti-retroviral treatment
BV	Bacterial Vaginosis
ClaSS	Chlamydia Screening Studies
CSI	Chlamydia Screening Intervention
CT	Chlamydia trachomatis
CDC	Centre for Disease Control
ECDC	European Centre for Disease Control
ED	Emergency department
FPC	Family planning clinic
FSW	Female Sex Worker
GSH	General Household Survey
GUM	Genitourinary medicine
HIV	Human Immunodeficiency Virus
LCR	Ligase chain reaction
MSM	Men-who-have-sex-with-men
MicroCOSM	Microsimulation for the Control of South African Morbidity and Mortality
NAAT	Nucleic acid amplification test
NCSP	National Chlamydia Screening Program
NG	Neisseria gonorrhea
PCR	Polymerase chain reaction
PID	Pelvic inflammatory disease
PLWHA	People living with HIV/Aids,
PN	Partner Notification
POC	Point-of-care
POPI	Prevention of Pelvic Infection
RCT	Randomised controlled trial
SDA	Strand displacement amplification
SM	Syndromic Management
STIs	Sexually transmitted diseases
TV	Trichomonas vaginalis
UK	United Kingdom
US	United States

PART A: PROTOCOL

1. Background

Bacterial sexually transmitted infections (STIs) are a major contributor to the global burden of disease, especially in developing countries with limited resources for diagnosis and treatment (1). If undiagnosed or untreated, sexually transmitted bacterial infections such as *Chlamydia Trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) can result in serious reproductive problems including pelvic inflammatory disease (PID), ectopic pregnancy and infertility in women (2) as well urethritis and epididymitis (3) in men. Bacterial STIs during pregnancy are associated with pre-term delivery and a range of adverse birth outcomes such as low birth weight and post-partum endometritis (4). CT and NG can be transmitted perinatally causing inclusion infant conjunctivitis, pneumonia and in some cases, neonatal death (4). As well as being a significant contributor to morbidity in their own right, bacterial STIs have been shown to increase the risk of both the transmission and acquisition of Human Immunodeficiency Virus (HIV) (5, 6). Effective STI case management and treatment are essential in a country like South Africa where a large proportion of new HIV cases are thought to be attributable to other curable STIs (7). Historically, limited access to laboratory diagnostic services have stood as a barriers to STI testing but developments in rapid point-of-care (POC) STI tests have increased the feasibility of on-site STI diagnosis in resource-poor settings (8–11).

1.1 STI Management in South Africa

South Africa currently follows a syndromic management approach to STI control where patients are treated based on the symptoms with which they present rather than deferring treatment until laboratory tests are available (12). The introduction of syndromic management in the early 1990s was followed by a documented decline in STI prevalence in the South Africa population, a trend that modelling studies indicate might also be attributable to increased condom usage and HIV/Aids mortality (13). Despite the declines in STI prevalence, the prevalence of curable bacterial STIs such as CT and NG is higher in South Africa (7) compared to other African countries and global averages (14). For example, the prevalence of chlamydia and gonorrhoea in South African women in 2005 was estimated to be 10.1% and 4.4% respectively (7) compared to levels of 3.0% and 0.3% respectively in high-income countries (14).

It has been well established that 60-70% of chlamydial and gonococcal infections in women (15), and possibly a similar proportion in men (15), are asymptomatic. Based on this, in a country like South Africa where syndromic management is practiced, it is likely that a large proportion of asymptomatic curable STIs go untreated. Unrecognized infection puts women at an increased risk for long term reproductive health complications (16) and contributes to a continuously high rate of transmission in the population. A study of South African women found vaginal discharge, one of the most commonly treated syndromes under syndromic management guidelines, to be a poor predictor for STI status and genital tract inflammation (17). Another study, in the rural district of Mopani, Limpopo, found 25% of female study participants to be positive for chlamydial and/or gonococcal infections, although only 28% of the chlamydia positive and 31% of the gonorrhoea positive women reported having symptoms (18). These data bring into question the validity of a syndromic approach to STI control.

1.2 STI screening programmes

Over the last 20 years, STI screening programs have been implemented in developed countries as a cost effective method to identify and treat asymptomatic STI cases and interrupt the spread of infection through the population (19–21). Screening for CT was first introduced in Sweden in 1982, initially targeting women under the age of 30 and then later expanding to offer mandatory free CT testing, treatment and contact tracing in anyone with a suspected CT infection (22). While the initiation of this program was followed by a temporary reduction in CT rates up until the mid 1990s, CT prevalence in Sweden has continued to rise since 1995 (23). In a survey conducted by the European Centre for Disease Prevention and Control (ECDPC) in 2012, 18 European countries reported having clinical guidelines recommending opportunistic STI testing for at least one high risk population group including youth, pregnant women, sex-workers, men-who-have-sex-with-men (MSM) and migrants (24).

The ECDPC additionally reported that while the majority of European countries have STI case management guidelines, England was the only country with an organised opportunistic national chlamydia screening program (24). In 2003 the National Chlamydia Screening Program (NCSP) was initiated in England targeting all sexually active men and women under

the age of 25 (19). While testing coverage has increased dramatically over the past 10 years (25), the NCSP has not yet reached the target of 35% screening coverage of 15-24 year olds required to achieve a population wide reduction in CT prevalence (26). In the United States (US), CT screening of sexually active women under the age of 25 was implemented in 1988 in Region X (Alaska, Idaho, Oregon, Washington) and later expanded across the country. While this program has been accredited with a reduction in CT prevalence in certain regions, nationwide CT rates continue to rise in the US. A registry-based chlamydia screening program implemented in the Netherlands found no reduction in CT prevalence after three rounds of annual CT screening (27, 28).

While the population effect of STI screening programs is difficult to determine, multiple studies have evaluated the impact of STI screening in clinical trial settings (27–29).
A meta-analysis of randomized control trial (RCT) evidence for the impact of CT screening found that while CT screening does reduce the risk of PID in women, the size of the effect is difficult to determine due to the low quality of the clinical evidence available (30). Only two studies investigating the impact of CT screening on CT prevalence were identified (27, 28, 31). A trial investigating the effectiveness of a registry-based chlamydia screening in the Netherlands found no reduction in CT prevalence after three rounds of annual CT screening (27, 28) while a trial in Peru found a reduced risk of CT and NG infection in sex workers targeted by mobile STI clinics (32). All of the STI screening guidelines that have been developed focused on chlamydia specifically, and none have called for gonorrhoea screening. This reflects the STI disease burden in high-income countries, in which the prevalence of NG is negligible compared to the prevalence of CT (14). In South Africa, however, the prevalence of NG is almost half the prevalence of CT (7), and there is thus a need for both CT and NG screening.

1.3 Mathematical modelling of STI screening

Due to the lack of empirical evidence on the efficacy of opportunistic STI screening, dynamic mathematical modelling has been used to help understand what levels of coverage and frequency of screening are required to reduce STIs levels (26, 33, 34). Modelling studies of the impact of STI screening in high-income countries have resulted in substantially different

conclusions (35). However, very few modelling studies have been conducted to assess the potential impact of opportunistic STI screening programmes in developing countries (36–38). It is important to evaluate how an intervention such as opportunistic screening might impact STI prevalence in a South African context, given the high STI prevalence levels that persist in South Africa. This study aims to utilise an agent based stochastic mathematical model to evaluate the impact of opportunistic screening on CT and NG in South Africa in addition to the syndromic management currently offered.

2. Aim

The aim of this study is to estimate the potential impact of opportunistic STI screening programs on the incidence and prevalence of *Chlamydia Trachomatis* and *Neisseria gonorrhoea* in South Africa through the use of dynamic mathematical modelling.

2.1 Specific Objectives

2.1.1 Objective One: Extension of an existing mathematical model to estimate the impact of STI screening of key sub-populations on the prevalence and incidence of and CT and NG in South Africa

Rationale: High rates of asymptomatic STIs in South Africa indicate there is an urgent need for a revision of the South African syndromic management policy. Due to the lack of empirical data on the impact of STI screening in the South African context, dynamic mathematical models calibrated to available STI data can provide insights into the likely population wide impact on STI transmission after the introduction of opportunistic screening programs. This study will assess the impact of opportunistic STI screening among those at a high risk of STIs (adolescents and female-sex-workers) and those who are already being serviced through primary health care access points (pregnant women and those in HIV care).

2.1.2 Objective Two: Comparison of the impact of a chlamydia screening program estimated by our model to results obtained from other published mathematical models of chlamydia screening.

Rationale: Previous studies have reported substantially different outcomes predicted by three published models of opportunistic chlamydia screening, simulating the identical hypothetical screening strategy (33, 35), creating uncertainty in how they may be interpreted to inform health policy decision making. We will adjust our model to simulate the same screening strategy in order to compare the outcomes to the above-mentioned studies.

3. Methodology

3.1 Study Design

This study will make use of dynamic modelling of infectious disease using the C++ coding language through the platform Visual Studio. As such, there will be no human subject data collection.

3.2 Overview of the HIV-STI model

The study will extend an agent-based version of the STI-HIV interaction model, a previously developed model of heterosexual HIV and STI transmission in South Africa (39). For each STI, assumptions are made regarding probabilities of transmission per act of unprotected sex, proportions of cases that become symptomatic and the average duration of infection in the absence of treatment, as has been previously described (39). The model has been fitted to South African STI prevalence data, and for each STI a set of 100 STI parameter combinations has been identified that yield the best model fit to the STI prevalence data. These 100 parameter combinations will be used in the current analysis, i.e. the model will be run 100 times in each scenario in order to generate a distribution of model outputs. The distributions will be summarized by medians and inter-quartile ranges.

3.3 Extension of the HIV-STI model

We shall introduce structural changes to the STI-HIV interaction model so as to accommodate the impact of STI screening interventions. We will introduce the components of a hypothetical screening intervention while keeping parameters describing transmission and duration of infection the same as in the original model. Those individuals belonging to the targeted key populations will be eligible to be screened once every year. The mathematical modelling of the natural history of chlamydia and gonorrhoea in this model has been described previously (39) and will be updated to include opportunistic screening as illustrated in Figure 1.

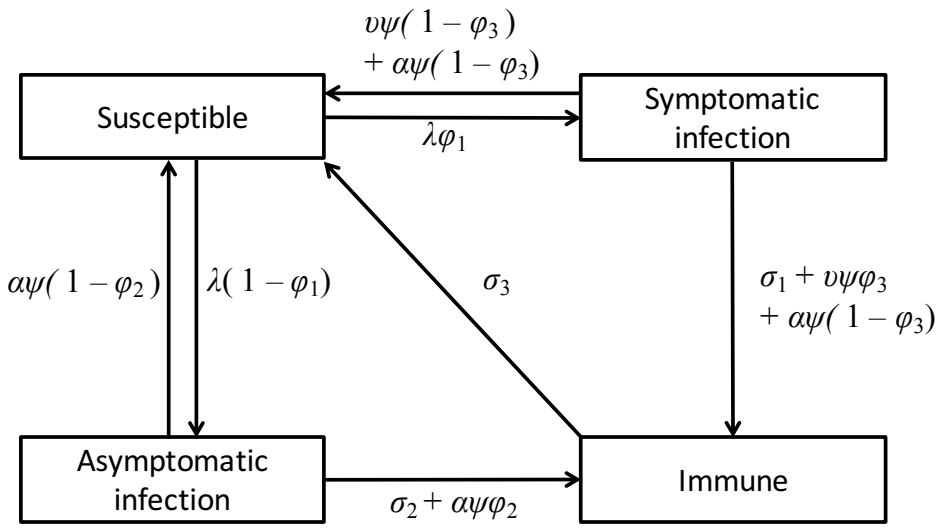

Figure 1: Figure S2: Multi-State model of the natural history of chlamydia and gonorrhoea Updated from the HIV-STI model (39) to include opportunistic STI screening

The models used for CT and NG are identical in structure but different parameters are assigned to each, as previously described (39). In short, infected individuals may develop symptoms or remain asymptomatic (Figure 1). Both states may result in temporary immunity after spontaneous resolution of infection or after receiving treatment. Symptomatic individuals seek treatment at rate υ, which is successful at curing the infection with the probability ψ. Asymptomatic individuals will be screened at rate α, which is a product of three independent probabilities:

(1) The probability of attending a health service where screening is available

(2) The probability of being offered a screening test

(3) The probability of accepting a screening test

These parameters will be calculated separately for each key population based on estimates from the literature. Other parameters of the STI models are summarised in Table 1.

Table 1: Variables of the STI model used for to simulate the natural history of Chlamydia and Gonorrhoea

Symbol	Definition
φ_1	Proportion of people who become symptomatic
φ_2	Proportion of people temporarily immune after experiencing resolution of an asymptomatic infection after treatment
φ_3	Proportion of people temporarily immune after experiencing resolution of a symptomatic infection after treatment
σ_1	Rate at which symptomatic people recover in the absence of treatment
σ_2	Rate at which asymptomatic people recover in the absence of treatment
σ_3	Rate at which immunity wanes

3.4 Estimation of parameters

Where possible, the health seeking behaviour of different South African populations has been calculated from South African national survey data and epidemiological studies on the impact and behaviours associated with STI screening. In the cases where there is no current data on these behaviours in the South African population, data sources from other countries, where opportunistic screening for CT and NG has been implemented, have been considered. Studies selected for calibration comprise of observational studies, where investigators have reported samples of youths, pregnant women, female sex workers and those in HIV care, in South Africa and other countries.

4. Assessment of Objectives

4.1 STI screening in key subpopulations

In each scenario, a hypothetical ten-year screening programme is simulated, starting in 2018. Symptomatic individuals seek healthcare and are treated as described in the previous model (39). Individuals are screened simultaneously for chlamydia and gonorrhoea with a POC test assumed to have the same sensitivity as the chlamydia/gonorrhoea GeneXpert (40). In each scenario, we investigate the impact of targeted screening with and without partnership notification. The effectiveness of different screening programs will be assessed by comparing the cumulative incidence of new STI cases over the 10-year screening program and the reduction in STI prevalence after 10 years of screening, relative to a base scenario in which no screening takes place.

Four targeted screening programs are simulated:

1. **Youth screening:** Males and females between the ages of 14 and 25 are eligible for annual screening. This screening strategy is in line with global Chlamydia screening policies (41, 42)
2. antenatal STI screening for CT and NG is for all women at the onset of prenatal care, and again in the third trimester for women who are younger than 25 years or at increased risk (43). Our model does not simulate the duration of pregnancy but rather occurrence of a new birth. Due to this, antenatal screening is simulated as occurring at birth.
3. **Female Sex Worker (FSW) screening**: All FSWs are eligible for annual screening.
4. **HIV Care Screening:** HIV positive individuals, above the age of 14 and on ART-Care are eligible for annual STI screening. Recent changes in South African guidelines mandate that all HIV positive individual should be initiated onto ART treatment regardless of CD4 counts (44), therefore theoretically all individuals with a known HIV positive status should be accessing ARTs .

4.2 Standardized screening program

We will adjust our model to simulate the standardised screening program described by Kretzschmar et al. (30) in order to compare the predicted impact of a 10-year screening chlamydia program to that estimated by the HPA, RIVM and ClaSS models. We will additionally assess how differences in model specifications may explain the difference in the predictions produced by our model and those previously published. This will include a comparison of model characteristics and assumptions regarding CT natural history as well as the calculation of measures such as the effective contact rate and Gini coefficient describing the heterogeneity in sexual behaviour specified in each model structure.

