Periodic presumptive treatment of curable sexually transmitted infections among sex workers: recent experience with implementation

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Purpose of review
Curable sexually transmitted infections (STIs) are common occupational hazards for female sex workers in low-income and middle-income countries. Yet, most infections are asymptomatic and sensitive screening tests are rarely affordable or feasible. Periodic presumptive treatment (PPT) has been used as a component of STI control interventions to rapidly reduce STI prevalence.

Recent findings
Six recent observational studies confirm earlier randomized controlled trial findings that PPT reduces gonorrhoea and chlamydia prevalence among sex workers. One modeling study estimated effects on *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Haemophilus ducreyi*, and HIV prevalence at different levels of PPT coverage and frequency, among sex workers who take PPT and among all sex workers. Important operational issues include use of single-dose combination antibiotics for high cure rates, conditions for introducing PPT, frequency and coverage, and use of PPT together with other intervention components to maximize and sustain STI control and reinforce HIV prevention.

Summary
PPT is an effective short-term measure to rapidly reduce prevalence of gonorrhoea, chlamydia, and ulcerative chancroid among female sex workers. It should be implemented together with other measures – to increase condom use, reduce risk and vulnerability – in order to maintain low STI prevalence when PPT is phased out.

Keywords
female sex workers, periodic presumptive treatment, prostitution, sexually transmitted infections

INTRODUCTION

Curable sexually transmitted infections (STIs) are common occupational hazards for female sex workers in low-income and middle-income countries [1]. Combined prevalence of gonorrhoea (*Neisseria gonorrhoeae*), chlamydia (*Chlamydia trachomatis*), and syphilis (*Treponema pallidum*) among sex workers frequently surpasses 30–50% [2]. In settings with large HIV epidemics and weak STI control, ulcerative chancroid (*Haemophilus ducreyi*) remains an important HIV cofactor [3].

High STI prevalence, when combined with frequent partner change in sex work networks, also influences transmission dynamics at population level. Upstream transmission in sex work networks is capable of generating high STI incidence, which drives downstream transmission among lower risk populations (Fig. 1). Interventions that have raised condom use and reduced STI prevalence among sex workers have also documented downstream impact on male 'bridge' groups and general populations [4–6]. Importantly, the public health benefits of controlling curable STIs extends to HIV prevention [7].

For these reasons, intervention programmes often offer STI treatment to symptomatic sex workers in addition to promoting condom use. However, a major weakness of STI services in resource-limited

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KEY POINTS

- Periodic presumptive treatment (PPT) has been shown to reduce prevalence of gonorrhoea and chlamydia among female sex workers by half, and to have even greater effect on ulcerative chancroid.
- Addition of PPT to other condom and sexually transmitted infection (STI) control measures may lead to rapid control of several curable STIs among sex workers and male bridge groups, and contribute to population-level STI reductions.
- Empirical data and modeling have highlighted important operational factors including appropriate conditions for PPT introduction, as well as estimated levels of coverage and frequency for STI control.
- Related operational considerations include use of single-dose combination antibiotics for high cure rates, reinforced condom promotion to reduce rates of reinfection, strong outreach and peer interventions to increase coverage and utilization of services, and use of PPT together with other intervention components to reinforce STI control and HIV prevention.
- Adding PPT to interventions with sex workers can strengthen HIV prevention by reducing the prevalence of STI cofactors, particularly where ulcerative chancroid is prevalent.

settings is the lack of sensitive screening methods to identify and treat asymptomatic and unrecognized STIs. Two of the most common curable STIs – gonorrhoea and chlamydia – are asymptomatic in the majority of women with infection, and common vaginal symptoms have low predictive value for STIs. Furthermore, ulcerative STIs, which may be painless and internal, frequently go unnoticed. Many curable STIs are thus missed, leading to serious and life-threatening sequelae including pelvic inflammatory disease, infertility, ectopic pregnancy, sepsis, and congenital infections.

PERIODIC PRESUMPTIVE TREATMENT

Periodic presumptive treatment (PPT) is an STI treatment strategy that extends treatment to sex workers on the basis of their high risk and prevalence of infection, rather than limiting it to those with symptoms, signs, or positive diagnostic tests [2]. As such, it is analogous to epidemiologic treatment of identified sex partners of STI index cases, or presumptive treatment of fever with antimalarials in endemic areas.

