Prevention of sexually transmitted infections in urban communities (Peru PREVEN): a multicomponent community-randomised controlled trial

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Summary

Background Previous community-randomised trials of interventions to control sexually transmitted infections (STIs) have involved rural settings, were rarely multicomponent, and had varying results. We aimed to assess the effect of a multicomponent intervention on curable STIs in urban young adults and female sex workers (FSWs).

Methods In this community-randomised trial, baseline STI screening was done between August, and November, 2002, in random household samples of young adults (aged 18–29 years) and in FSWs in Peruvian cities with more than 50 000 inhabitants. Geographically separate cities were selected, matched into pairs, and randomly allocated to intervention or control groups with an S-PLUS program. Follow-up surveys of random samples were done after 2 years and 3 years. The intervention comprised four modalities: strengthened STI syndromic management by pharmacy workers and clinicians; mobile-team outreach to FSWs for STI screening and pathogen-specific treatment; periodic presumptive treatment of FSWs for trichomoniasis; and condom promotion for FSWs and the general population. Individuals in control cities received standard care. The composite primary endpoint was infection of young adults with Chlamydia trachomatis, Trichomonas vaginalis, or Neisseria gonorrhoeae, or syphilis seroreactivity. Laboratory workers and the data analyst were masked, but fieldworkers, the Peruvian study team, and participants in the outcome surveys were not. All analyses were done by intention to treat. This trial is registered, ISRCTN43722548.

Findings We did baseline surveys of 15 261 young adults in 24 Peruvian cities. Of those, 20 geographically separate cities were matched into pairs, in each of which one city was assigned to intervention and the other to standard of care. In the 2006 follow-up survey, data for the composite primary outcome were available for 12 930 young adults. We report a non-significant reduction in prevalence of STIs in young adults, adjusted for baseline prevalence, in intervention cities compared with control cities (relative risk 0·84, 95% CI 0·69–1·02; p=0·096). In subgroup analyses, significant reductions were noted in intervention cities in young adult women and FSWs.

Interpretation Syndromic management of STIs, mobile-team outreach to FSWs, presumptive treatment for trichomoniasis in FSWs, and condom promotion might reduce the composite prevalence of any of the four curable STIs investigated in this trial.

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Introduction

Many randomised trials have shown that interventions to reduce transmission or acquisition of sexually transmitted infections (STIs) are effective.1 Community-randomised trials of STI prevention have used several approaches: strengthened STI syndrome management;2,3 mass treatment;4 community mobilisation, behaviour change, condom promotion and distribution, income-generating projects, and clinic-based STI syndromic treatment;5 and sexual and reproductive health interventions for adolescents.6 These trials—in rural African settings—have had variable effects on STI incidences. A neighbourhood randomised intervention with peer opinion leaders used in five countries, including Peru, did not reduce STI prevalence in high-risk populations.7

Longitudinal training of pharmacy workers in Peru has resulted in improvements in STI services,8,9 and longitudinal studies of clinic-based STI service improvement for female sex workers (FSWs) have shown reductions in STI prevalences in FSW clinic attendees.10 The effect of such improvements on STI morbidity should be rigorously assessed at the population level (especially in urban settings). Additionally, feasibility assessments and results of multicomponent public health interventions are of growing importance. The Peru PREVEN Study targeted FSWs and the general population in Peruvian cities. We aimed to assess the effect of the PREVEN intervention on community-level prevalences of four curable STIs (chlamydial infection, vaginal trichomoniasis, gonorrhea, and syphilis), primarily in young adults and secondarily in FSWs.
Methods

Study population
In accordance with the protocol, we identified cities in Peru with more than 50 000 inhabitants, and excluded those that were involved in another STI prevention trial. Geographically separate cities (classed as separate when more than 30 minutes travel by land between the cities) eligible for inclusion were matched into pairs that were randomly assigned to intervention or standard care.