5. Ethical Considerations

As there will be no human subject involvement in this study, there is no potential harm to human subjects. The primary benefit of this study is to provide evidence for a revision of the syndromic management strategies currently implemented in SA and to increase support for opportunistic STI screening in order to decrease population wide STI prevalence and incidence.

6. Potential Outcomes

From this study we hope to evaluate the effectiveness of opportunistic STI screening as a method of reducing STIs in South Africa and to identify key populations in which STI screening may have a population-wide impact. This study aims to provide data to improve sexual health of the South African population through informing policy-making decisions regarding STI management.

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PART B: LITERATURE REVIEW

1. Introduction

Bacterial sexually transmitted infections (STIs) are a major contributor to the global burden of disease, with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea* (NG) responsible for 155 million new infections in 2012 (1). CT infection is predominately asymptomatic with approximately 70% of cases in women (2, 3) and 40% in men clinically silent (4, 5). NG infections are asymptomatic in up to 60% of women (6, 7) and 20-40% of men (4). If undiagnosed or untreated, CT and NG can result in serious reproductive problems including pelvic inflammatory disease (PID), ectopic pregnancy and infertility in women (8) as well urethritis and epididymitis (9) in men. Bacterial STIs during pregnancy are associated with pre-term delivery and a range of adverse birth outcomes such as low birth weight and post-partum endometritis (3). CT and NG transmitted perinatally can cause inclusion conjunctivitis, pneumonia and in some cases, neonatal death (3). As well as being a significant contributor to morbidity in their own right, bacterial STIs have been shown to increase the risk of both the transmission and acquisition of Human Immunodeficiency Virus (HIV) (10, 11). Co-infection with CT and/or NG has also been associated with higher rates of mother-to-child HIV transmission (12).

The transmission of CT and NG occurs via direct mucosal contact through vaginal, anal or oral sex and perinatally through the birth canal. Due to the largely asymptomatic nature of infection and gaps in knowledge regarding the natural history of both STIs, transmission probabilities from cross-sectional partnership studies are difficult to determine (13). Young age and behavioural factors such as unprotected sex, multiple or new partners and previous STIs are associated with an increased risk of incident CT or NG infection (14). A number of studies have found high rates of reinfection in those who have already been treated for CT and/or NG (15–18). In a study of adolescent females, 47% of participants had at least one recurrent CT infection after treatment (19). Sexual behaviour data combined with CT genotyping, indicated that it is likely that 67% of reinfections originated from new partners, 17% from the same partner, 14% due to treatment failure and 3% persisted without treatment (19).

Recurrent CT infections are also associated with an increased risk of PID (20), possibly caused by immune-mediated inflammation and adhesion formations in the fallopian tubes after repeat exposure to CT antigens (21). There is evidence of partial strain-specific immunity after both NG (22, 23) and CT (19, 24) infections although the underlying mechanisms that mediate mucosal immune interactions with bacterial STIs are poorly understood. The rise in chlamydia infections observed after an initial reduction of chlamydia prevalence following CT control programs, has led researchers to hypothesize that early treatment of CT may interrupt the natural immunity process (25, 26).

2. STI screening

Over the last 20 years, many developed countries have implemented CT screening guidelines (27–29) aimed at identifying and treating asymptomatic STIs, interrupting the spread of infection and reducing the incidence of long term reproductive tract complications. These recommendations have been implemented despite a lack of high quality clinical evidence on the optimal frequency and screening strategy required for population wide effectiveness (30). Proactive STI screening strategies identify members of the population eligible for screening using population registers (31), with individuals being invited to be screened through healthcare services or by receiving a testing kit that may be self-administered and returned to the laboratory (32). Alternatively, opportunistic screening is targeted at individuals who are attending healthcare services for reasons other than STI testing (31).

Nucleic acid amplification tests (NAATs) are currently considered the gold standard of CT and NG screening and diagnostics. NAATs are more sensitive and the majority are more specific than previously available diagnostic methods including cell culture, enzyme hybridisation and antigen detection (33). NAATs can be performed on non-invasive samples including urine or self-collected vaginal swabs and many commercially available NAATs can identify the presence of CT and NG simultaneously (34, 35). In resource poor settings, limited access to laboratory diagnostic services have stood as a barriers to STI testing, but developments in rapid point-of-care (POC) STI tests have increased the feasibility of on-site STI diagnosis (36, 37). In order to be cost effective, many laboratories batch test NAATs and as result the time

between diagnosis and treatment can range from a few days to weeks, increasing the risk of patients not receiving their results. POC tests can significantly reduce the time between detection and treatment and would be particularly effective in populations with high STI prevalence where limited access to healthcare facilities makes it difficult for patients to return for results.

Mathematical modelling indicates that a CT rapid POC test with a 65% sensitivity would lead to higher rates of treatment and a lowered incidence of PID compared to laboratory-based NAATs with higher sensitivity and reduced patient return rates (38). POC tests for CT and NG developed over the past 5 years utilising antigen detection, enzyme hybridisation and various immunoassays have displayed high specificities although the majority have performed poor sensitivity (39). However, qualitative real-time polymerase chain reaction tests, such as the Cepheid Xpert CT/NG, demonstrated sensitivities of above 97% for detection of CT in endocervical, vaginal, and urine samples, with all specificity estimates above 99.4% (35). NG detection was equally robust, with a sensitivity 100% for endocervical and vaginal samples, sensitivity of 95.6% for urine samples and all estimates of specificity above 99.8% (35). The Xpert CT/NG has a significantly higher per test cost than commercially available NAATs and the feasibility of implementing this test in resource poor settings has yet to be determined (39–41). There is a need for simple and inexpensive POC tests that can be delivered in a single patient visit.

3. Clinical Evidence for STI Screening

There are several clinical trials that have evaluated the feasibility and acceptability of a variety of CT screening strategies (42–51), although fewer high-quality randomised controlled trials (RCTs) have reported the impact of CT screening on PID and CT prevalence and incidence. The Chlamydia Screening Intervention (CSI) trial in the Netherlands used a registry-based screening strategy where all men and women aged 16-29 listed on the municipal population registers were invited to be screened through postal notifications (52). Results from the CSI found no reduction in CT prevalence after three rounds of annual CT screening (52) and based on low rates of participation, concluded that register-based CT screening is not cost effective at low levels of coverage (53). Ostergaard et al. randomised 17 high schools to either receive

CT self-testing kits or utilise existing free STI-testing services at local healthcare facilities (54). Only 7.6% of eligible participants in the control group pursued CT testing at healthcare facilities, compared to the 93.4% of students who returned the self- testing kits (54). There was a significant reduction in CT prevalence after one year of follow up in girls at schools that received the self-testing kit (55). While the impact of these two screening strategies on CT prevalence was largely dependent on screening uptake (low in the CSI trial and high in the Ostergaard trial), proactive screening studies are not generalizable to the hypothetical impact of population-wide opportunistic screening (32).

The Peru PREVEN study, a community randomised trial targeting female sex workers (FSWs) and young adults in the general population, employed a multicomponent STI control program (56). The intervention comprised of strengthened syndromic management of STIs by pharmacies and clinicians in addition to mobile outreach teams targeting FSWs offering STI testing and treatment, presumptive periodic treatment for trichomonis vaginalis and condom promotion (56). After 3 years of implementation, a significant reduction in STI prevalence was observed in FSWs and young women but not in young males (56, 57). Authors noted that the discrepancy in the effect of the intervention seen between FSWs and young males may be a result of higher healthcare seeking behaviors in women as well as movement of FSWs between cities and infrequent use of condoms with non-client partners (57). A recent meta-analysis found insufficient clinical evidence to determine the effect of CT screening on population wide CT prevalence and incidence and recommended that the Peru PREVEN trial be duplicated in order to determine whether the results are generalizable to other populations (58). There are currently two on-going large scale trials in Australia (59) and Denmark (60) investigating the impact of opportunistic screening of CT screening on CT prevalence and incidence.

Five RCTs (52, 55, 61–63) have measured the impact of a single round of CT screening on the incidence of PID using both register-based (52, 55, 61, 62) and opportunistic (63) enrolment methods. Four trials reported reductions in the incidence of PID in women screened for CT compared to those not screened (52, 55, 63, 64) and one trial reported that CT screening had no effect on the incidence of PID and ectopic pregnancy in women or epididymitis in men (65). Meta-analysis of the combined trial data indicated that while CT screening does reduce

the risk of PID in women, the size of the effect is difficult to determine due to the low quality of the clinical evidence available (58). PID can be caused by a variety of factors other than CT infection, a mediator that was not addressed in the majority these trials. Only the Prevention of Pelvic Infection (POPI) trial assessed the prevalence of PID and CT infection at baseline and identified incident PID cases that resulted from untreated CT infections (63). This trial reported a non-significant 35% reduction in PID in women screened for CT compared to those not screened, noting that overall incidence of PID was low (66). The majority of cases of PID occurred in women who tested negative for CT at baseline, indicating that a single round of CT screening over a period of 12 months did not prevent the majority of PID cases resulting from incident CT infections (66). The time taken for a CT infection to ascend to the fallopian tubes following endocervical infection, represents a window in which CT screening and treatment may prevent immune-mediated tubal pathology (67). The impact of CT screening on fertility outcomes is currently unknown, but the results from the POPI trial indicate that annual opportunistic screening might fail to reduce PID outcomes in those at high risk for a repeat infection.

Despite the strong associations between bacterial STIs and adverse birth outcomes, there is currently no high quality clinical trial evidence on the impact of antenatal STI screening programs. Antenatal screening and treatment for bacterial vaginosis (BV), high vaginal pH and abnormal vaginal flora has been shown to reduce birth adverse outcomes (68). Recent clinical trials have demonstrated antenatal STI screening to be feasible and acceptable in both high (69) and low-resource settings (48, 49). A pilot study in Papua New Guinea found POC testing for CT, NG and BV during routine antenatal visits to be feasible (70), prompting a cluster randomised trial investigating the efficacy, cost-effectiveness and health system requirements for POC antenatal STI testing which is currently on-going (71).

4. Chlamydia screening globally

CT screening was first introduced in Sweden in 1982, targeting women under the age of 30 attending family planning clinics as well as male partners of those infected (72). A change in legislation in 1988 introduced mandatory free CT testing, treatment and contact tracing of anyone with a suspected CT infection, as well as mandatory notification of any confirmed CT

cases (72). The widespread introduction of these screening activities, in combination with educational campaigns and the provision of youth friendly STI clinics, are thought to have contributed to the decline in Sweden's CT notifications up until the mid 1990s (73). However, the decline in CT notifications in Sweden was preceded by nationwide HIV prevention campaigns and resultant changes in sexual behaviours, which may have contributed to decreased STI rates (74) as observed in other countries where no CT control interventions were in place (75). Despite continued screening services, CT notifications in Sweden have steadily risen since 1995 (30). While the increase in CT notifications in Sweden may be partly attributable to increased sensitivity of laboratory diagnostics and increased screening in men, CT rates in both men and women aged 15-19 began to rise prior to the introduction of NAATs and were observed in laboratories that had not yet implemented more sensitive diagnostics (76).

In a survey conducted by the European Centre for Disease Control (ECDC) in 2012, 18 European countries reported having clinical guidelines recommending opportunistic STI testing in asymptomatic individuals in at least one population group including youth, pregnant women, sex-workers, men-who-have-sex-with-men (MSM) and migrants (77). However, implementation of these guidelines has not been successful, with only 5 countries reporting that opportunistic STI testing was actually practiced (77). Between 2008 and 2011 a registry-based chlamydia screening program was implemented in the Netherlands targeting all men and women aged 16-29 listed on the municipal population register but was halted after RCT findings that annual register based screening was not cost-effective in this population due to low participation rates (52, 53).

The ECDC additionally reported that while the majority of European countries have STI case management guidelines, England was the only country with an organised opportunistic national chlamydia screening program (77). In 2003 the National Chlamydia Screening Program (NCSP) was initiated in England, recommending annual screening for all sexually active men and women under the age of 25, screening after change of a sexual partner and rescreening 3 months after a positive test in addition to partner notification (27). While testing coverage has increased dramatically over the past 10 years (78), the NCSP has not yet reached the target of 35% screening coverage of 15-24 year olds required to achieve a

population wide reduction in CT prevalence (79). In 2015, 32% of women and 13% of males in this age group were testing for CT in England (78). While CT screening in the UK is primarily utilised at specialist and non-specialist sexual health centres, the NCSP also offers online services through which home based CT testing kits can be freely accessed (80). The usage of internet testing has risen considerably in the UK, particularly in young males, a population in which CT screening coverage is low (81). Since nationwide implementation of the NCSP, CT diagnoses in the UK have risen consistently (78). This is partially due to increased screening coverage and higher diagnostic sensitivity but most likely a reflection of on-going unsafe sexual behaviours in this population (78).

In the United States (US), CT screening of all sexually active women under the age of 25 attending family planning clinics was implemented in 1988 in Region X (Alaska, Idaho, Oregon, Washington) (82). For the first 9 years of this program, while CT notifications in women rose nationwide (83, 84) , CT notifications decreased by more than 60% in women aged 15-24 attending family planning clinics in region X (85). Over this time period, decreases in CT positivity were also observed in other regions of the US where screening was being broadly implemented (86, 87). However, from 1997 to 2004 there was a 46% increases in CT positivity in women attending family planning clinics in Region X (85). This increase in CT infections could not be accounted for by increased sensitivity of laboratory diagnostics (88) and some have hypothesised that widespread early treatment interrupting the development of natural immunity to CT may have contributed to an increased number of susceptible individuals in the population (88). CT prevalence continues to rise in the US with 1.5 million cases, the highest number of annual cases, reported in 2015 (89).

5. Gonorrhoea Screening Globally

Due to a hypothesized combination of changing sexual behaviours and the introduction of hormonal contraceptives (90) NG rates in US increased rapidly from the 1960s reaching a peak in the mid 1970s (91). The introduction of the national gonorrhea control program resulted in a 74% decline in the rate of NG notifications between 1975 and 1997 (91) with NG rates reaching a historical low in 2009 (92). Since then, NG rates have risen consistently (92) and NG resistance to first-line antibiotics is becoming a global concern (93, 94).While CT and NG

are the two most frequently reported bacterial STIs, the global prevalence of NG is only a tenth of that of CT (95) and the majority of STI screening programs have therefore focused on CT screening. The WHO recommends discontinuing the use of a given first line antibiotic when resistance has been identified in more than 5% of circulating NG strains(96). As of 2010, there is only a single first line antibiotic combination that is effective above this threshold (97).Due to the overall low prevalence of NG and the threat of increasing antimicrobial resistance, opportunistic screening for gonorrhoea is not recommended unless clinically indicated (98). There are currently no formalised NG screening programs but many countries recommend NG screening in high risk population groups such as MSM (98, 99). Extra genital screening (pharyngeal and rectal) for both NG and CT is recommended in this population with studies reporting that the majority of asymptomatic STI cases would be missed using urethral only screening (100, 101).