The efficacy of PPT has been demonstrated in one published randomized controlled trial (RCT), which measured significant reductions of *N. gonorrhoeae* [relative risk (RR) = 0.46; 95% confidence interval (CI) = 0.31–0.68] and *C. trachomatis* (RR = 0.38; 95% CI = 0.26–0.57), but no effect on serologic syphilis [RR = 1.02; 95% CI = 0.54–1.95] [8]. Based on available evidence, a 2005 WHO technical consultation recommended that PPT be considered, in areas with high STI prevalence, as part of a package of services for sex workers that includes

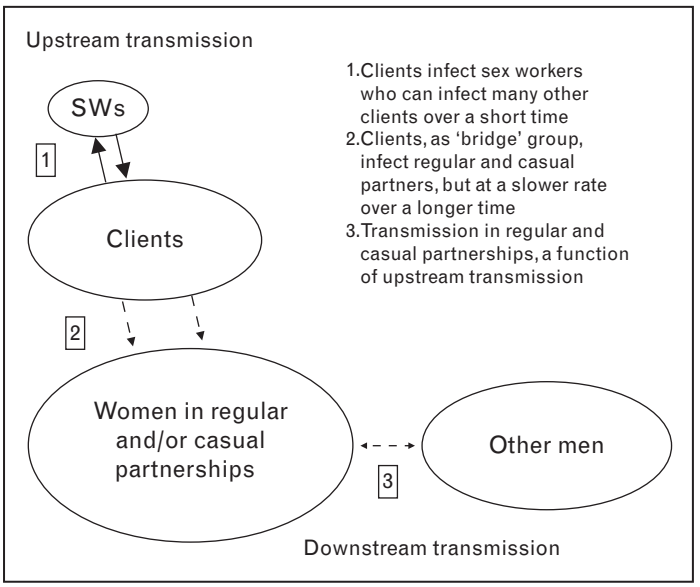


FIGURE 1. Sexually transmitted infections/HIV transmission dynamics within and beyond sex work networks. 1, clients infect sex workers (SWs) who can infect many other clients over a short time; 2, clients, as 'bridge' group, infect regular and casual partners, but at a slower rate over a longer time; 3, transmission in regular and casual partnerships is a function of upstream transmission.

condom promotion, syndromic case management, and regular screening for syphilis [9]. Additionally, involving sex workers in outreach and other peer interventions was strongly recommended to increase uptake and utilization of services and to reinforce primary prevention [9].

Beyond the benefit to individual sex workers in need of treatment, PPT is promoted as a temporary measure to rapidly reduce population prevalence in areas of poor STI control [2,9]. As STI prevalence declines and subsequent risk decreases, however, many programmes have attempted to reduce the frequency of PPT, or withdraw it entirely, relying on other interventions to maintain low prevalence. Such operational issues have received recent attention in the literature and are the focus of this review.

METHODS

This article reviews the recent literature to identify factors that are important in implementing interventions with sex workers that include a PPT component. We conducted a *MEDLINE* search of articles from 2008 to 2011 with search terms related to sex work, STI, and presumptive treatment. Studies describing PPT interventions and outcomes were searched for information on operational issues including choice of antibiotic regimen, appropriate conditions for introducing PPT, PPT frequency and coverage, and use of PPT together with other intervention components to maximize and sustain STI control and reinforce HIV prevention.

RECENT EVIDENCE OF PERIODIC PRESUMPTIVE TREATMENT EFFECTIVENESS

Six observational studies included data on PPT interventions and outcomes, three from Indonesia, two from India, and one from Papua New Guinea [10▪–12▪,13▪▪,14▪,15▪]. One modeling study included earlier data from South Africa, Benin, Ghana, and Laos [16▪▪]. All studies reported STI prevalence reductions among female sex workers. The efficacy and effectiveness of PPT was recently assessed in a systematic review [17▪].

One time-series study among Indonesian brothel-based sex workers included PPT (azithromycin 1 g–cefixime 400 mg), syndromic treatment and condom promotion [10▪]. *N. gonorrhoeae* decreased by 44% ($P < 0.01$) and 79% ($P < 0.01$) at two sites, and *C. trachomatis* by 25% ($P = 0.13$) and 70% ($P = 0.01$), after 15 months. *N. gonorrhoeae* and/or *C. trachomatis* prevalence among sex workers who received PPT at least once was lower than for newcomers (19.6 versus 35.9%, $P < 0.01$).