Of 30 Peruvian cities with more than 50 000 inhabitants, we excluded Lima because its large population of 9 million precluded matching with another city, two cities because effects could be altered by proximity to Lima, and three cities involved in another STI prevention trial, leaving 24 cities. Population-based baseline surveys of young adults occurred from August to November, 2002 (table 1). We then selected 20 cities, matched them into pairs, and randomly assigned them to intervention or standard care. Outcome surveys in 2005 included random samples of young adults in these 20 cities. In 2006, a data and safety monitoring board recommended continuation of the interventions, with final outcome surveys in late 2006.

Baseline surveys in 2002, and subsequent outcome surveys in 2005 and 2006, were done in random household samples of young adults and in FSWs. Young adults aged 18–29 years who had lived in the city for 6 months were eligible for inclusion in our analysis. For the baseline survey, we also did a comprehensive census of commercial sex venues. FSWs working at these venues, or attending screening clinics, were non-randomly, consecutively selected until all venues had been visited or the quota of 200 FSWs per city was reached. Subsequent FSW surveys used sampling of individuals at randomly selected venues and times.

Institutional review boards at the University of Washington, Universidad Peruana Cayetano Heredia, and US Naval Medical Research Center Detachment approved the protocol, consent forms, and instruments. Eligible FSWs older than 14 years and survey participants provided verbal consent. All review boards exempted pharmacy workers and clinicians from informed consent. Young adult survey participants received study caps and T-shirts; FSW survey participants received free condoms.

Randomisation and masking
US and UK investigators (except JPH) were masked to identities of intervention cities until completion of all surveys and laboratory testing. Identified cities were paired based first on 2002 city-specific composite STI prevalences in young adults, secondarily on region (coastal, Andean, or jungle), and thirdly on population size. Within each pair, one city was randomly assigned to an intervention and patients across the network. Individuals who completed the programme of training were included in the network. Six key activities for improvement of syndromic management were adapted from our early programmes. First, workshops and materials were provided for pharmacy workers, emphasising recognition

| Procedures |

All surveys of young adults used identical sampling methods, with paper questionnaires for the baseline survey and computer-assisted self-interviews with personal digital assistants in the later surveys. Men were asked to provide blood and urine samples, and women to provide blood and self-obtained vaginal swabs, or urine if unwilling to provide swabs. Participants received information about STIs and HIV, and referrals for test results, counselling, and treatment when indicated. FSWs answered face-to-face questionnaires in the baseline survey, followed by collection of blood and one endocervical and two vaginal swab specimens during speculum examination. All FSW participants completed questionnaires and provided three self-obtained vaginal swabs in 2005, and four in 2006. After completion of a census of all pharmacies, and of pharmacy workers, clinicians, and midwives in each city, the PREVEN network was created in intervention cities; STI training was undertaken for each group, involving STI syndromic management, and cross-referral of clients and patients across the network. Individuals who completed the programme of training were included in the network.

Timeline for the study

| Table 1: Timeline for the study |
| Start | End |
| 2002 general population baseline survey | August, 2002 | November, 2002 |
| 2005 general population survey | September, 2005 | December, 2005 |
| 2006 general population survey | September, 2006 | December, 2006 |
| Client survey | November, 2002 | April, 2003 |
| 2002 FSW baseline survey | November, 2002 | April, 2003 |
| 2005 FSW survey | September, 2005 | December, 2005 |
| 2006 FSW survey | September, 2006 | December, 2006 |
| PREVEN network intervention | July, 2003 | December, 2006 |
| Mobile team intervention for FSWs | July, 2003 | December, 2006 |
| Mobile team intervention for male sex workers | April, 2006 | December, 2006 |
| Social marketing of condoms and treatment packets | October, 2003 | October, 2004 |
| First health communication campaign | October, 2003 | October, 2004 |
| Second health communication campaign | April, 2005 | August, 2005 |
| Meeting of data and safety monitoring board | April, 2006 | April, 2006 |
| Laboratory analyses for 2002 surveys | January, 2003 | December, 2003 |
| Laboratory analyses for 2005 surveys | January, 2007 | March, 2006 |
| Laboratory analyses for 2006 surveys | January, 2007 | April, 2008 |
| Quality control of laboratory results | June, 2006 | May, 2009 |
| Analysis of study outcome | May, 2009 | June, 2010 |