6. Use of mathematical models to evaluate the impact of STI Screening

Due to the lack of empirical evidence on the efficacy of opportunistic STI screening in both clinical and population intervention settings, dynamic mathematical modelling has been used to help understand the levels of coverage and frequency of screening required to reduce STIs levels (79, 102, 103). Modelling the impact of STI screening has been achieved using both deterministic and stochastic frameworks. Parameters such as the duration of infection, treatment efficacy and rates of health care utilisation are generally based on estimates from nationally representative surveys and clinical studies. The transmission dynamics of STI models are highly dependent on the specified mixing patterns through which members in the hypothetical population interact and models differ in the assumptions of age- and sex-specified sexual behaviours (104). Deterministic, population-based models simulate interactions between homogenous compartments of individuals within the population and therefore represent the average behaviour of a system. Stochastic, individual-based models simulate individual interactions based on randomly assigned characteristics sampled from specified probability distributions and randomly simulated times to events (events might include, for example, formation of a new sexual partnership, or acquisition of an STI). In terms of modelling STIs such as CT and NG, stochastic simulations do a better job of capturing the

dynamics of sexual partnerships (105) although they require greater computational power to run.

Kretzschmar *et al.* compared three different stochastic individual-based models of CT screening strategies that reported substantially different outcomes (106). The first model, developed by Kretzschmar *et al.,* compared the impact of condom usage, contact tracing and screening for CT and NG on population wide prevalence of CT and NG (107). The model predicted that all three prevention strategies were more effective in reducing NG prevalence than CT prevalence and recommended that contact tracing and treatment of at least 50% of partners would be required for a sustained reduction in CT prevalence (107). The second model, developed by Turner *et al.,* identified ideal levels of screening coverage for the National Chlamydia Screening Program in the UK (108). This model indicated that a screening coverage of 35% would be required for a population wide decrease in CT prevalence, a target which has been adopted by the NCSP (109). A similar model was developed by the UK Chlamydia Screening Studies (ClaSS) to evaluate register-based screening with home collected CT testing kits (110).

While the Turner model estimated a 50% reduction in chlamydia prevalence after 10 years of annual screening with a 10% annual screening uptake (79), the ClaSS model estimated that a 35% annual screening uptake in all sexual activity groups would only result in a 10% reduction in CT prevalence over the same period of time (111). A comparison of the Turner, Kretzschmar and ClaSS models, simulating the identical hypothetical CT screening strategy, predicted a 85%, 25% and 5% reduction in CT prevalence in women respectively (106). These disparities arose as a result of different assumptions about the sexual partnership dynamics and the parameters regarding the natural history of chlamydia (106).

In lieu of more reliable data collection methods, self-reported national surveys often constitute the only empirical data on population wide sexual behaviours. In comparison to a survey of sexual behaviours in the UK, as well as the Kretzschmar and ClaSS models, the Turner model estimated significantly higher rates of sexual contacts in young adults (112). This may have resulted in an unrealistically high prevalence of CT in the population eligible to be screened, explaining the larger impact of the same screening intervention observed in this

model in comparison to the others (106, 112). In the same comparison, the ClaSS model was shown to overestimate the proportion of single members of the population, resulting in a reduced effect of the intervention, as screening those in partnerships in the population is more effective in reducing CT transmission (112). Overall, the Kretzschmar model was found to best describe the dynamics of the CT transmission, sexual partnerships and the distribution of CT in the population (112, 113), despite it being the earliest and least complex of the models compared.

One of the caveats of stochastic individual-based models is that the inclusion of many complex parameters, in the absence of reliable empirical data, can lead to difficulties in interpretation of the results (114). Althaus *et al.* developed a novel stochastic individual-based framework, creating three different models with simplifying assumptions that may be easily compared and adjusted (115). A comparison of the impact of two different partner notification strategies on CT screening effectiveness demonstrated that notifying current or most recent sexual partners has a larger impact on reducing population wide CT transmission compared to notifying all partners within a defined look-back period (115).

The concept of core sexual activity groups, now adopted by most sexual infection transmission models, was introduced by Yorke et al. in 1978 in mathematical model describing the natural history and transmission dynamics of NG (116). More recent mathematical models of NG have focused on the transmission dynamics of antibiotic resistance in NG networks. The use of risks structured "susceptible-infectious-susceptible' model revealed that a significant reduction in NG infection can only be achieved by screening and treating core sexual groups although this strategy increases the spread of antimicrobial resistance (117). A deterministic model created by Xiridou *et al.* predicted that in MSM, a short term reduction of NG prevalence as a result of increased treatment may be overshadowed by increased antimicrobial resistance and a resultant increased prevalence in the long term (118). A recent modelling study identified higher rates of treatment, as opposed to higher numbers of partners, as the main reason for the more rapid emergence of antibiotic-resistant NG in MSM when compared to heterosexuals (119). These modelling studies highlight the necessity to consider the spread of NG resistance when developing public health recommendations for NG screening (120). With the exception of the Kretzschmar model (107), there have been no

recent mathematical models evaluating the population wide impact of a hypothetical NG screening strategy.

Few modelling studies have been conducted to assess the potential impact of opportunistic STI screening programmes in developing countries (121–123). A deterministic model evaluating the impact of periodic presumptive treatment (PPT) found that a PPT coverage above 30% could significantly reduce the prevalence of CT and NG in South African FSWs (121). Another study assessed the cost effectiveness of rapid POC testing for antenatal syphilis screening in Tanzania (123). A stochastic model was used to compare the time-to-detection of the emergence of microbial resistance using POC molecular testing and culture methods in resource limited settings (37). When modelling the impact of public health interventions on CT and NG transmission, there are still concerns about the validity of assumptions of treatment rates estimated from clinical trials that may not be generalizable to the greater population (106) and empirical data from high quality RCTs of screening programs are needed to better inform health policy decisions.

7. STI Management in South Africa

South Africa follows a syndromic management approach to STI control where patients are treated based on the symptoms with which they present rather than deferring treatment until laboratory tests are available (124). The introduction of syndromic management in the early 1990s was followed by a documented decline in STI prevalence in the South Africa population, a trend that modelling studies indicate might also be attributable to increased condom usage and HIV/Aids mortality (125). Despite the declines in STI prevalence, the prevalence of curable bacterial STIs such as CT and NG is higher in South Africa (41, 126) compared to other African countries and global averages (1). A study of South African women found vaginal discharge, one of the most commonly treated syndromes under syndromic management guidelines, to be a poor predictor for STI status and genital tract inflammation (127). Another study, in the rural district of Mopani, Limpopo, found 25% of female study participants to be positive for chlamydial and/or gonococcal infections, although only 28% of the chlamydia positive and 31% of the gonorrhoea positive women reported having symptoms (128). The presumably high levels of asymptomatic STIs in the South African population bring into question the

adequacy of a syndromic approach to STI control, yet the feasibility of an STI screening program in this country has yet to be determined.

8. STI epidemiology and targeted screening strategies

8.1 Adolescents and young adults

In the USA, 14-25 year olds account for 65% of CT infections and 53% of NG infections (89) making them disproportionately affected by STIs compared to other age groups. High rates of bacterial STIs within this age group have directed STI screening strategies in the US, UK, Sweden and Australia. Barriers to accessing healthcare, multiple concurrent sexual partners and limited knowledge of sexual health contribute to increased risk of STIs during adolescence(129). Additionally, cervical ectopy during adolescence may place young women an increased risk of bacterial STI acquisition (130). In the US, annual routine screening for CT and NG is recommended for all sexually active females under the age of 25, young men who have sex with men and sexually active young males in settings with a high STI prevalence (correctional facilitates and STD clinics) (99).

The burden of bacterial STIs is lower in the UK with 368.7 cases of CT and 75.8 cases of NG reported per 100,000 population in 2015 in comparison to the 456,1 cases of CT and 110,7 cases of NG reported per 100,000 population in the US in 2014 (87) (131). Similar to the US, CT diagnoses are highest in female adolescents and NG diagnoses are concentrated in high risk groups such as MSM (78). In the UK, annual CT screening is recommended for all sexually active men and women under the age of 25 or after change of sexual partners (78). Opportunistic screening for gonorrhoea is not recommended unless clinically indicated (98).

There is no empirical data on the population wide epidemiology of bacterial STIs in South Africa and clinical studies employing laboratory testing of STIs report varying levels of STI prevalence in different regions and sentinel populations (132). The prevalence of chlamydia and gonorrhoea in South African women in 2005 was estimated to be 10.1% and 4.4% respectively (126) compared to levels of 3.0% and 0.3% respectively in high-income countries (1). Consistent with global trends, CT rates in South African adolescent females are generally higher than their male counterparts (133, 134). At the initiation of an HIV RCT in South African

adolescents aged 15-19, 23.1% and 8.2% of females and males tested positive for CT while 10.6% and 1.8% of females and males tested positive for NG (134). Another study assessing youth-directed HIV prevention services reported CT prevalence to be 9.1% and 10.8% in women aged 15-19 and 20-24, while CT prevalence in men of the same ages was 3.5% and 10.1% (133). In the same study, NG prevalence in was 3.5% in both female age groups and 1.1% and 3.2% for men aged 15-19 and 20-24, respectively (133). A study in the peri-urban township of Masiphumelele reported unusually high rates of asymptomatic STIs in female adolescents, with 41% and 20% of the girls testing positive for CT and NG at screening in the absence of symptoms (Barnabas et al. unpublished). These data indicate that bacterial STIs are prevalent in South African adolescents, possibly to a greater extent than their global counterparts.

8.2 Female Sex Workers

Globally, female sex-workers (FSWs) have been identified as a key target group for STI screening studies (135–138) and in South Africa have been identified as a key population at a high risk for both HIV (139) and other STIs (140). Global studies in both high- (141, 142) and low-income countries have reported FSWs to have higher bacterial STI prevalence compared to the sexually active females in the general population. A study of FSWs in Johannesburg, South Africa revealed a CT prevalence of 11% and an NG prevalence of 35% in 1999 (143). The same population was retested two years later and while NG prevalence had decreased by 10%, CT prevalence had risen by 6% (143). Similar to other high risk groups, clinical studies reporting bacterial STI prevalence in FSWs vary (143–145), although they consistently report higher NG rates than the estimated average among female South Africans (126). STI screening in FSWs has been shown to be acceptable and feasible in other low-income countries and mathematical modelling demonstrated that POC testing for CT and NG in South African FSWs would have averted 18 000 additional CT and/or NG infections compared to the current syndromic management approach (122). The recent introduction of pre-exposure prophylaxis for FSWs in SA provides the opportunity to build onto existing infrastructure to reach a population at high risk for both HIV and STIs concurrently.

8.3 Antenatal Screening

In addition to targeting adolescents and FSWs, STI screening can be employed to at-risk populations who are already accessing health care services. The majority of developed countries have policies for antenatal CT and NG screening, although implementation varies (146). Southern Africa has a high prevalence of curable STIs among pregnant women in comparison to other middle- to low-income countries (147). Clinical trials have reported high levels of undiagnosed and untreated curable STIs in pregnant women in South Africa (148, 149), indicating that a large majority of curable STIs in South African pregnant women may be undetected by current syndromic management practices. South African antenatal screening policies currently include laboratory diagnosis of only HIV and syphilis (124). Universal antenatal screening, which refers to screening pregnant women for CT and NG regardless of symptoms or risk factors, has been shown to be acceptable and feasible in low-income setting where women are already attending antenatal clinics for routine checkups (41, 49, 150, 151). Since the introduction of universal antenatal syphilis screening in the early 1990s, national antenatal syphilis levels have decreased from 11% in 1998 to 2.8% in 2001 (152) although this trend may have been impacted by the introduction of syndromic management and changing sexual behaviours (125). Since the majority of pregnant South Africans access antenatal health services at least once before giving birth (153), antenatal screening provides a potential STI screening service entry point.

8.4 HIV Care Screening

Reports of high levels of asymptomatic CT and NG cases at North American HIV clinics resulted in the Centre for Disease Control (CDC) recommending at-least annual CT and NG screening for PLWHA (154). North American studies report high levels of STIs and increased high risk behaviours for STI acquisition in MSM on antiretroviral (ART) treatment (155). It is unclear whether these risk behaviours are specific to MSM, or extend to the general population on ARTs. Result from an HIV cohort in Kenya reported low levels of sexual risk behaviour and bacterial STI prevalence (1-2%) in PLWHA (156). A systematic review reported lower levels of unprotected sex and STIs in those on ARVs compared to those not on ARVs (157). While the prevalence of bacterial STIs in South African PLWHA is currently unknown, a study of PLWHA offered opportunistic STI screening at an HIV clinic in Johannesburg reported CT and NG levels of 4.4% and 2% respectively in men as well as 6.4% and 2.2% in women (158).

There is evidence that CT and/or NG infection may increases genital viral load in HIV positive people on antiretroviral (ARV) treatment and therefore increase the risk of HIV transmission from people living with HIV (PLWHA) (159). In the absence of any other intervention, detecting and treating STIs in PLWHA has been estimated to be responsible for an approximately 27% reduction in HIV transmission (160). While ART treatment significantly reduces the risk of HIV transmission (161), PLWHA may represent a population with a high burden of asymptomatic STIs (162, 163).

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PART C: MANUSCRIPT

Abstract

Background: A large proportion of chlamydial and gonococcal infections are asymptomatic. In lower- and middle-income countries like South Africa, where syndromic management is practiced, it is likely that a large proportion of curable sexually transmitted diseases (STIs) go untreated, as opportunistic screening for asymptomatic STIs is rarely conducted. Due to the lack of empirical data on the effectiveness of STI screening programs, dynamic mathematical modelling has been used to assess the impact of screening, although most previous modelling studies have focused on high-income settings.

Methods: Here we utilize dynamic mathematical modelling to evaluate the potential impact of opportunistic STI screening programs on the incidence and prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoea* in South Africa. We extended an existing agent-based model of heterosexual HIV and STI transmission in South Africa to investigate the impact of targeted screening strategies directed at high risk groups including youth, female sex workers, pregnant women and patients in HIV care. Additionally, we compared the modelled impact of a standardized screening program to results obtained from other published mathematical models of chlamydia screening.

Results: All four screening strategies resulted in reductions in general and key population STI transmission. Differences between models could be attributed to differences in the modelled heterogeneity in sexual behaviour as well as differences in assumptions about immunity following chlamydia recovery.

Conclusions: Opportunistic STI screening of youth and ART patients were shown to be most effective and represent viable interventions for reducing STI transmission in the South African population**.**

Keywords: STI screening; mathematical model; chlamydia; gonorrhoea; South Africa

Introduction

Sexually transmitted infections (STIs) are a major contributor to the global burden of disease, especially in developing countries with limited resources for diagnosis and treatment. Globally, bacterial STIs such as *Chlamydia trachomatis* and *Neisseria gonorrhoea* were responsible for 155 million new infections in 2012 (1). South Africa currently follows a syndromic management approach to STI control where patients are treated based on the symptoms with which they present rather than deferring treatment until laboratory tests are available (2). Despite documented declines in STI prevalence (3), the prevalence of curable bacterial STIs such as chlamydia and gonorrhoea remains high in South Africa (4) compared to other African countries and global averages (1).

It has been established that 60-70% of chlamydial and gonococcal infections in women (5), and possibly a similar proportion in men (6), are asymptomatic. If undiagnosed or untreated, chlamydia and gonorrhoea can result in serious reproductive problems including pelvic inflammatory disease (PID), ectopic pregnancy and infertility in women (7) as well urethritis and epididymitis (8) in men. Reports from clinical studies indicate a high burden of asymptomatic STIs in South African women (9, 10), bringing into question the adequacy of a syndromic approach to STI control.