Two population-based, cross-sectional, biobehavioral studies from Indonesia examined associations between STIs and previous PPT after adjusting for condom use and other factors [11▪,12▪]. One reported that female sex workers who received PPT (azithromycin 1 g–cefixime 400 mg) three or more times in the past 6 months had lower combined prevalence of *N. gonorrhoeae* and/or *C. trachomatis* [adjusted odds ratio (aOR) 0.54; 95% CI = 0.42–0.7] [11▪]. The second study measured syphilis prevalence and associated factors among female sex workers in 10 cities of Indonesia in 2007, compared with earlier surveillance in 2003 and 2005 [12▪]. Prevalence of active syphilis was lower among those who had received at least one dose of PPT (azithromycin 1 g–cefixime 400 mg) compared with those who had not received PPT (3.9 versus 6.0%; $P = 0.008$).

In Mysore district, India, PPT was introduced as part of sexual health services that were an integral part of a community-led structural intervention to empower sex workers and strengthen HIV/STI prevention [13▪▪]. STI prevalence declined from baseline to follow-up 2 years later: *N. gonorrhoeae* from 5 to 2% ($P = 0.03$); *C. trachomatis* from 11 to 5% ($P = 0.001$); and *Treponema pallidum* from 25 to 12% ($P < 0.001$). Reductions in *N. gonorrhoeae* (aOR 0.45, 95% CI = 0.20–1.02) and *C. trachomatis* (aOR 0.32, 95% CI = 0.17–0.61) were associated with self-report of having received PPT (prepackaged and color-coded as a 'grey pack').

Elsewhere in Karnataka state, India, targeted interventions also included peer outreach with promotion of condoms and services; sexual health services for female sex workers and their regular partners, syndromic case management, speculum examination, PPT (azithromycin 1 g–cefixime 400 mg) every 3–6 months, and syphilis screening [14▪]. Compared with baseline, reductions were measured in the prevalence of *N. gonorrhoeae* and/or *C. trachomatis* (8.9 versus 7.0%, $P = 0.02$) and high-titre *T. pallidum* (5.9 versus 3.4%, $P = 0.001$). Reductions in *N. gonorrhoeae* and/or *C. trachomatis* were associated with self-report of receiving PPT 'grey pack', $P < 0.001$.

In Papua New Guinea, female sex workers received a 3 monthly oral combination of amoxicillin with clavulanic acid, probenecid, and azithromycin [15▪]. Nine months later, after three PPT rounds, significant declines were measured for *N. gonorrhoeae* from 56 to 23% ($P < 0.001$) and for *C. trachomatis* from 38 to 16% ($P = 0.001$).

ANTIBIOTIC REGIMENS

PPT based on monthly azithromycin 1 g alone was first used empirically in South African mining

communities in 1996 [9]. Based on reported reductions of *N. gonorrhoeae*, *C. trachomatis* and genital ulcers, PPT protocols using azithromycin at different treatment intervals were adapted for the Philippines and Laos [9]. RCT evidence supports the efficacy of monthly PPT with azithromycin 1 g for *N. gonorrhoeae* and *C. trachomatis* [8].

Subsequent PPT interventions have employed combination regimens – azithromycin 1 g and either cefixime 400 mg or ciprofloxacin 500 mg – to maximize cure rates, particularly for gonorrhoea. It is argued that risk of developing antimicrobial resistance to *N. gonorrhoeae* would be minimized by administering, under observation, two single-dose antibiotics that are highly effective against *N. gonorrhoeae*. The importance of using an effective regimen was highlighted in one study from Indonesia, which reported an increase in *N. gonorrhoeae*/*C. trachomatis* following substitution of less effective antibiotics [10▪].

INTRODUCING PERIODIC PRESUMPTIVE TREATMENT

Conditions related to sex work – including condom use, STI prevalence, and incidence – are important factors in deciding when and how to start PPT. Several recent studies were conducted in areas where sex workers were already reached by outreach, condom and STI interventions, and STI prevalence had declined to moderate or even low levels (Fig. 2, white symbols) [13▪▪,14▪]. Others, where PPT was initiated at the start of interventions when STI prevalence was higher, reported larger STI declines (Fig. 2, black symbols) [10▪,15▪].