FSW=female sex worker.
of four STIs (male urethritis, vaginal discharge, genital ulcer disease, and pelvic inflammatory disease). Second, physicians and midwives were trained in STI syndromic management. Third, so-called prevention salespersons made monthly visits with educational materials to network members and pharmacy clients. Fourth, clinicians (including those certified by the network) were given a year 2 booster online STI course. Fifth, health-communication campaigns for the general population were run in 2003–04, and in 2005, to improve recognition of STI symptoms and seeking of early appropriate STI health care. Finally, social marketing of low-cost condoms and inexpensive STI treatment packets for urethral discharge (containing ciprofloxacin, 500 mg, and azithromycin, 1·0 g) and for vaginal discharge (containing metronidazole, 2·0 g) were placed in pharmacies in 2003–04. Network training began in July, 2003, with all trainees certified by January, 2004. Prevention salesperson activities continued throughout 2006.

We created mobile teams and laboratory support systems in intervention cities to deliver clinical and preventive services to FSWs from July, 2003, to December, 2006. Each mobile team was made up of a nurse or midwife and an FSW peer educator. Mobile teams' activities included two visits to each sex venue in each of 20 cycles of 8 weeks to provide periodic presumptive treatment with metronidazole for trichomoniasis and bacterial vaginoses to FSWs who were not pregnant or breastfeeding, and willing to forego alcohol consumption for 72 h. Self-obtained vaginal swabs were collected for local T vaginalis culture and for nucleic acid amplification in Lima for N gonorrhoeae and C trachomatis. The teams returned 1 week later, providing test results and treatment for specific infections identified (ciprofloxacin for gonorrhoea, azithromycin for chlamydia, and metronidazole for positive T vaginalis cultures not treated a week earlier). FSWs were encouraged to visit local government clinics for periodic syphilis and HIV testing, and for interim STI symptoms. Laboratory technicians joined mobile teams from February, 2005, to December, 2006, and did rapid syphilis testing.

Separate mobile team outreach to male sex workers by a nurse or midwife and a peer occurred from April to December, 2006. Initial presumptive treatment was 1 g azithromycin for infection with C trachomatis and 500 mg oral ciprofloxacin for N gonorrhoeae, with screening for syphilis and HIV. Seropositive male sex workers were referred to government clinics for care.

Mobile teams also provided motivational interviewing to promote condom use by sex workers, and gave up to 15 condoms to each FSW in each 8 week cycle in the first 1·5 years, then increased to 50 condoms per cycle. For the general population, the local non-governmental organisation APROPO implemented social marketing of a low-cost condom, the OK condom, through pharmacies in intervention cities only, from October, 2003, to October, 2004, then more widely.

For all surveys, urine specimens, two polyester swab specimens stored in cryovials, and blood samples were promptly placed into coolers and transported to local laboratories. Trichomonas vaginalis culture media (InPouch, Biomed Diagnostics, White City, OR, USA) inoculated with cotton swabs were transported at ambient temperature to local laboratories. For the first survey, an additional swab was collected using the APTIMA Specimen Collection kit (Gen-Probe, San Diego, CA, USA). Serum, urinary aliquots, and dry swabs in cryovials were frozen to −20°C at local laboratories and shipped weekly to Lima, where 1 mL of 2-sucrose-phosphate was added to each cryovial, and serological testing and nucleic acid amplification were done. Initial analysis of results identified a need for additional confirmatory testing for

Figure 1: Study profile
Chlamydia trachomatis and Neisseria gonorrhoeae infections because prevalences were high and inconsistent in some cities, and to improve N gonorrhoeae test specificity. Duplicate specimen collection allowed such testing. On the basis of the interim report from the data and safety monitoring board, nucleic acid amplification testing for T vaginalis was also added. Final analyses followed completion of these tests.