Opportunistic STI screening programs have been implemented in developed countries to identify and treat asymptomatic STI cases and interrupt the spread of infection through the population (11–13). Despite this, rates of curable bacterial STIs have risen consistently in the United States (US), United Kingdom (UK) and Sweden where STI screening programs have been widely established (14). This has raised questions about the quality, or absence, of the clinical evidence currently informing STI screening strategies (14). Due to the lack of empirical data on the effectiveness of opportunistic STI screening, dynamic mathematical modelling has been used to help understand the levels of coverage and frequency of screening required to reduce STIs levels (15–17). However, very few modelling studies have been conducted to assess the potential impact of opportunistic STI screening programmes in developing countries (18–20).

Effective STI case management and treatment are essential in a country like South Africa where a large proportion of new Human Immunodeficiency Virus (HIV) cases are thought to be attributable to other curable STIs (4). Historically, limited access to laboratory diagnostic services has stood as a barrier to STI testing but recent developments in rapid point-of-care (POC) STI tests have increased the feasibility of on-site STI diagnosis in resource-poor settings (21, 22). This study uses a previously developed agent-based model of STIs in South Africa to estimate the effectiveness and efficiency of opportunistic STI screening in a South African setting. We investigate the impact of targeted screening strategies directed at high risk groups including youth, female sex workers, pregnant women and those in HIV care. Additionally, we compare the modelled impact of a standardized screening program to results obtained from other published mathematical models of chlamydia screening.

Materials and Methods

We extended a previously developed model of heterosexual HIV and STI transmission in South Africa (23). MicroCOSM (Microsimulation for the Control of South African Morbidity and Mortality) is an agent based model simulating the behaviour and disease profile of a representative sample of South Africans; the initial population size in 1985, at the start of the simulation is 20 000, and the model is projected to 2028. A detailed description of the sexual behaviour parameterization can be found elsewhere (23). Briefly, the population is stratified by sexual risk behaviour. High risk individuals have a propensity for concurrency and engaging in sex work and low risk individuals engage only in monogamous relationships. Both short-term (non-cohabitating) and long-term (cohabiting) relationships are simulated. High risk individuals may have a maximum of two concurrent partners.

We have introduced the components of a hypothetical screening intervention while keeping parameters describing the transmission and duration of infection the same as in the original model (23). For the purpose of this study, only chlamydia, gonorrhoea and HIV transmission are simulated. Assumptions are made regarding probabilities of transmission per act of unprotected sex, proportions of cases that become symptomatic and the average duration of infection in the absence of treatment, as has been previously described (23). The model has been fitted to South African STI prevalence data, and for each STI a set of 100 parameter combinations has been identified that yield the best model fit to South African STI prevalence data (Tables S2 and S3).

STI Screening

In each scenario, a hypothetical ten-year screening programme is simulated, starting in 2018. Symptomatic individuals seek healthcare and are treated as described in the previous model (23). A description of the screening and testing strategies is detailed in the appendix. Individuals are screened simultaneously for chlamydia and gonorrhoea with a POC test assumed to have the same sensitivity as the chlamydia/gonorrhoea GeneXpert (24). In each scenario, we investigate the impact of targeted screening with and without partner notification. In partner notification scenarios, if screening produces a positive result, both primary and secondary (when applicable) partners are screened with a probability of 50%. These estimates are based on studies implementing standard patient referral whereby index

cases are given the responsibility of notifying partners (Table S5, Appendix). Partners are successfully treated with the same probability as index cases. The effectiveness of different screening programs was assessed by comparing the cumulative incidence of new STI cases over the 10-year screening program and the reduction in STI prevalence after 10 years of screening, relative to a base scenario in which no screening takes place.

Targeted screening strategies

In the case of antenatal screening, a single screening probability was applied to all pregnant women based on the current rates of antenatal syphilis screening in South Africa (25). The other screening strategies, for which the probability of screening is unknown, are as follows:

Youth screening: Males and females between the ages of 15 and 24 are eligible for annual screening.

Female Sex Worker (FSW) screening: All FSWs are eligible for annual screening.

HIV care screening: HIV positive individuals, above the age of 14 and either on ART or in the symptomatic stages of HIV disease (WHO stage III or IV) are eligible for annual STI screening.

The annual rate of STI screening in these populations was calculated as the product of the probability of health care utilisation, STI screening acceptability and screening coverage (the probability of being offered an STI test). STI screening parameters were specified separately for each key population, as summarised in Table 1.

Table 1: Model parameters

Parameter	Females	Males	Source
Probability of screening in populations with known screening rates			
ANC	0.71	N/A	Literature (25)
Assumed rate of screening in populations for which screening rates are unknown			
Screening coverage	0.80	0.80	
Annual Health Care Utilisation rate			
Adolescents	0.48	0.32	GHS (26)
FSWS	0.50	N/A	Literature (27–31)
ART patients	0.90	0.90	Literature (32, 33)
Screening acceptability			
Adolescents	0.60	0.60	Literature (34–42)
FSWS	0.80	N/A	Literature (29, 43, 44)
HIV care	1.00	1.00	Literature (32)*
Annual screening rate			
Adolescents	0.23	0.15	The total screening probability was calculated as a
FSW	0.32	N/A	combination of heath care utilisation, screening
HIV care	0.72	0.72	acceptability and screening coverage.
Partner Notification**			
Proportion of partners screened	0.50	0.50	Literature (45–52)

ANC = antenatal care, FSW = female sex worker, GHS = General Household Survey

* Based on reports that that the majority of South Africans on ART receive laboratory monitoring at least annually (32)

** Only applicable in scenarios where partner notification is implemented

Standardized screening program

Previous studies have compared three published models of opportunistic chlamydia screening, simulating the identical hypothetical screening strategy in European settings (16, 53). We adjusted our model in order to simulate the same screening strategy and compared the outcomes to the above-mentioned studies. In order to be comparable, the following adjustments were made: 16-24 year olds were screened with an annual probability of 35% and partner notification resulted in 45% of partners successfully screened and treated (16). This was for done for men and women simultaneously and women alone. Assumptions regarding test sensitivity and treatment success of index cases were consistent with our original model. We calculated the Gini coefficient, a measure of the distribution of chlamydia infections among individuals with different levels of sexual activity (53). A Gini coefficient of 0 represents a situation where the distribution of chlamydia infections is equal across all sexual behaviour groups. A Gini coefficient of 1 represents a situation of maximum inequality where chlamydia infections occur only in the group with the highest rate of sexual contacts. We also assessed how model characteristics and assumptions regarding chlamydia natural history may explain the difference in the predictions produced by our model and those previously published.

Results

Population level impact of targeted STI screening

Figure 1 illustrates the predicted change in population level chlamydia and gonorrhoea incidence and prevalence after different screening strategies, relative to the base scenario. Tables S11-13 detail the estimated population chlamydia and gonorrhoea incidence and prevalence over the period of the screening program. For both chlamydia and gonorrhoea incidence, HIV care screening resulted in the largest decrease in cumulative incidence over the 10 years of the screening period, followed by youth, ANC and FSW screening (Table S11). The same trend was seen for population wide chlamydia prevalence in both males and females, with all screening strategies resulting in significant reductions relative to the base scenario (Figure 1, Tables S11 and S12). Significant reductions in population wide gonorrhoea prevalence were only seen for HIV care screening (Figure 1). Partner notification resulted in significantly fewer incident and prevalent cases of chlamydia for both men and women for all screening scenarios in comparison to screening without partner notification (Figure 1). Across all scenarios, partner notification did not significantly reduce the number of incident or prevalent cases of gonorrhoea. Screening FSWs was the most efficient screening strategy resulting in significantly more STI cases averted per screening test than any of the other screening strategies (Table 2).

Key population impact of targeted STI screening

Estimates of chlamydia and gonorrhoea prevalence in key populations after different STI screening scenarios are summarised in Table 3. Chlamydia prevalence in women was highest in sex workers, lower among youth and pregnant women, and lowest in ART patients, but chlamydia prevalence in men was higher among ART patients than among youth. Similar prevalence differentials were estimated in the case of gonorrhoea. Significant reductions in chlamydia prevalence were predicted in ART patients, youth, pregnant women and FSWs after respective targeted screening strategies (Tables 3 and S13). Significant reductions in gonorrhoea prevalence after targeted screening were predicted in all key populations with the exception of male youth and pregnant women (Tables 3 and S13). Partner notification resulted in significantly fewer prevalent cases of chlamydia in all key populations but had no impact on the reduction in gonorrhoea prevalence in comparison to targeted screening without partner notification (Tables 3 and S13).

Sensitivity analysis

Sensitivity analysis correlating the reduction in chlamydia and gonorrhoea incidence and prevalence with the 100 best fitting parameter combinations revealed that the probability of chlamydia transmission per sex act was positively correlated with the reduction in chlamydia incidence and prevalence due to screening (Table S9). Additionally, the duration of asymptomatic chlamydial infection and the duration of chlamydial immunity were negatively associated with the reduction in chlamydia incidence and prevalence (Table S9). The same relationships were not observed between gonorrhoea transmission factors and reductions in gonorrhoea incidence and prevalence (Table S10).

Standardized screening program

The predicted chlamydia prevalence prior to screening, annual number of partners and effective contact rate for women and men stratified by age is summarised in Table S14. The model characteristics and chlamydia natural history parameters of three previously published individual-based stochastic models of chlamydia transmission and the model used in this study (the MicroCOSM model) are summarised in tables S15 and S16. The RIVM, ClaSS and HPA models predicted a pre-screening chlamydia prevalence of 3.2%, 2.6%, 2.8% in women and 2.9%, 3.1%, 3.7% in men respectively (16). In our model, pre-screening chlamydia prevalence in 16- 44 year olds was substantially higher, at 10.16% (95% CI: 9.94-10.39%) for females and 7.40% (95% CI: 7.18-7.16%) for males. The MicroCOSM model estimated the impact of the standardized chlamydia screening programme to be similar to that estimated by the RIVM model, but substantially less than that estimated by the HPA model and substantially more than that estimated by the ClaSS model (Figure 2). The Gini coefficient calculated for the MicroCOSM model (0,37) was similar to that calculated from empirical data collected in the Natsal 2000 population-based survey in Britain (0,38) (53), but was slightly higher than that estimated for the HPA model (0,32) and lower than that estimated for the RIVM (0,46) and ClaSS (0,84) models (53).

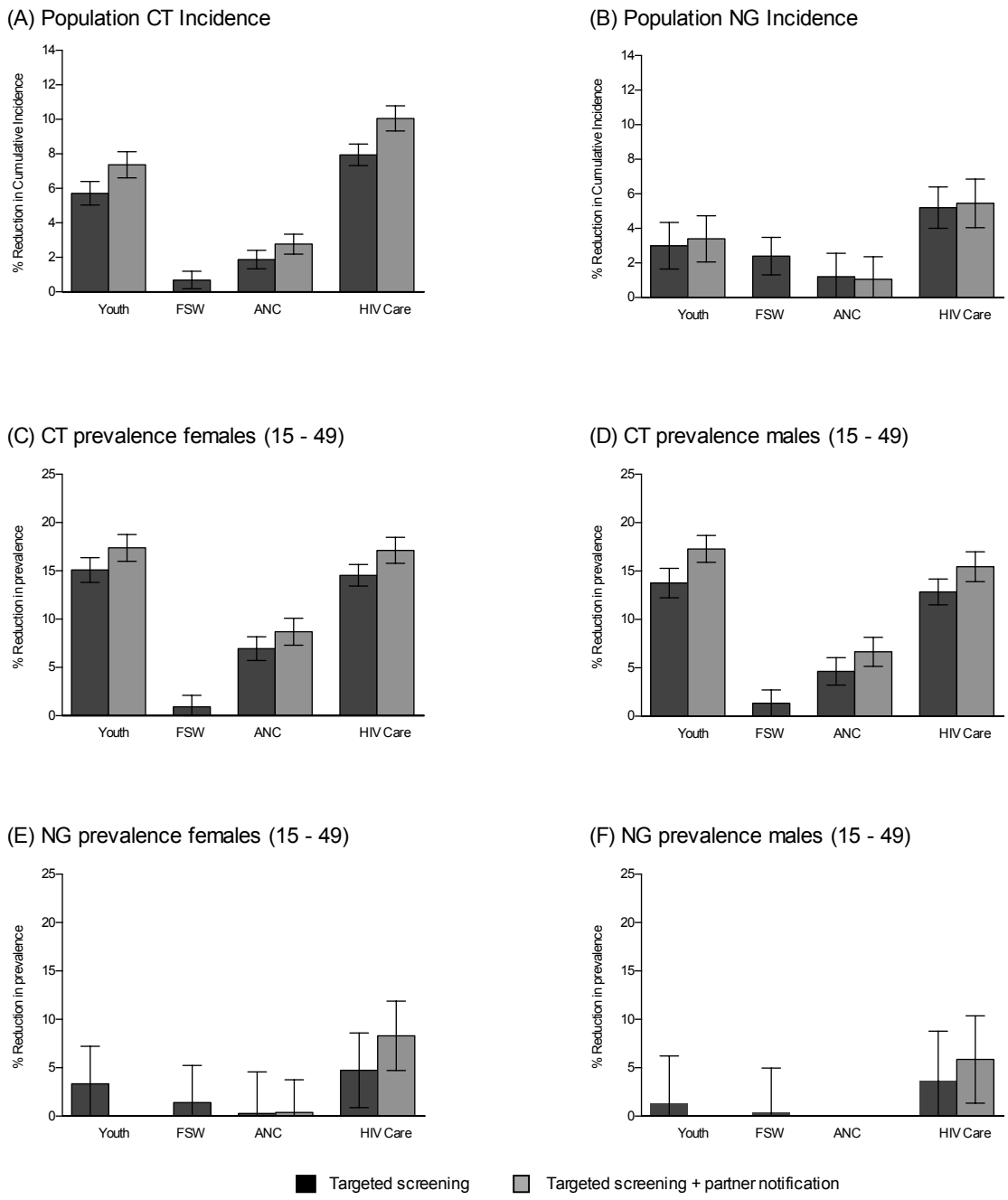

Figure 1: Comparison of estimated population level effect of youth, female sex-worker (FSW), antenatal care (ANC) and HIV care targeted STI screenings strategies. Both targeted screening and targeted screening in combination with partnership notification (PN) are shown. Bars represent mean reductions in the cumulative number of new chlamydia (CT) and gonorrhoea (NG) cases (A+ B) or CT and NG prevalence (C - F) 10 years after the implementation of targeted STI screening programs (errors bars represent 95% confidence intervals). Lower limits of the 95% CI are not shown if they extend past zero. The means and 95% CIs are calculated from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into each model. The hypothetical implementation of STI screening programs is simulated as starting in 2018, and the reduction in incidence and prevalence is calculated relative to the level that would be expected in the absence of any screening program.