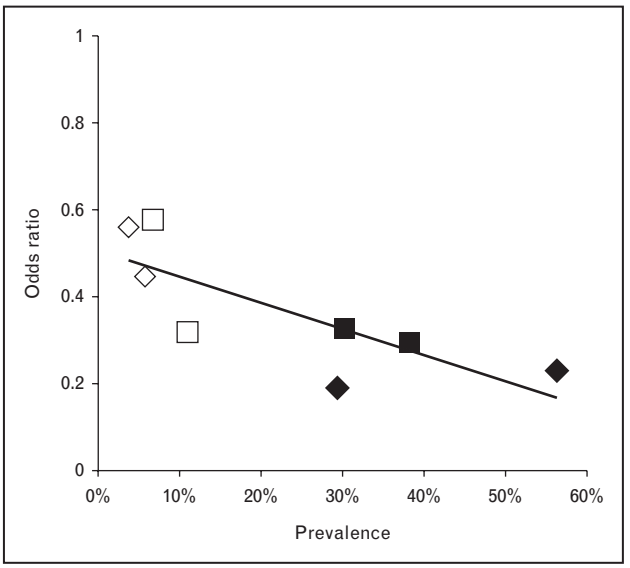


FIGURE 2. *N. gonorrhoeae* and *C. trachomatis* declines (odds ratios) as a function of initial prevalence. diamonds, *N. gonorrhoeae*; rectangles, *C. trachomatis*; black, new intervention; white, established intervention.

STI surveillance can identify epidemiologic hotspots, pockets of poor STI control that may be driving larger epidemic spread. PPT is most beneficial in such settings, and may have little or no effect if STIs are already well controlled. The Benin/Ghana RCT (described in the WHO report and article by Vickerman *et al.* [16▪▪]) demonstrates this point [9]. In a setting with greater than 90% reported condom use with last client, and where sex workers had access to regular STI screening and treatment, chlamydia prevalence was only 3.2% when PPT was introduced. Adding PPT resulted in no additional reduction of *C trachomatis* prevalence (data not shown).

FREQUENCY AND COVERAGE OF PERIODIC PRESUMPTIVE TREATMENT

STI incidence, a function of exposure and condom use, determines how often PPT may need to be given to control transmission. Recent studies report on interventions with quarterly PPT, whereas earlier studies (including one RCT) provided PPT monthly. Vickerman *et al.* [16▪▪] used mathematical modeling to estimate the effect of PPT at different frequencies and levels of coverage. Assuming an azithromycin-based PPT regimen, the model estimated that control of *N. gonorrhoeae* and *H. ducreyi* would improve by increasing PPT frequency from quarterly to monthly, at which point little additional benefit would be gained by giving PPT more frequently.

In India (including the two studies reported here), targeted interventions initially offered PPT at sex workers' first visit, then for sex workers who failed to attend clinical checkups for more than 6 months [18▪]. Subsequent operations research showed that 50% of new *N. gonorrhoeae*/*C. trachomatis* infections occurred within 3 months of PPT, and guidelines were revised to recommend quarterly PPT [19].

Coverage of interventions is another important determinant of STI outcomes. The Vickerman *et al.* model assumed low PPT coverage (only 10% of sex workers reached by the intervention, based on Johannesburg data) as a starting point. The effect of reaching a larger proportion of sex workers was estimated for *N. gonorrhoeae* and *H. ducreyi* among sex workers reached by the intervention and for all sex workers. The model estimated that PPT interventions can effectively reduce STI prevalence among all female sex workers – a population effect related to reduced STI transmission in sex work networks – when coverage levels surpass 30% of the sex workers population.

Coverage rates well above 30% have been reported. Reza-Paul *et al.* [13▪▪] examined STI and

behavioral outcomes as a function of programme exposure following initiation of a community-led intervention. Within 2.5 years, more than 90% of sex workers reported having been visited by a peer educator, having visited the project drop-in centre and dedicated sexual health clinic, and having received presumptive STI treatment. The study measured substantial increases in self-reported condom use with all sexual partners in addition to significant reductions in STI prevalence. Programme exposure was associated with increased condom use with last client, with visiting the clinic and with receiving PPT. *N. gonorrhoeae* and *C. trachomatis* reductions were in turn significantly associated with PPT after adjusting for condom use and other covariates. Fig. 3 [13▪▪] is a simplified version of the causal pathways to reduced STI prevalence described in the article.