Baseline and 2005 detection of Chlamydia trachomatis was with Amplicor assays (Roche Diagnostics, NJ, USA). Indeterminate specimens were later tested by Aptima Combo 2 assay (Gen-Probe, San Diego, CA, USA). Results were counted as positive if Amplicor was positive, or if indeterminate and Aptima positive. The 2006 survey used Aptima assays. To exclude possible specimen contamination during collection or testing, positive tests were confirmed with concurrently collected urine or swab specimens suspended in 2-sucrose-phosphate.

For N gonorrhoeae, Amplicor assays were used for samples collected in the baseline survey. Positive specimens were later confirmed by Aptima Combo 2 assay, with urine or swab specimens suspended in 2-sucrose-phosphate. In 2006, we defined infection with N gonorrhoeae by positive Aptima results in initial specimens, with repeat confirmatory tests on concurrently collected specimens.

Culture specimens incubated at local laboratories were examined every day for 5 days for motile trichomonads. Urine and vaginal swabs collected during baseline and 2006 surveys were later tested in Lima with T vaginalis analyte-specific reagents and Aptima General Purpose Reagents (Gen-Probe, San Diego, CA, USA). Specimens consistently yielding relative light unit values of more than 100 000 were classed as positive. We counted specimens as positive for syphilis if they were seroreactive at titres of 1:8 or more by rapid-plasma-reagin test and confirmed by Treponema pallidum particle agglutination assay. Specimens that twice tested positive on the enzyme-linked immunosorbent assay were confirmed by western blot assay in Lima; indeterminate specimens were retested at the University of Washington (Seattle, WA, USA).

Statistical analysis

The coefficient of variation across cities in the 2002 young-adult survey was 0.26 for the primary endpoint. Further calculations suggested matching could reduce this number to about 0.10. With ten city-pairs, 500 individuals sampled per city, and a composite STI prevalence of 0.10 in the control group, we anticipated 90% power to detect a relative risk (RR) of 0.75 (α=0.05, two-tailed; formula 7-14). Similarly, 200 FSWs surveyed per city provided 87% power to detect a 30% reduction in the combined STI outcome, with the assumption of a control community prevalence of 14%. A data and safety monitoring board reviewed the trial in 2006, with an analysis that would stop the trial if the intervention was highly effective (α <0.01) on the combined STI endpoint in both FSWs and young adults.

Continuous measures were summarised by medians and IQR, and categorical measures by proportions. The composite STI outcome for each participant was defined as positive if any of the C trachomatis, N gonorrhoeae, vaginal T vaginalis (by GenProbe nucleic acid amplification tests), or syphilis seroreactivity results were positive; as negative if all were negative; and otherwise as missing. However, 563 missing syphilis serology values in young adults were classed as negative for composite endpoint calculation in the 2006 young adult survey (results were essentially unchanged by this classification).

The primary analysis of young adults regressed differences in STI prevalence between intervention and control communities of the ith pair in 2006 outcome surveys against corresponding differences in baseline surveys. In this regression, the intercept gives the adjusted difference in prevalence between intervention and control communities in 2006. We tested the null hypothesis that the intercept was zero. Standard linear regression methods were used to fit the model and generate 95% CIs for adjusted risk differences. We used one-way ANOVA to estimate intraclass correlation. We used generalised estimating equations with a log link to compute RR and 95% CIs, adjusted for city-specific
baseline prevalences with a modified approach\(^a\) to account for variance bias that can occur with few clusters. RR analyses do not incorporate information on pairing and are, therefore, conservative. Methods giving RR for paired data\(^b\) often failed to converge for rare infections; for consistency, we present unpaired RR analyses for all outcomes. All analyses were intention to treat. We did all statistical analyses with Stata (version 10·1). This study is registered, number ISRCTN43722548.