Table 2: Estimated number of new STI cases averted (in the general population) per 100 individual STI tests *

Screening strategy	Chlamydia	Gonorrhoea
Adolescent	5.7 (5.1-6.3)	5.2 (3.1-7.2)
Adolescent PN	6.9 (6.2-7.5)	5.9 (4-7.8)
FSW	45 (13-78)	248 (140-357)
ANC	5.5 (4-7)	8.2 (1.5-14.9)
ANC PN	7.5 (6-9)	6.5 (1.1-11.9)
HIV Care	5.2 (4.8-5.6)	5.5 (4.3-6.7)
HIV Care PN	6.3 (5.8-6.7)	5.8 (4.5-7.1)

*Number of STI cases averted per single dual screening test was calculated as the cumulative reduction in incident STI cases divided by the total number of screening tests over the 10-year screening period.
The means and 95% CIs are calculated from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into each model.
ANC = antenatal care, ART = antiretroviral treatment, FSW = female sex worker, PN = partner notification

Table 3: Estimated STI prevalence in key populations in 2028, after the implementation of a 10-year targeted screening program

	Chlamydia		Gonorrhoea	
Scenario	Females	Males	Females	Males
Prevalence in the general population (aged 15 to 49 years)				
Base scenario*	8.87 (8.69-9.05)	6.56 (6.39-6.74)	2.97 (2.79-3.15)	1.51 (1.40-1.63)
Youth screening	7.52 (7.35-7.69)	5.66 (5.48-5.84)	2.82 (2.65-3.00)	1.45 (1.34-1.56)
Youth screening + PN	7.33 (7.14-7.52)	5.44 (5.26-5.62)	2.85 (2.67-3.02)	1.46 (1.35-1.57)
FSW screening	8.77 (8.59-8.96)	6.47 (6.29-6.65)	2.88 (2.71-3.06)	1.48 (1.36-1.60)
ANC screening	8.25 (8.06-8.44)	6.26 (6.07-6.46)	2.89 (2.72-3.07)	1.51 (1.40-1.63)
ANC screening + PN	8.10 (7.90-8.30)	6.13 (5.94-6.33)	2.90 (2.74-3.06)	1.47 (1.36-1.57)
HIV Care screening	7.57 (7.40-7.74)	5.72 (5.55-5.88)	2.77 (2.61-2.94)	1.41 (1.31-1.52)
HIV Care screening + PN	7.35 (7.16-7.53)	5.55 (5.37-5.73)	2.68 (2.52-2.84)	1.38 (1.28-1.49)
Prevalence in youth (aged 15 to 24 years)				
Base scenario*	12.27 (11.96 - 12.57)	6.35 (6.59 - 6.1)	3.91 (3.66 - 4.17)	1.52 (1.40 - 1.64)
Youth screening	9.10 (8.82 - 9.38)	4.88 (4.65 - 5.10)	3.53 (3.31 - 3.76)	1.41 (1.30 - 1.51)
Youth screening + PN	8.49 (8.20 - 8.78)	4.34 (4.15- 4.53)	3.49 (3.27 - 3.70)	1.41 (1.30 - 1.52)
Prevalence in FSWs				
Base scenario*	15.19 (14.51 - 15.88)		24.15 (23.2 - 25.09)	
FSW screening	13.84 (13.22 - 14.46)		22.59 (21.69 -23.49)	
Prevalence in pregnant women				
Base scenario*	12.15 (11.92 - 12.38)		4.27 (4.01 - 4.53)	
ANC screening	11.28 (11.02 - 11.53)		4.16 (3.91 - 4.41)	
ANC screening + PN	11.06 (10.79 - 11.33)		4.14 (3.92 - 4.37)	
Prevalence in patients linked to HIV care				
Base scenario*	8.37 (8.10 - 8.65)	8.24 (7.94 - 8.55)	291 (2.71 – 3.11)	.1.95 (1.79 - 2,12)
HIV Care screening	3,94 (3.76 - 4.12)	3.93 (3.71 - 4.14)	2.21 (2.04 - 2.38)	1.50 (1.36 - 1.64)
HIV Care screening + PN	3.63 (3.46 - 3.79)	3.70 (3.52 - 3.88)	2.09 (1.93 - 2.26)	1.44 (1.30 - 1.57)

*Base scenario prevalence estimates are the prevalence levels that would be expected in 2028 in the absence of any screening intervention.
The means and 95% CIs are calculated from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into each model. The hypothetical implementation of STI screening programs is simulated as having been initiated in 2018.
ANC = antenatal care, ART = antiretroviral treatment, FSW = female sex worker, PN = partner notification

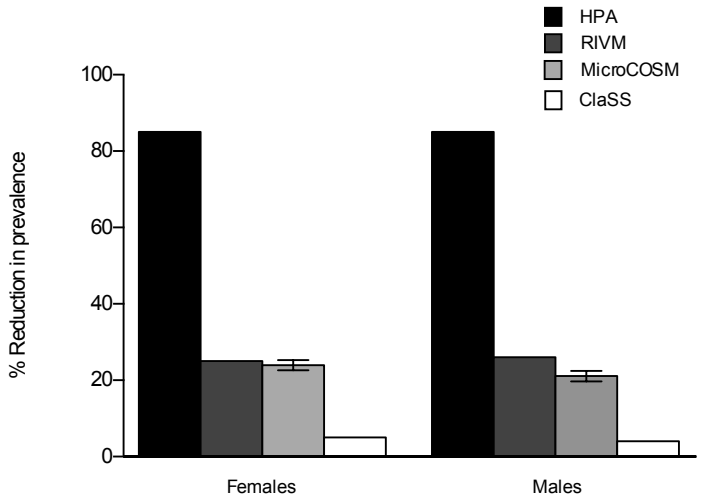

Figure 2: Comparison of modelled effects of a standardised chlamydia screening program on chlamydia prevalence, as estimated by different mathematical models. Bars represent the percentage reduction in chlamydia prevalence in 16-44 year olds after 10 years of chlamydia screening in women only (errors bars represent 95% confidence intervals). For the MicroCOSM model, the means and 95% CIs are calculated from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into the model.

Discussion

This study extended an existing individual based model of chlamydia and gonorrhoea in high risk South African populations who are already accessing routine healthcare services, making them possible targets for opportunistic STI screening. In agreement with empirical studies, chlamydia and gonorrhoea prevalence in female youth, FSWs and pregnant women was significantly higher than the general population (Table 3). Screening those in HIV care was the most effective strategy despite low levels of STI prevalence in females in the subpopulation, especially compared to youth. This is due to the fact that they comprise a large fraction of the population and they have a higher level of healthcare engagement than youth. Male STI prevalence in those in HIV care was slightly lower than male youth possibly explaining why the overall efficiency of screening in youth is not that much greater than that of screening ART patients. Our model demonstrated that while partner notification results in significantly larger reductions in STI transmission, it is not necessary for a sustained reduction in population wide chlamydia and gonorrhoea prevalence.

A limitation of our model is that it assumes ART initiation occurs only in the advanced stages of HIV infection, though South Africa has recently adopted a policy of treating all HIV-positive individuals, regardless of CD4 count (54). For this reason, we have included the untreated HIV-positive population in WHO stages III and IV in the definition of 'linked to HIV care', on the assumption that most of these individuals would already be diagnosed or treated under the new guidelines. The size of the modelled 'linked to HIV care' population in 2018, using this definition, is 4.5 million, similar to the number of projected South Africans on ART by 2018 in more detailed ART models (4.8 million)(55). Since those on ART receive laboratory monitoring at least annually (32), routine HIV care may represent a potential STI screening access point.

When modelling the impact of STI screening, there are concerns about the validity of assumptions surrounding sexual contact structure and the natural history of STIs (17). Comparative modeling studies have demonstrated how differences in the specifications of heterogeneity in sexual risk behaviour can explain the differing results of previously published models evaluating the effectiveness of STI screening (16, 53). A limitation of our analysis is that we do not consider this uncertainty when assessing the impact of STI screening. A further limitation of this study is that our model has been calibrated using South African STI data from

sentinel population reports, as there is currently no routine CT and NG surveillance in South Africa. Additionally, the model is not geographically stratified and therefore cannot evaluate screening strategies targeting high risk areas.

High rates of bacterial STIs in youth have directed STI screening strategies in the US, UK, Sweden and Australia. Based on estimates from the South African GHS of low levels of health seeking behaviours in South African youth, we assumed that only 23% of female and 15% of male youths would be opportunistically screened per annum in a South African setting (26). This study demonstrates that even at such low levels of coverage, opportunistic STI screening of youth may be an effective intervention to reduce STI transmission among youth and in the general population.

We estimated that ANC targeted screening resulted in a modest reduction in STI transmission in comparison to other strategies, despite high screening coverage in this sub-population. South Africa has the lowest fertility rate in sub-Saharan Africa (56) and as a result the pregnant population comprises a relatively small fraction of the total population. The modest impact of the intervention may be due to the relatively small population size of pregnant women when compared to the sizes of the populations targeted in the youth and HIV care screenings strategies. While STI screening has been shown to be acceptable and feasible in low-income setting where women are already attending antenatal clinics for routine check-ups (57–59), there is limited empirical data on its effectiveness at reducing both STI transmission and adverse birth outcomes (60, 61).

FSW screening was shown to be the least effective but most efficient screening strategy overall. This is partly due to the high prevalence of STIs in FSWs and the small size of the FSW population relative to the other subpopulations. The prevalence of chlamydia in FSWs is slightly higher than the general population and as a result FSWs do not play a large role in sustaining chlamydia transmission at a population level. In contrast, gonorrhoea prevalence in FSWs is almost 10 times that of the general population so there is a relatively higher impact of FSW screening on gonorrhoea incidence. In line with international STI screening guidelines, this study modelled the impact of annual STI screening. There is the potential to increase in frequency of screening in high risk group such as FSWs and women in ANC resulting in a larger

population wide impact of this intervention. This increased effectiveness might be coupled with a decrease in efficiency as as more frequent screening is less likely to pick up new diagnoses per test performed.

Previously published stochastic models of chlamydia screening have reported substantially different outcomes (15, 62, 45), creating uncertainty in health policy decision making. We considered the standardised screening program described by Kretzschmar et al. to compare the predicted impact of a 10-year screening chlamydia program to that estimated by the HPA, RIVM and ClaSS models (16). Our model yielded similar estimates to those from the RIVM model, but not to the ClaSS and HPA models. The previously published models discussed in this study were developed to inform STI screening guidelines in high-income setting (15, 17, 62). The MicroCOSM model has been parametrized to the South African setting and as a consequence we would not necessarily expect the simulated intervention impact to be the same across models.

There were substantial differences in the model characteristics and chlamydia natural history parameters between the MicroCOSM model and the three previously published models (tables S16 and S18). Most notably, our model assumed a significantly longer duration of asymptomatic infection and included the possibility of temporary immunity after treatment which was not present in the other models. In our model, both the duration of immunity and duration of asymptomatic infection were negatively correlated with the impact of the screening intervention. The rise in chlamydia infections observed after an initial reduction of chlamydia prevalence following chlamydia screening programs has led researchers to hypothesize that early treatment of chlamydia may interrupt the development of natural immunity resulting in a higher proportion of susceptible individuals in the population (63, 64). There is evidence of partial strain-specific immunity after both chlamydia (65, 66) and gonorrhoea (67, 68) infections, although the underlying mechanisms that mediate mucosal immune interactions with bacterial STIs are poorly understood. A previous modelling study demonstrated that including partial immunity for both chlamydia and gonorrhoea resulted in estimates that better fit empirical STI prevalence compared to models that do not allow for immunity(69). Additionally, models that included temporary immunity predicted significantly lower impacts of therapeutic STI interventions, most likely because the direct benefit of the

intervention in the short term is offset by a longer-term reduction in the prevalence of immunity (69). All other things being equal, we might therefore expect MicroCOSM to estimate a lower impact of chlamydia screening than the other models.

However, model differences can also be explained in terms of behavioural factors. The impact of the 10-year screening program estimated by the ClaSS model was significantly lower than the other models (16, 53). As described by Althaus et al., in comparison to empirical estimates this model significantly overstated the extent of heterogeneity in the distribution of chlamydia risk (Gini coefficient = 0.84) (53), and previous studies have shown that overestimating the extent of heterogeneity in susceptibility to infection means underestimating the impact of interventions (70). The HPA model predicted a significantly higher impact of the same screening program despite assuming similar heterogeneity in risk behaviour when compared to empirical estimates (53) and the MicroCOSM model. It has been suggested that this is a result of significantly higher assumed rates of sexual contacts in young adults creating an unrealistically high rate of chlamydia in those eligible to be screened (53). In addition to this, the HPA model assumes very short durations between partnerships resulting in a higher proportion of partners treated through partner notification compared to other models (53).The impact of the standardised screening program estimated by our model was similar that of RIVM model, which was found to best describe the dynamics of chlamydia transmission, sexual partnerships and the distribution of chlamydia infection in the UK population (53). Although our allowance for immunity and greater assumed duration of asymptomatic infection would be expected to lead to a lesser impact of screening in our model compared to the RIVM model, this effect is offset by the greater degree of heterogeneity in the distribution of chlamydia risk in the RIVM model (Gini coefficient = 0.46) compared to our model (Gini coefficient = 0.37).

A strength of this study is that we utilized a model that has been parametrized to South African sexual behaviour and STI epidemiology to investigate the impact of dual screening for chlamydia and gonorrhoea in a low-resource setting. Globally, STI screening guidelines that have been developed focused on chlamydia specifically, and none have called for gonorrhoea screening. This reflects the STI disease burden in high-income countries, in which the prevalence of gonorrhoea is negligible compared to the prevalence of chlamydia (1). Due to

the overall low prevalence of NG and the threat of increasing antimicrobial resistance, opportunistic screening for gonorrhoea is not recommended unless clinically indicated (71). In South Africa, however, the prevalence of gonorrhoea is almost half the prevalence of chlamydia (4), and there is thus a need for both chlamydia and gonorrhoea screening. A deterministic model predicted that in MSM, a short term reduction of NG prevalence as a result of increased treatment may be overshadowed by increased antimicrobial resistance and a resultant increased prevalence in the long term (72). Another recent modelling study identified higher rates of treatment, as opposed to higher numbers of partners, as the main reason for the more rapid emergence of antibiotic-resistant NG in MSM when compared to heterosexuals (73). These studies highlight the necessity to consider the spread of NG resistance when developing public health recommendations for NG screening (74).

This model assumed STI test specifications consistent with the Cepheid Dual Xpert CT/NG rapid POC test that is commonly used in high income countries. The Xpert CT/NG has a significantly higher per test cost than commercially available NAATs and the feasibility of implementing this test in resource poor settings has yet to be determined (75). There is a need for simple and inexpensive POC tests that can be delivered in a single patient that may be utilized in a South African setting.

Conclusion

While all four screening strategies resulted in reductions in general and key population STI transmission, opportunistic chlamydia and gonorrhoea screening of those accessing ART treatment and youth represent viable interventions for reducing bacterial STI transmission in the South African population.

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PART D: APPENDIX

Appendix I: Technical Appendix

1. Model of Sexual Behaviour

The model is an extension of the MicroCOSM (Microsimulation for the Control of South African Morbidity and Mortality) model, a previously developed mathematical model of heterosexual Human Immunodeficiency Virus (HIV) and sexually transmitted infection (STI) transmission in South Africa (1). For the purpose of the STI screening model we will simulate the transmission of HIV, *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG). Briefly, this is an agent based model simulating a representative sample of the South African population. The simulation begins with a starting population of 20 000 people in mid 1985, and allows for population growth over time. Section 1.1 has been published previously (1) but is reproduced here for convenience.

1.1 Risk groups and relationship types

The population is divided into two broad risk groups: a high risk group (representing individuals with a propensity for concurrent sexual partners and commercial sex) and a low risk group (representing individuals who do not engage in concurrent partnerships or commercial sex). Within each of these risk groups a number of sub-groups (or states) are defined, based on the individual's current relationship status; movements between these states occur as individuals form new partnerships and end previously-formed partnerships. Figure S1 illustrates the state space that is defined for women in the high risk group. The model distinguishes between short-term (non-cohabiting) and long-term (cohabiting or marital) relationships; in addition the model allows for once-off sex acts between sex workers and clients. All long-term relationships are assumed to start as non-cohabiting relationships. For the sake of simplicity, it is assumed that individuals in the high risk group do not have more than two partners at any point in time (although high risk men can have contact with sex workers if they have two current partners). It is also assumed in the interests of simplicity that individuals do not have more than one long-term partner at any point in time, as rates of polygamy in South Africa are relatively low (2).