The feasibility of implementing combined interventions including PPT on a large scale, with high coverage and utilization by sex workers, has been demonstrated by the Avahan India AIDS Initiative [18▪]. Over 2.7 million clinical visits by 431 434 individuals, including 331 533 female sex workers, were captured by an individual tracking system [20▪]. The number of visits per person increased annually from 1.2 in 2005 to 8.3 in 2009. The proportion attending clinics more than four times per year increased from 4% in 2005 to 26% in 2009 ($P < 0.001$), and the proportion seeking regular STI checkups increased from 12 to 48% ($P < 0.001$).

IMPLEMENTING PERIODIC PRESUMPTIVE TREATMENT AS PART OF A PACKAGE OF INTERVENTIONS

As described above, PPT is generally introduced together with other condom and STI interventions.

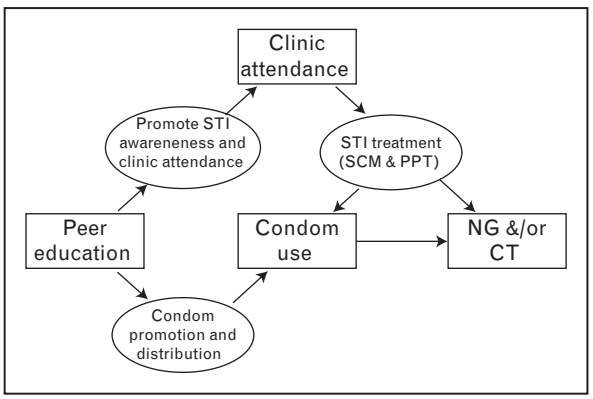


FIGURE 3. Causal pathways. CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; PPT, periodic presumptive treatment; SCM, syndromic case management; STI, sexually transmitted infection. Adapted from [13▪▪].

Promotion of correct and consistent condom use during penetrative sex remains one of the most important prevention components for sex worker interventions [4]. Concern has been raised that some interventions, such as male circumcision, may undermine condom use, however. Such risk compensation has been raised as a possible negative effect of PPT. For this reason, most studies describe condom promotion interventions implemented alongside PPT, and all recent studies reported condom use increases (Fig. 4) [10▪,13▪▪,14▪,15▪].

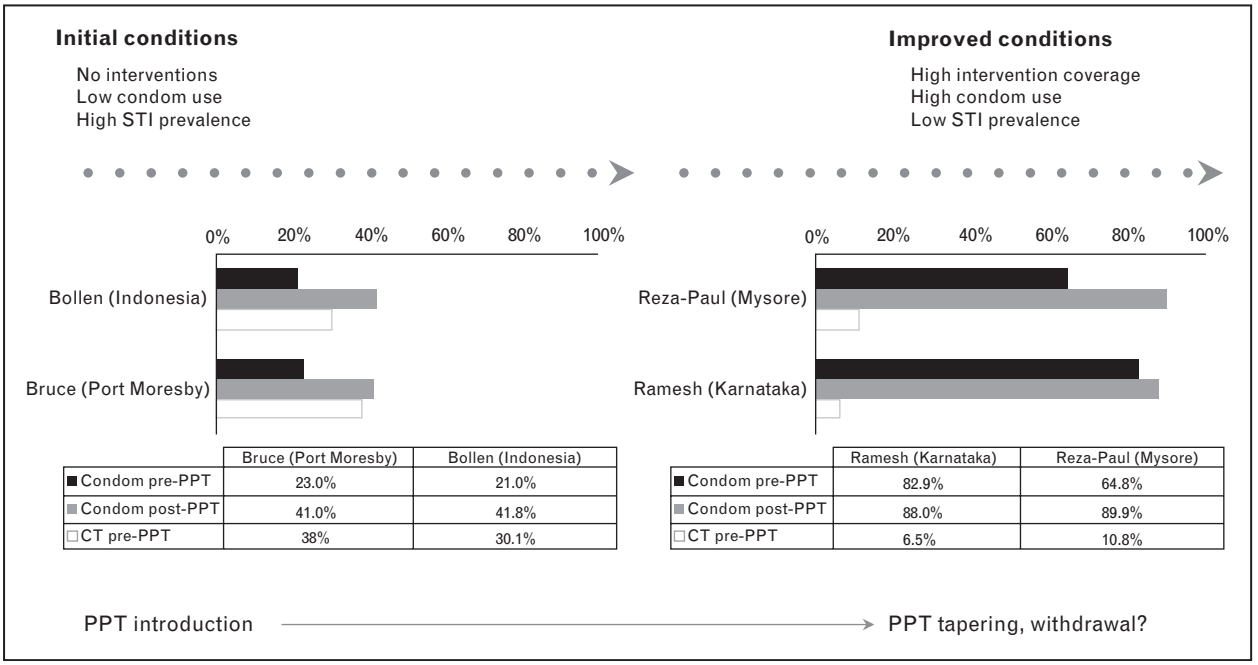
Condom and STI interventions are also needed to maintain reduced prevalence once short-term interventions like PPT bring them down. Although PPT-specific data are limited, studies show that low STI prevalence can be maintained if sex worker condom use is high enough and other STI services are available. 100% condom use programmes, for example, have been able to maintain very low incidence and prevalence of curable STIs using combinations of outreach, condom promotion, and STI services [4]. Others have adapted protocols that combine PPT at a sex workers' first visit with clinical and laboratory-based screening at subsequent visits [13▪▪,14▪].