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Table 2: Characteristics of the general-population and FSW participants at baseline and outcome surveys

| Young adults | 2002 survey | 2006 survey | 2002 survey | 2006 survey |
|--------------|-------------|-------------|-------------|-------------|
|              | Control cities | Intervention cities | Control cities | Intervention cities |
| Total number enrolled | 6307 | 6298 | 6945 | 6838 |
| Men | 3076 (48.8%) | 3107 (49.3%) | 3354 (48.5%)* | 3346 (49.1%)* |
| Women | 3231 (51.2%) | 3191 (50.7%) | 3559 (51.5%)* | 3467 (50.9%)* |
| Median age (years) | 22 (20–26) | 22 (20–26) | 22 (20–26) | 23 (20–26) |
| <3 years residence in city | 531 (8.4%) | 538 (8.5%) | 409 (5.9%) | 419 (6.1%) |
| Region |            |            |            |            |
| Coast | 3118 (49.4%) | 2580 (41.0%) | 3612 (52.0%) | 2799 (40.9%) |
| Andes | 1969 (31.2%) | 2490 (39.5%) | 1998 (28.8%) | 2592 (37.9%) |
| Jungle | 1220 (19.3%) | 1228 (19.5%) | 1334 (19.2%) | 1447 (21.2%) |
| Education |            |            |            |            |
| Did not complete primary school | 265 (4.2%) | 267 (4.3%) | 192 (2.8%) | 195 (2.9%) |
| Completed primary school\(^d\) | 1227 (21.2%) | 1216 (19.4%) | 1210 (17.4%) | 995 (14.6%) |
| Completed secondary school\(^d\) | 2186 (34.8%) | 2222 (35.4%) | 2551 (36.7%) | 2393 (35.0%) |
| Beyond secondary school | 2497 (39.8%) | 2568 (40.9%) | 2916 (42.0%) | 3162 (46.2%) |
| Living with last sex partner | 1690 (26.7%) | 1629 (25.9%) | 1981 (28.5%) | 1986 (29.0%) |
| Ever had sex | 4930 (81.8%) | 4464 (75.7%) | 5574 (82.0%) | 5371 (79.9%) |
| Female participants |                       |            |            |            |
| Report having had sex for money or gifts | 117 (4.0%) | 72 (2.5%) | 83 (2.4%) | 71 (2.1%) |
| Male participants |            |            |            |            |
| Sex with FSW in last year | 465 (18.0%) | 471 (18.2%) | 538 (16.4%) | 531 (16.3%) |
| Mean age of those who had been clients of FSW (years) | 22·7 (3·1) | 22·7 (3·4) | 23·2 (3·4) | 23·3 (3·4) |
| Sex with man in past year | 165 (7.5%) | 108 (4.9%) | 136 (4.1%) | 136 (4.1%) |
| FSW |            |            |            |            |
| Total number enrolled | 1844 | 1888 | 2063 | 2093 |
| Reporting a non-paying sex partner | 922 (50.0%) | 825 (43.7%) | 912 (44.2%) | 1335 (63.8%) |
| Living with non-client sex partner | 517 (32.1%) | 703 (41.0%) | 571 (28.0%) | 813 (40.0%) |
| Age (years) | 24 (20–30) | 25 (21–31) | 23 (20–29) | 25 (21–30) |
| Education |            |            |            |            |
| Did not complete primary school | 208 (12.2%) | 217 (12.4%) | 222 (11.5%) | 174 (8.8%) |
| Completed primary school\(^d\) | 709 (41.6%) | 663 (37.9%) | 828 (42.9%) | 867 (43.7%) |
| Completed secondary school\(^d\) | 589 (34.6%) | 621 (35.5%) | 772 (40.0%) | 776 (39.1%) |
| Beyond secondary school | 197 (11.6%) | 247 (14.1%) | 109 (5.7%) | 167 (8.4%) |
| Median nuevos soles charged last client | 20 (15–50) | 15 (10–35) | 35 (20–70) | 20 (10–78) |
| Place of work in past week |            |            |            |            |
| Brothel | 290 (16.5%) | 451 (23.4%) | 293 (15.0%) | 552 (26.0%) |
| Bar, night club, videopub, disco | 1050 (59.6%) | 1040 (56.3%) | 1004 (51.6%) | 1129 (53.3%) |
| Street | 167 (9.5%) | 201 (10.9%) | 195 (10.0%) | 246 (12.0%) |
| Other | 214 (11.4%) | 111 (5.6%) | 269 (19.0%) | 64 (3.3%) |
| More than one of above | 42 (2.4%) | 45 (2.4%) | 54 (2.8%) | 57 (2.7%) |
| Last vaginal sex with client unprotected | 103 (6.8%) | 122 (7.1%) | 76 (4.0%) | 67 (3.3%) |
| Last vaginal sex with non-paying partner unprotected\(^e\) | 638 (69.2%) | 562 (68.1%) | 708 (77.6%) | 908 (68.0%) |