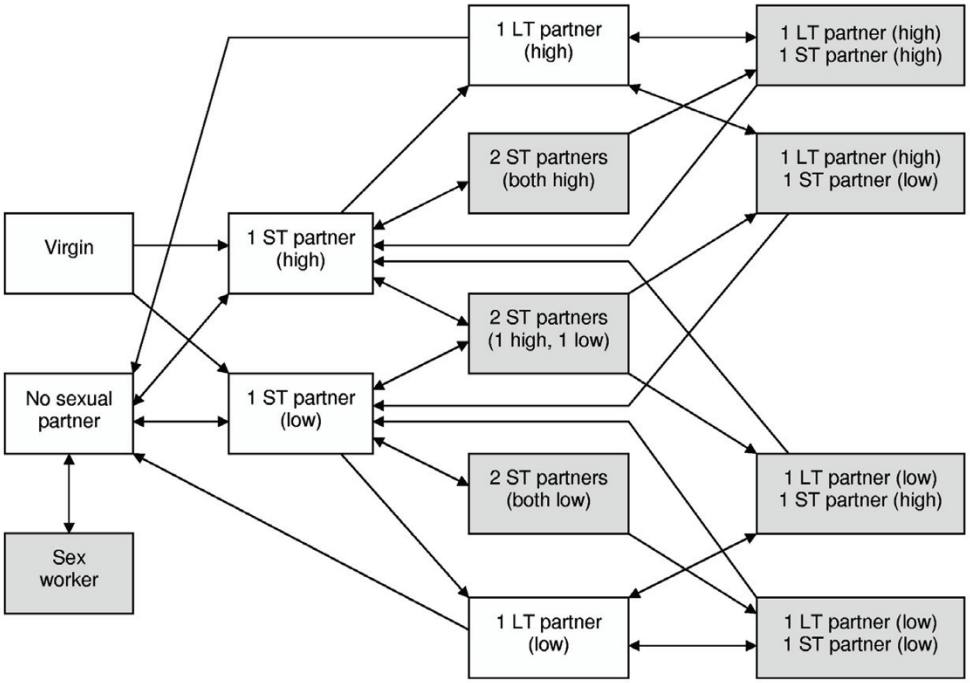

Figure S1: Multi-state model of sexual behaviour of 'high risk' females
LT = long-term (spousal). ST = short-term (non-spousal). 'High' and 'low' refer to the risk group of the sexual partner. The model for low risk females is the same as that shown here, except that the shaded states are omitted. The model for high risk men is also the same as that shown here, except that the 'sex worker' state is omitted.

By definition, individuals in the low risk group cannot have more than one partner at any point in time, and many of the states that are defined for the high risk group (shaded in grey in Figure S1) therefore do not apply to the low risk group. The fraction of the population in the high risk group has been set at 35% for men and 25% for women, based on South African studies evaluating the fraction of individuals reporting concurrent partnerships (3, 4). Only heterosexual partnerships are considered. A detailed description of the specifics of the sexual behaviour model and partner matching algorithm has been previously published (1).

2. Mathematical modelling of STI Transmission and Natural History

2.1 Mathematical model of chlamydia and gonorrhoea

The mathematical model of the natural history of Gonorrhea and Chlamydia has been described previously (1) and has been updated to include opportunistic STI screening as illustrated in Figure S2 and summarised in Table S1. The models used for CT and NG are identical in structure but different parameters are assigned to each. In short, susceptible individuals become infected at rate λ, and newly infected individuals may develop symptoms or remain asymptomatic. Both states may result in temporary immunity after spontaneous resolution of infection or after receiving treatment. Symptomatic individuals seek treatment at rate υ, which is successful at curing the infection with the probability ψ. The natural history parameters assigned to chlamydia and gonorrhea have been previously described (1) and are summarised in Table S2 and S3.

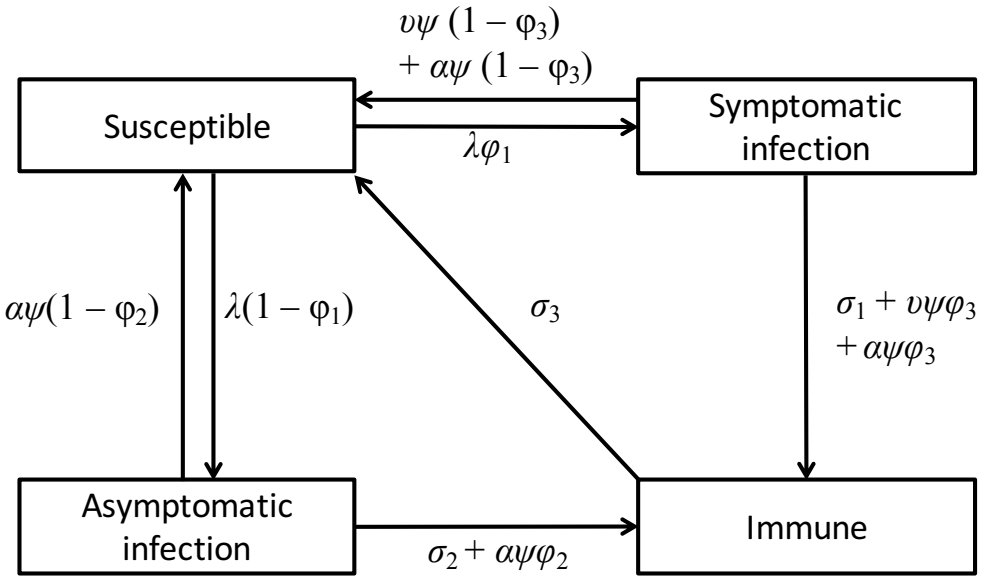

Figure S2: Multi-State model of the natural history of chlamydia and gonorrhoea
Updated from the HIV-STI model (1) to include opportunistic STI screening

Both symptomatic and asymptomatic individuals will be screened at rate α, which is a product of three independent probabilities:

(1) The probability of attending a health service where screening is available

(2) The probability of being offered a screening test

(3) The probability of accepting a screening test

These parameters have been calculated separately for each population based on estimates from the literature.

Table S1: Natural history and transmission parameters

Symbol	Definition
φ_1	Proportion of people who become symptomatic
φ_2	Proportion of people temporarily immune after experiencing resolution of an asymptomatic infection after treatment
φ_3	Proportion of people temporarily immune after experiencing resolution of a symptomatic infection after treatment
σ_1	Rate at which symptomatic people recover in the absence of treatment
σ_2	Rate at which asymptomatic people recover in the absence of treatment
σ_3	Rate at which immunity wanes

For both CT and NG, probability distributions were specified to represent uncertainty around key natural history and transmission parameters as described previously (1). A likelihood function was defined for each STI to represent the degree of model consistency with South African STI prevalence data, for a given set of parameter combinations. For each STI, a sample of 20,000 parameter combinations were drawn from the probability distributions and the 100 parameter combinations that yielded the highest likelihood values were selected as summarized in table S2 and S3. These 100 parameter combinations are used to generate the results presented in the current paper.

In the previous application of the model, immunity following successful treatment of asymptomatic infection was not considered, since the model considered only treatment of symptomatic infection. Due to lack of data on immunity following successful treatment, we assume here that the extent of immunity following the successful treatment of asymptomatic infection is the same as that for symptomatic infection (i.e. $\varphi_2 = \varphi_3$).

Table S2: Parameters for Chlamydial infection

Parameter	Symbol	Best Fitting Parameters, Median (IQR)
% of cases that become symptomatic		
Male	φ_1	36.7% (26.5% -45.0%)
Female		11.6% (7.0% -15.9%)
Average duration if untreated (weeks)		
Symptomatic	$1/\sigma_2$	15.0 (10.2- 19.5)
Asymptomatic		106.6 (96.7 - 116.6)
Average duration of immunity (weeks)	$1/\sigma_3$	295 (241 - 343)
Proportion immune after treatment cure	φ_2	73.2% (59.5% - 88.4%)
Transmission probability per act of sex		
Male-to-female	-	16.2% (11.8% - 20.5%)
Female-to-male	-	9.75% (7.13% - 15.4%)
Fraction of symptoms correctly treated prior to introduction of SM*		71.1% (63.0% - 78.2%)

* SM = syndromic management

Table S3: Parameters for Gonorrheal infection

Parameter	Symbol	Best Fitting Parameters, Median (IQR)
% of cases that become symptomatic		
Male	φ_1	86.6% (83.5% -89.6%)
Female		29.9% (22.6% - 39.2%)
Average duration if untreated (weeks)		
Male	$1/\sigma_2$	34.0 (25.8 – 38.3)
Female		33.6 (29.5 – 38.9)
Average duration of immunity (weeks)	$1/\sigma_3$	48.8 (41.8 - 61.8)
Proportion immune after treatment cure	φ_2	40.1% (20.4% - 59.0%)
Transmission probability per act of sex		
Male-to-female	-	45.9% (40.1% - 53.1%)
Female-to-male	-	23.7% (19.8% - 27.2%)
Fraction of symptoms correctly treated prior to introduction of SM*		70.4% (65.2% - 76.2%)

* SM = syndromic management

2.2 Mathematical model of STI screening

We have introduced the components of a hypothetical 10-year screening intervention while keeping parameters describing transmission and duration of infection the same as in the original model (1).

Four targeted screening programs are simulated:

1. **Youth screening:** Males and females aged 15-24 are eligible for annual screening. This screening strategy is in line with global Chlamydia screening policies (5, 6)
2. **Antenatal care (ANC) screening:** The Centres for Disease Control recommend antenatal STI screening for CT and NG for all women at the onset of prenatal care, and again in the third trimester for women who are younger than 25 years or at increased risk (7). Our model does not simulate the duration of pregnancy but rather occurrence of a new birth. Because of this, antenatal screening is simulated as occurring at the time of birth.
3. **Female Sex Worker (FSW) screening**: All FSWs are eligible for annual screening.
4. **HIV Care Screening:** HIV positive individuals, above the age of 14 and either on ART or in the symptomatic stages of disease (WHO stages III and IV) are eligible for annual STI screening. Recent changes in South African guidelines recommend that all HIV positive individual should be initiated onto ART treatment regardless of CD4 counts (8), therefore theoretically all individuals with a known HIV positive status should be accessing ART.

For the populations in which the coverage of STI screening is known (ANC), a single probability of screening is applied. For populations in which the coverage of screening in not known (youth, FSW and ART patients), an annual rate of screening has been calculated as the product of the the probability of annual health care utilisation, STI screening acceptability and screening coverage. A random number between 0 and 1 is assigned to each eligible individual at the start of each weekly time step. All individuals assigned random probabilities below the probability of screening are screened for STIs and treated with a rate of success described by the model above (Figure 1).

In all scenarios individuals are screened for both chlamydia and gonorrhoea simultaneously under the assumption that point of care (POC) testing would be performed with a POC test with dual testing capabilities, such the Cepheid GeneXpert CT/NG (Xpert) assay (9). The GeneXpert CT/NG is considerably more accurate than other commercially available POC tests (10) and demonstrates higher sensitivities using endocervical/urethral samples in comparison to urine samples (9). Despite the slightly reduced sensitivity, urine based STI testing yields higher rates of acceptability compared to more invasive sample collection (11–13). Based on this, the sensitivity of STI testing in youth, FSW and HIV care targeted screening scenarios is assumed to be the same as the GeneXpert sensitivity for urine samples (97.4% in females and 97.5% in males for CT, 95.6% in females and 98.0% in males for NG) (9). STI testing using vaginal swab collection has been found to be acceptable when implemented as part of routine antenatal check-ups (14–16) and the sensitivity of the screening test in the antenatal strategy is therefore assumed to be the same as the GeneXpert sensitivity for vaginal samples (97.4% for CT and 100% for NG)(9).

2.2.1 Partner notification

Partner notification (PN) has been identified as an integral component of prevention of curable STIs, specifically STIs such as CT which is predominately asymptomatic (17). PN is currently recommended as part of global STI screening programs and involves identifying partners of patients that test positive for curable STIs (index cases) so that they may be screened or presumptively treated (17). Index cases in this model can have a maximum of two current partners. If screening produces a positive result, both primary and secondary (when applicable) partners are screened with a probability of 50% based on estimates from literature (Table S5). These estimates are based on studies implementing standard patient referral whereby index cases are given the responsibility of notifying partners (Table S5). Partners are treated with the same rate of success as index cases. In this model only current sexual partners are considered eligible for partner notification. It is currently unknown whether index cases are more likely to notify current as opposed to former partners of their STI status, but mathematical modelling has shown that notification of only current partners is sufficient to achieve population level reduction in STI prevalence (17). Women engaging in sex work are

assumed not to form short-term or long-term relationships during the periods in which they are active as sex workers. Due to this, partner notification cannot be simulated in the FSW population.

2.2.2 Partner notification sensitivity analysis

Previously published studies of CT screening have assumed that primary and secondary partners would be notified and screened with equal probability (18). In order to investigate this further we ran a sensitivity analysis comparing youth targeted screening utilizing three different partner notification scenarios.

Run 1: Primary and secondary partners are screened with equal probability (50%). (This is the default scenario.)

Run 2: Only primary partners are screened, all with the same probability (50%).

Run 3: Only primary partners are screened. Primary partners that are marital partners are screened with a higher probability (100%) compared to non-marital partners (50%).

A comparison of these scenarios revealed that the highest number of partners screened resulted from screening primary and secondary partners with equal probabilities (Figure S3).

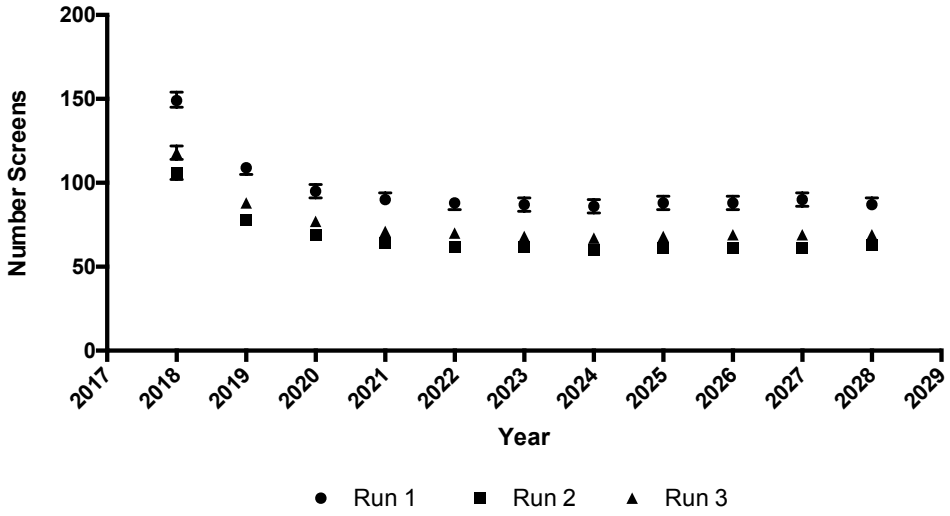

Figure S3: Comparison of number of partners screened under 3 partner notification scenarios over 10 years of youth targeted screening. Shapes represent mean number of partners screened from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into each model (error bars represent 95% CIs). The population grew dynamically over the 10-year screening period with an average population size close to 36 000 mid-way through the screening period in 2023.