Interventions should, thus, adapt to changing STI transmission dynamics. Figure 4 fits data from four recent PPT studies with condom use trends to a conceptual implementation timeline beginning under conditions of low condom use and poor STI control [10▪,15▪]. In this scenario, in which intervention coverage and condom use are high, the additional benefits of PPT in reducing and maintaining low STI prevalence may decrease to the point wherein PPT can be phased out [13▪▪,14▪].

There is little reported evidence of the effects of tapering or withdrawing PPT once STI prevalence has declined, however. Based on limited empirical evidence, the 2005 WHO consultation suggested 10% combined *N. gonorrhoeae*/*C. trachomatis* prevalence and 70% reported condom use (by sex workers with last client) as thresholds for tapering or withdrawing PPT. Several recent studies cautioned that without increasing condom use, STIs would likely rebound if PPT were withdrawn [10▪,15▪].

POTENTIAL CONTRIBUTION TO HIV PREVENTION

In places where STIs are poorly controlled, adding PPT to interventions with sex workers can strengthen HIV prevention by lowering the prevalence of STI cofactors. The model by Vickerman *et al.* [16▪▪] estimates a moderate-to-strong impact on HIV transmission, PPT interventions with sufficient coverage (40%) and follow-up (2 years) could



	Bruce (Port Moresby)	Bollen (Indonesia)
Condom pre-PPT	23.0%	21.0%
Condom post-PPT	41.0%	41.8%
CT pre-PPT	38%	30.1%

	Ramesh (Karnataka)	Reza-Paul (Mysore)
Condom pre-PPT	82.9%	64.8%
Condom post-PPT	88.0%	89.9%
CT pre-PPT	6.5%	10.8%

FIGURE 4. Intervention timeline: condom use, sexually transmitted infections (STI) prevalence and periodic presumptive treatment (PPT) [10▪,13▪▪,14▪,15▪]. Left: early interventions under conditions of low condom use and high STI prevalence [10▪,15▪]. Right: established interventions with high condom use and reduced STI prevalence [13▪▪,14▪].

noticeably decrease sex worker HIV incidence (>20%). Larger effects were modeled in simulations that included chancroid due to the high HIV cofactor effect of genital ulcers.

Limited empirical data support this indirect effect on HIV. Ramesh *et al.* [14▪] reported reductions in HIV prevalence (19.6 versus 16.4%, $P=0.04$). Reza-Paul *et al.* [13▪▪] reported that although overall HIV prevalence remained stable, detuned assay suggested a decline in recent HIV infections, and lower HIV prevalence was measured among women without a regular partner. Finally, in a study among Indonesian sex workers, Morineau *et al.* [21▪] demonstrated higher HIV incidence among those not receiving PPT for STIs during the previous 6 months, as well as sex workers who had active syphilis or genital ulcers in the past year.

CONCLUSION

PPT has been shown to reduce *N. gonorrhoeae* and *C. trachomatis* prevalence among sex workers. Earlier studies and modeling suggest a larger effect on ulcerative chancroid, and population-level impact on STI/HIV transmission. Considerable experience implementing PPT in over a dozen countries supports the feasibility of PPT and provides evidence to guide important operational decisions. High coverage of PPT, given at sufficient frequency and as part of broader interventions with sex workers, could make a substantial contribution to strengthen overall STI control and HIV prevention.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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