Table S4: % increase in STI estimates for general population (aged 15 to 49) with differing partner notification scenarios, in the context of youth-targeted screening

		Run 1 vs. Run 2	Run 1 vs. Run 3	Run 3 vs. Run 2
% increase in cumulative incidence (2018 -2028)				
Chlamydia		-1.05 (0.26-1.83)	-0.20 (-0.50-0.90)	0.88 (0.23-1.53)
Gonorrhea		0.15 (-1.58-1.28)	-1.38 (-0.58-3.35)	-1.00 (-2.64-0.64)
Chlamydia	**Females**	-1.58 (-0.26-3.42)	0.02 (-1.53-1.49)	1.91 (0.05-3.76)
	Males	-1.46 (-0.33-3.26)	-0.64 (-1.01-2.30)	1.21 (-0.66-3.09)
Gonorrhea	**Females**	-3.96 (-0.47-8.39)	-2.51 (-1.75-6.78)	3.23 (-0.88-7.35)
	Males	-7.34 (-1.56-13.13)	-7.03 (1.75-12.32)	2.41 (-2.4-7.21)

3. Estimation of screening parameters

Where possible, the health seeking behaviour of different South African populations has been calculated from South African national survey data and epidemiological studies on the impact and behaviours associated with STI screening. In the cases where there is no current data on these behaviours in the South African population, data sources from other countries, where screening for CT and NG has been implemented, have been considered. Studies selected for parameterization comprise of observational studies, where investigators have reported samples of youths, pregnant women, female sex workers and those in HIV care, in South Africa and other countries.

The probability of antenatal screening for bacterial STIs is assumed to be 0.71, equal to the current coverage of antenatal syphilis screening in South African women (19). This probability is applied to all pregnant women at the occurrence of childbirth.

For all other sub-populations, a screening coverage of 80% is assumed from 2018 until 2028 for all screening strategies, i.e. eligible individuals who attend health facilities are assumed to be offered screening with 80% probability. Youth are assumed to access healthcare at an annual rate of 0.48 for females and 0.32 for males (20). Based on estimates from literature on the acceptability of STI screening using urine based testing, youth acceptability of STI

screening is assumed to be 60% (Table S6). There is no empirical data on the STI screening acceptability in South Africans linked to HIV care. South African HIV treatment guidelines recommend viral load testing 6 and 12 months after initiating ART treatment and annually thereafter (21). As this population is undergoing regular viral load testing, we can assume that the majority of those on ART attend a clinic at which STI screening may be offered at least annually. Even if patients are in WHO stages III/IV but not on ART, it is likely that they would attend HIV services regularly to receive treatment for opportunistic infections, and STI screening could also be offered at these services. We assume that 90% of those on ART or in WHO stages III and IV access healthcare annually and would be amenable to opportunistic STI testing. Based on literature regarding FSWs within South Africa and internationally, FSWs are assumed to access healthcare with an annual rate of 0.50 (Table S7) and FSWs acceptability of STI screening is assumed to be 0.90 (Table S8).

Table S5: Literature review of Partner Notification rates

Study	Year	Sample	Location	STI	Partner notification type	Proportion of partners screened
Estcourt et al. (22)	2015	Females aged 16 +, in GP, GUM and pharmacies	East London, United Kingdom	CT & NG	Standard referral	45% (N=102)
Herzog et al. (23)	2011	Men and women attending GUM clinics	UK	CT	Not recorded	47% (N =4616)
Cameron et al. (24)	2009	Women attending FPCs or GUM clinics	Edinburgh	CT	Standard referral	41% (N=134)
Golden et al. (25)	2005	Heterosexual men and women	Washington, USA	CT & NG	Standard referral	78% (N= 1375)
Kissinger et al. (26)	2005	Men attending an STD clinic	New Orleans	NG & CT	Standard referral	71% (N=285)
Low et al. (27)	2005	Men and women visiting primary care facilities and GUM clinics	Bristol and Birmingham, UK	CT	Standard referral	52.9% (N= 68)
van de Laar et al. (28)	1997	Men and women attending an STI clinic	Amsterdam, Netherlands	CT & NG	Self-referral using referral cards	40% (N = 580)

CT = Chlamydia trachomatis , FPC = family planning clinic, GUM = genitourinary medicine, NG = Neisseria gonorrhoeae, UK = United Kingdom, USA = United States of America

Table S6: Literature review of Youth STI screening acceptability

Study	Year	Sample	Location	STI	Test	Screening acceptability
Goyal et al. (29)	2016	14-21-year-old asymptomatic males and females presenting to ED	Washington, DC	CT & NG	Urine based PCR	59% (N= 553)
Goldenkranz et al. (30)	2012	10-14-year-old females visiting Title FP X clinics	Region X (Alaska, Idaho, Oregon and Washington)	CT	Not reported	34.5% (N= 2697)
		15-19-year-old females visiting Title FP X clinics				40.7% (N = 56 400)
		20-24-year-old females visiting Title FP X clinics				40.7 % (N= 81 180)
Marrazzo et al. (31)	2007	Asymptomatic males in adolescent primary care	Baltimore, Denver, San Francisco and Seattle	CT	Urine based PCR or SDA	61% (N= 93)
		Asymptomatic males in adolescent school based clinics				49% (N= 412)
		Asymptomatic males in Juvenile detention centers				68% (N=879)
Kent et al. (32)	2004	Male and female students at 4 high schools	San Francisco	CT & NG	Urine based LCR	14% (N= 4497)
Monroe et al. (33)	2003	14 -20-year-old asymptomatic males and females presenting to ED	Texas	CT & NG	Urine based LCR	71% (N= 1231)
Shafer et al. (34)	2002	14-18-year-old females in schools	Northern Caroline	CT	SDA	47% (N= 1071)
Cohen et al. (13)	1999	9-12th grade high school male and females	Louisiana	CT	Urine based LCR	52 – 65% (N= 6000+)

CT = Chlamydia trachomatis, ED = emergency department, FP = family planning, LCR = ligase chain reaction, NG = Neisseria gonorrhoeae, PCR = polymerase chain reaction, SDA = strand displacement amplification

Table S7: Literature review of FSW STI Health seeking

				Health Seeking in the last year (at least once)	
Study	**Year**	**Sample**	**Location**	**General**	**STI Screening**
Kohler et al. (35)	2016	FSWs ≥14	Peru	Not reported	52.3 -57.2 %
SAHMS Final Report (36)	2015	FSWs ≥ 16	Johannesburg	53.8%	Not reported
			Cape Town	36.2%	
			Durban	58.8%	
Wong et al. (37)	2015	FSWs	Hong Kong	Not reported	45% (N = 340)
Richter et al. (38)	2014	FSWs	South Africa	60% interacted with health service in the last month	Not reported
Ramesh et al. (39)	2009	FSWs	Karnataka, India	68.4% had visited project sexual health clinic (baseline)	Not reported

Table S8: Literature review of FSW STI Screening acceptability

Study	**Year**	**Sample**	**Location**	**STI**	**Test**	**Screening acceptability**
Wong et al. (37)	2015	FSWs	Hong Kong	HIV, Syphilis, CT & NG	Self -collected Urine/ physician collect ectocervical swab based NAAT	41.6% (N=818)
Morton et al. (40)	1999	Male, female and transsexual sex-workers	Melbourne	CT, NG & TV	Self-collected tampon (females) or urine (males/ transsexuals) based PCR	78% (N=81)
Ramjee at al. (41)	1997	FSWs	Kwa-Zulu Natal	HIV, Syphilis, CT, NG, Trichomonas and BV	Clinician obtained cervical samples based direct immunofluorescence	100% (N=145)

BV = Bacterial Vaginosis , CT = Chlamydia trachomatis, HIV = Human Immunodeficiency Virus, NAAT = Nucleic acid amplification test ,NG = Neisseria gonorrhoeae, PCR = polymerase chain reaction, TV = Trichomonas vaginalis

4. Correlates of Model Outputs

Tables S9 and S10 show the relationship between natural history and transmission parameters of chlamydia and gonorrhea and the reduction in STI transmission using different screening strategies. This relationship is described by the Pearson correlation coefficient, and was calculated using the 100 parameter combinations that yielded the best fit to the STI prevalence data. When considering which parameters had the largest effect on the impact of the screening intervention, a number of points emerge:

- The CT transmission probabilities were positively correlated with the reduction in chlamydia incidence and prevalence.
- The average duration of CT immunity was negatively associated with a reduction in chlamydia incidence and prevalence. This is because the direct benefit of the intervention in the short term is offset by a longer-term reduction in the prevalence of immunity (42), and longer durations of immunity are associated with greater offsets.
- The duration of asymptomatic CT infection was also negatively associated with impact of the screening intervention. Since the average duration of asymptomatic infection is strongly positively associated with average duration of immunity (correlation = 0.61), it is likely that the association is confounded by the immunity parameter and it is the latter that is driving the observed association.
- For the most part, the same relationship between the average duration of immunity was not observed for NG. The strongest relationships between immunity parameters for CT and the impact of the screening intervention were observed in the screening strategies that showed the largest impacts (targeted at youth and HIV Care in comparison to ANC and FSWs). Only in the case of FSW screening, targeting a subpopulation with the highest NG prevalence, was the impact of screening negatively correlated with the average duration of NG immunity. We suspect that NG immunity is generally associated with the impact of the screening intervention but the low population prevalence of NG in this model results in less statistical power to observe this relationship.

- The proportion of female NG cases that become symptomatic was positively correlated with the impact of the screening intervention. In scenarios in which there is a higher proportion of symptomatic STI cases, there would be a higher rate of health seeking behaviour resulting in lower baseline prevalence on average. Since NG is closer to the threshold of persistence relative to CT (i.e. closer to R_0 = 1), this may result in NG becoming extinct in scenarios where a larger proportion of cases become symptomatic, resulting in the same intervention having a relatively higher impact on NG prevalence compared to CT.

Table S9: Correlates of reductions in chlamydia incidence and prevalence

Scenario	% Change relative to baseline	Transmission Probability		% of cases that become symptomatic		Average duration (in years)				
		M-to-F	F-to-M	Male	Female	Symptomatic infection	Asymptomatic infection	Immunity post treatment	% immune after treatment	% Correctly treated
Youth Screening										
Cumulative incidence (2018 -2028)		0.16	0.29**	0.02	-0.02	-0.15	-0.33**	-0.28**	-0.02	-0.01
Prevalence (2028)										
	Females (15 – 49)	0.17	0.16	-0.06	-0.02	-0.09	-0.46**	-0.13	-0.24*	0.01
	Males (15 – 49)	0.13	0.22*	-0.02	-0.10	-0.15	-0.26**	-0.08	-0.01	-0.03
	Females (15 – 24)	0.07	-0.01	-0.15	-0.11	0.01	-0.36**	-0.22*	-0.12	0.05
	Males (15 – 24)	0.12	0.15	-0.14	-0.10	0.04	-0.22*	-0.14	0.10	0.07
Youth Screening with Partner Notification										
Cumulative incidence (2018 -2028)		0.24*	0.24*	0.08	0.14	0.05	-0.38**	-0.53**	-0.12	0.01
Prevalence (2028)										
	Females (15 – 49)	0.26**	0.11	-0.14	-0.03	0.07	-0.57**	-0.33**	-0.30**	-0.03
	Males (15 – 49)	0.13	0.22*	-0.02	-0.10	-0.15	-0.26**	-0.08	-0.01	-0.03
	Females (15 – 24)	0.14	0.02	-0.14	-0.09	0.08	-0.46**	-0.33**	-0.21*	-0.04
	Males (15 – 24)	0.03	0.19	0.02	-0.08	0.15	-0.34**	-0.19	-0.25*	-0.01
Female Sex Worker										
Cumulative incidence (2018 -2028)		0.22*	0.03	0.01	0.09	-0.22*	-0.11	-0.02	0.04	0.02
Prevalence (2028)										
	Females (15 – 49)	0.20*	0.00	-0.07	0.18	-0.11	-0.12	0.00	-0.05	-0.07
	Males (15 – 49)	0.14	0.05	-0.04	0.09	-0.18	-0.03	-0.09	0.09	-0.02
	FSW	0.05	0.04	0.00	0.07	-0.09	0.03	0.01	0.08	-0.02

*p <0,05 **p <0,01

Table S9 continued

Antenatal Screening									
Cumulative incidence (2018 -2028)	0.12	0.14	0.02	-0.05	-0.21*	-0.17	-0.19*	0.00	0.00
Prevalence (2028)									
Females (15 – 49)	0.11	0.05	-0.07	0.04	-0.15	-0.14	0.00	-0.08	-0.04
Males (15 – 49)	0.00	0.14	0.09	-0.04	-0.18	0.05	-0.02	0.08	0.00
ANC	0.13	0.03	-0.04	0.05	-0.16	-0.11	-0.07	-0.04	0.00
Antenatal Screening with Partner Notification									
Cumulative incidence (2018 -2028)	0.15	0.24*	0.12	-0.03	-0.17	-0.20*	-0.10	-0.04	-0.09
Prevalence (2028)									
Females (15 – 49)	0.12	0.26**	0.07	0.06	-0.12	-0.21*	-0.12	-0.06	-0.08
Males (15 – 49)	0.09	0.27**	0.07	-0.01	-0.15	-0.07	-0.18	0.06	-0.10
ANC	0.10	0.25**	0.05	0.05	-0.10	-0.19*	-0.15	-0.06	-0.06
HIV Care Screening									
Cumulative incidence (2018 -2028)	0.27**	0.33**	0.05	0.08	-0.17	-0.13	-0.33**	0.18	-0.10
Prevalence (2028)									
Females (15 – 49)	0.17	0.06	-0.12	0.09	-0.16	-0.11	-0.18	0.03	-0.12
Males (15 – 49)	0.09	0.08	0.03	0.02	-0.24*	0.03	-0.17	0.09	-0.15
Females HIV care	0.21*	0.17	-0.09	0.03	-0.06	-0.53**	-0.26**	-0.24*	-0.25*
Males HIV care	0.19	0.10	-0.08	-0.05	-0.10	-0.41**	-0.31**	-0.14	-0.11
HIV Care Screening with Partner Notification									
Cumulative incidence (2018 -2028)	0.21*	0.41**	0.19	-0.04	-0.12	-0.18	-0.26**	0.14	-0.02
Prevalence (2028)									
Females (15 – 49)	0.28**	0.23*	0.03	0.04	-0.06	-0.13	-0.05	0.04	-0.06
Males (15 – 49)	0.16	0.31**	0.09	-0.03	-0.18	0.00	-0.08	0.17	-0.07
Females HIV care	0.22*	0.21*	0.01	0.13	0.06	-0.38**	-0.27**	-0.13	-0.23*
Males HIV care	0.14	0.11	-0.10	0.00	-0.01	-0.32**	-0.29**	-0.04	-0.05

*p <0,05 **p <0,01

Table S10: Correlates of Gonorrhea natural history parameters and model outputs

Scenario	% Change relative to baseline	Transmission Probability		% of cases that become symptomatic		Average duration (in years)			Immunity	
		M-to-F	F-to-M	Male	Female	Symptomatic infection	Asymptomatic infection	Immunity post treatment	% immune after treatment	% Correctly treated
Youth Screening										
Cumulative incidence (2018 -2028)		-0.01	-0.02	0.09	0.07	-0.03	-0.22*	-0.17	-0.03	-0.08
Prevalence (2028)										
	Females (15 – 49)	0.03	-0.12	-0.11	0.16	-0.01	0.03	-0.06	0.04	0.08
	Males (15 – 49)	0.03	-0.10	-0.09	0.15	-0.03	-0.05	-0.11	0.02	0.01
	Females (15 – 14)	0.02	-0.07	-0.16	0.05	-0.12	-0.09	-0.13	0.06	0.02
	Males (15 – 24)	0.01	0.13	0.06	0.09	-0.05	-0.11	-0.14	0.06	0.03
Youth Screening with Partner Notification										
Cumulative incidence (2018 -2028)		-0.08	0.11	-0.06	0.09	-0.03	0.00	-0.08	0.05	-0.14
Prevalence (2028)										
	Females (15 – 49)	-0.13	0.06	-0.09	0.20*	0.02	0.12	-0.07	0.08	0.01
	Males (15 – 49)	-0.08	0.03	-0.15	-0.09	-0.04	-0.06	0.11	-0.02	-0.18
	Females (15 – 14)	-0.12	0.12	0.00	0.07	-0.05	-0.04	-0.16	0.17	0.01
	Males (15 – 24)	-0.07	0.07	0.00	0.07	-0.11	-0.03	-0.24*	0.14	0.01
Female Sex Worker										
Cumulative incidence (2018 -2028)		0.01	-0.07	0.07	0.16	-0.11	-0.05	-0.30**	0.14	-0.07
Prevalence (2028)										
	Females (15 – 49)	-0.01	-0.07	-0.05	0.25**	0.15	0.04	-0.14	0.13	0.08
	Males (15 – 49)	-0.06	-0.05	-0.05	0.20*	0.08	0.07	-0.15	0.13	-0.06
	FSW	0.09	-0.09	0.12	0.15	0.10	0.07	-0.05	-0.03	-0.02

* p <0.05 **p <0.01

Table S10 continued

Antenatal Screening									
Cumulative incidence (2018 -2028)	-0.05	-0.01	-0.04	0.24*	0.12	-0.10	-0.06	-0.02	-0.06
Prevalence (2028)									
Females (15 – 49)	-0.01	-0.04	-0.11	0.27**	0.04	0.05	-0.17	0.10	0.03
Males (15 – 49)	-0.01	-0.13	-0.11	0.25**	0.06	0.08	-0.18	0.12	0.00
ANC	0.01	-0.04	-0.11	0.24*	0.03	0.05	-0.16	0.11	0.03
Antenatal Screening with Partner Notification									
Cumulative incidence (2018 -2028)	-0.03	-0.01	-0.08	0.18	0.01	0.00	-0.05	-0.06	0.04
Prevalence (2028)									
Females (15 – 49)	-0.09	-0.02	0.02	0.14	0.08	0.14	-0.05	0.02	0.06
Males (15 – 49)	-0.07	-0.03	0.08	0.21*	0.13	0.17	-0.08	0.07	0.00
ANC	-0.08	-0.04	0.00	0.12	0.08	0.16	0.00	0.00	0.08
HIV Care Screening									
Cumulative incidence (2018 -2028)	0.04	0.04	-0.03	0.05	-0.12	-0.11	-0.21*	0.09	0.00
Prevalence (2028)									
Females (15 – 49)	-0.06	0.09	0.08	0.20*	-0.06	0.03	-0.11	0.05	0.03
Males (15 – 49)	-0.09	0.07	0.04	0.20*	-0.07	0.04	-0.12	0.08	-0.05
Females HIV care	0.08	0.05	0.09	0.18	0.04	-0.10	-0.23*	0.06	-0.02
Males HIV care	-0.10	0.09	0.13	0.10	-0.16	0.16	-0.16	0.14	-0.05
HIV Care Screening with Partner Notification									
Cumulative incidence (2018 -2028)	0.05	0.11	0.00	0.34**	-0.02	-0.04	-0.14	-0.04	0.05
Prevalence (2028)									
Females (15 – 49)	-0.14	0.03	-0.06	0.25**	0.01	0.26*	-0.10	0.15	0.03
Males (15 – 49)	-0.19*	0.01	-0.06	0.25**	-0.07	0.24	-0.20*	0.18	-0.02
Females HIV care	0.09	-0.06	-0.03	0.03	0.12	-0.01	-0.16	0.17	-0.01
Males HIV care	-0.10	0.04	0.00	0.03	-0.25*	0.21	-0.14	0.12	-0.05

* p <0.05 **p <0,01

5. Additional model outputs

Table S11: Cumulative incidence over the 10-year targeted screening program

	Cumulative incidence over 10 years (95% CI)		% Reduction in Cumulative incidence relative to baseline	
Scenario	Chlamydia	Gonorrhea	Chlamydia	Gonorrhea
Baseline*	11292 (10866-11718)	19168 (18004-20333)		
Youth Screening				
Without PN	10670 (10239-11101)	18614 (17454-19774)	5.72 (5.05-6.39)	3.00 (1.67-4.32)
With PN	10496 (10061-10931)	18489 (17346-19632)	7.37 (6.62-8.11)	3.4 (2.07-4.72)
FSW Screening				
Without PN	11216 (10790-11642)	18737 (17567-19908)	0.68 (0.18-1.19)	2.40 (1.33-3.47)
Antenatal Care screening				
Without PN	11092 (10661-11523)	18869 (17731-20007)	1.87 (1.34-2.40)	1.20 (-0.14-2.55)
With PN	10991 (10565-11418)	18905 (17765-20045)	2.77 (2.2-3.34)	1.05 (-0.25-2.35)
HIV Care screening				
Without PN	10412 (9996-10827)	18214 (17061-19368)	7.94 (7.33-8.56)	5.20 (4.02-6.38)
With PN	10184 (9768-10601)	18130 (16996-19264)	10.05 (9.33-10.78)	5.45 (4.06-6.83)

The population grew dynamically over the 10-year screening period with an average population size close to 36000 mid-way through the screening period.
*Baseline incidence estimates were calculated over the same 10-year period as the hypothetical screening intervention
The means and 95% CIs are calculated from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into the model.

Table S12: Estimated impact of targeted screening programs on population level prevalence (aged 15 to 49) after the implementation of a 10-year targeted screening program

	% Reduction in prevalence 10th Year (95% CI)			
	Chlamydia		Gonorrhea	
Scenario	Females	Males	Females	Males
Youth vs. Baseline	15.09 (13.82-16.35)	13.75 (12.25-15.25)	3.34 (-0.50-7.18)	1.29 (-3.56-6.15)
Youth PN vs. Baseline	17.38 (16.00-18.75)	17.29 (15.91-18.67)	2.30 (-1.52-6.13)	1.12 (-3.67-5.91)
Youth vs. Youth PN	2.52 (1.17-3.87)	3.75 (2.20-5.30)	-2.77 (-6.54-1.00)	-2.34 (-6.71-2.03)
FSW vs. Baseline	0.94 (-0.23-2.10)	1.34 (-0.02-2.69)	1.41 (-2.35-5.18)	0.34 (-4.24-4.91)
ANC vs. Baseline	6.94 (5.72-8.15)	4.64 (3.23-6.04)	0.27 (-3.98-4.52)	-2.61 (-7.29-2.07)
ANC PN vs. Baseline	8.70 (7.32-10.07)	6.66 (5.18-8.14)	0.39 (-2.93-3.71)	-0.75 (-5.25-3.74)
ANC vs. ANC PN	1.66 (0.14-3.18)	1.89 (0.45-3.33)	-2.96 (-7.28-1.36)	-0.84 (-5.27-3.60)
HIV Care vs. Baseline	14.54 (13.44-15.63)	12.85 (11.52-14.17)	4.74 (0.94-8.54)	3.67 (-1.37-8.72)
HIV Care PN vs. Baseline	17.12 (15.81-18.44)	15.45 (13.93-16.96)	8.29 (4.76-11.83)	5.86 (1.40-10.32)
HIV Care vs. HIV Care PN	2.87 (1.43-4.30)	2.79 (1.21-4.36)	0.97 (-3.76-5.70)	-1.69 (-7.33-3.94)

The means and 95% CIs are calculated from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into each model. The hypothetical implementation of STI screening programs is simulated as having been initiated in 2018.
PN = partner notification, FSW = female sex worker, ANC = antenatal care, PLWHA = people living with HIV/Aids, ART = antiretroviral treatment

Table S13: Estimated impact of targeted screening programs in key populations after the implementation of a 10-year targeted screening program

	Chlamydia		Gonorrhoea	
Scenario	Females	Males	Females	Males
Youth targeted screening: % Reduction in Youth (aged 15 to 24) prevalence				
Youth vs. Baseline	25.70 (24.1 - 27.3)	23.06 (20.75 - 25.37)	7.14 (2.59 - 11.68)	3.06 (-2.85 - 8.97)
Youth PN vs. Baseline	30.66 (28.85 - 32.46)	31.4 (29.34 - 33.45)	7.99 (3.3 - 12.68)	2.23 (-4.56 - 9.02)
FSW targeted screening: % Reduction in FSW prevalence				
FSW vs. Baseline	5.93 (1.24 - 10.61)		4.88 (1.54 - 8.23)	
ANC targeted screening: % Reduction in pregnant women prevalence				
ANC vs. Baseline	7.16 (5.95 - 8.37)		0.14 (-4.20 - 4.49)	
ANC PN vs. Baseline	9.00 (7.61 - 10.4)		0.65 (-2.77 - 4.07)	
HIV Care targeted screening: % Reduction in STI prevalence in patients in HIV care				
HIV Care vs. Baseline	52.58 (50.72 - 54.44)	51.97 (49.66 - 54.28)	22.5 (18.2 - 26.80)	18.3 (11.54 - 25.05)
HIV Care PN vs. Baseline	56.27 (54.44 - 58.09)	54.72 (52.68 - 56.75)	27.26 (23.37 - 31.14)	20.04 (12.46 - 27.62)

The means and 95% CIs are calculated from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into each model. The hypothetical implementation of STI screening programs is simulated as having been initiated in 2018, and the reduction in incidence and prevalence is calculated relative to the level that would have been expected in the absence of any screening program.

PN = partner notification, FSW = female sex worker, ANC = antenatal care, PLWHA = people living with HIV/Aids, ART = antiretroviral treatment

6. Standardised screening programme

Table S14: Sexual partner estimates and chlamydia prevalence

	Age (years)	CT prevalence prior to screening %(%)	Average annual Partners	Effective Contact Rate *
Females	16 - 19	11.83 (11.46-12.2)	1.73 (1.73-1.74)	4.02 (4.01-4.02)
	20 - 24	15.34 (14.98-15.70)	2.68 (2.68-2.69)	4.02 (4.02-4.03)
	25 - 29	11.52 (11.25-11.78)	2.56 (2.55-2.56)	3.70 (3.70-3.71)
Males	16 - 19	4.30 (4.08-4.53)	0.89 (0.88-0.89)	3.51 (3.50-3.52)
	20 - 24	9.25 (8.91-9.59)	2.16 (2.15-2.17)	3.86 (3.85-3.87)
	25 - 29	9.93 (9.64-10.22)	2.59 (2.58-2.60)	3.80 (3.79-3.81)

The means and 95% CIs are calculated from the range of model outputs generated when the 100 best-fitting parameter combinations are entered into each model. The hypothetical implementation of STI screening programs is simulated as having been initiated in 2018.
* Effective contact rate (c), is calculated as c = m + v/ m, where m is the mean number of sex partners per year and v its variance. This is a measure of the heterogeneity of sexual partnerships that can be compared across network models with different structures (18)

Table S15: Chlamydia natural history parameters specified for individual-based stochastic simulation models of Chlamydia transmission

Parameter	RIVM	ClaSS	HPA	MicroCOSM*
Transmission probability per act of sex				
Male-to-female	0.11	0.154	0.0375	0.162
Female –to-male	0.11	0.122	0.0375	0.098
Frequency of sex acts				
	1/day casual 0.25/day steady	0.5/day	1/day for 30 days then 0.25/day	3/month short-term 5/month long term (declining by 50% for every 20 -year increase in age)
% of cases that become symptomatic				
Male	0.50	0.75	0.00	0.37
Female	0.30	0.30	0.045	0.11
Average duration asymptomatic infection (days)				
Males	200	200	180	683
Females	300	200	180	711
Average duration symptomatic infection (days)				
Males	33	33	30	15
Females	40	40	30	30
Proportion immune after treatment cure	0	0	0	73.2
Average duration of immunity (days)	0	0	0	2065

* Median of 100 best fitting parameters

Table S16: Characteristics of individual-based stochastic simulation models of Chlamydia transmission used to simulate standardised screening program (Updated from Kretzschmar et al. (18))

RIVM model	ClaSS	HPA	MicroCOSM
Simulation method			
Discrete time step simulation. Movement between STI states are calculated at daily intervals. Events occur each day with probabilities assigned or drawn from distributions			Discrete time step simulation. Movements between STI states are calculated at weekly intervals.
Model population size			
Closed population of 40 000	Closed population of 40 000	Closed population of 40 000	Population grows dynamically reaching a size of approximately 36 000 mid-way through the screening program
Model population age			
15-65 years 50% females	12-62 years 50% females	16-44 years 50% females	All ages. Projection begins with South Africa population profile in mid 1985, 50.39% births are male
Sexual activity levels			
Two risk groups Core (5% of 15–35-year-old women and men) Non-core (95% 15–35-year-old men and women, 100% 35+- year-old men and women)	Three risk groups High (5% of 15–35-year-old women, 9% of 15–35-year-old men) Medium (17% of 15–35-year-old women and men) Low (78% of 15–35-year-old women, 74% of 15–35-year-old men)	Two risk groups Core (propensity for short-term partnerships, initially 50% of 16-year-old women, 60% of 16-year-old men) Non-core (prefer long-term partnership) Each year 4% of men, 8% of women switch from core to non-core	Two risk groups High (propensity for concurrency and commercial sex, 35% of males, 25% of females) Low (no concurrent partnerships or commercial sex) Sexual debut occurs between ages of 10-30, 50% higher rate in high-risk group.
Partnership formation			
Heterosexual only determined by sexual activity group, existing partnership status, age difference	Heterosexual only determined by sexual activity group, existing partnership status, age difference	Heterosexual only; determined by sexual activity group, existing partnership status, age difference Two types of partnerships possible: short-term (core) and long-term (non-core).	Heterosexual only; determined by sexual activity group, existing partnership status and age of individual Three types of partnerships possible: short-term (non-cohabiting), long-term (cohabiting or marital), sex worker-client
Partnership duration			
Mean 10 days for casual partnerships, 6.9 years (2519 days) for steady partnerships	Mean 950 days if both partners in lowest activity group; lower means for higher activity groups	Mean 14 days for short partnerships, 900 days for long partnerships and increases by 200 days each year	Mean 180 days for short term, rates of dissolution of long term partnerships based on age specific divorce rates
Concurrent partnerships			
Core group can have up to two partners Non-core group has only one casual or steady partner at a time	Highest activity group can have more than two concurrent partners Very low (but non-zero) probability of concurrent partnerships in lowest activity group	5% of population can have two partners until 35 years (first partnership may be short or long, second partner always casual) All 35+ year olds prefer only one partner	High-risk individuals can have up to two partners. High-risk men can engage in commercial sex in addition to two concurrent partnerships. Low-risk group are serially monogamous.
Partner notification able to be modelled explicitly			
Yes	Yes	Yes	Yes

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