Data are n (%), median (IQR), or mean (SD). Percentages calculated on the basis of number of non-missing responses. Individuals aged 18–29 years are classed as young adults. FSW=female sex worker. *Sex was missing for 32 control and 25 intervention participants in the 2006 survey. †6 years of schooling. ‡11 years of schooling. §Sex without condom anytime in past 3 months with most recent non-paying partner.
Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study; the corresponding author had final responsibility for the decision to submit for publication.

Results
Baseline surveys of FSWs were done in the initial 24 cities (figure 1), and then outcome surveys in the 20 randomised cities (figure 2) in 2005, and in 2006. In baseline and final outcome surveys of young adults, more participants came from the coast in control cities than in intervention cities, and more came from the Andes in intervention cities other variables were similar (table 2). FSWs were older, and more lived with a sex partner and worked in brothels, in intervention cities than in control cities, but the median fee per client was lower; other variables were similar (table 2). Reported risk behaviours differed little between intervention and control cities for young adults in 2006 (table 2). Proportion of FSWs reporting vaginal sex without condom use with last client or with a non-paying partner did not differ significantly between intervention and control cities (table 2).

|                | Proportion positive in control cities (2002) | Proportion positive in intervention cities (2002) | Proportion positive in control cities (2006) | Proportion positive in intervention cities (2006) | Mean difference in 2006 prevalences (intervention–control cities) | Adjusted difference* | p value* | RR (95% CI)† |
|----------------|---------------------------------------------|-----------------------------------------------|---------------------------------------------|-----------------------------------------------|------------------------------------------------|---------------------|----------|---------------|
| All young adults (n=12 930) |
| Composite      | 0·084                                       | 0·076                                         | 0·081                                       | 0·063                                         | −0·018                                          | −0·011              | 0·096   | 0·84 (0·69–1·02) |
| Chlamydia trachomatis | 0·058                                       | 0·049                                         | 0·062                                       | 0·047                                         | −0·015                                          | −0·006              | 0·34    | 0·86 (0·70–1·05) |
| Neisseria gonorrhoeae | 0·002                                       | 0·001                                         | 0·001                                       | 0·002                                         | +0·004                                          | +0·003              | 0·62    | 1·39 (0·41–4·77) |
| Trichomonas vaginalis | 0·051                                       | 0·057                                         | 0·041                                       | 0·029                                         | −0·013                                          | −0·013              | 0·35    | 0·66 (0·48–0·92) |
| Syphilis seroreactive (titre ≥1:8) | 0·005                                       | 0·005                                         | 0·003                                       | 0·002                                         | −0·0002                                         | −0·0001             | 0·99    | 1·08 (0·66–1·77) |
| Syphilis seroreactive (titre ≥1:16) | 0·003                                       | 0·002                                         | 0·002                                       | 0·002                                         | −0·0002                                         | −0·0004             | 0·95    | 1·06 (0·47–2·36) |
| HIV            | 0·002                                       | 0·002                                         | 0·004                                       | 0·003                                         | −0·001                                          | −0·002              | 0·26    | 0·65 (0·32–1·30) |

| Young women (n=6556) |
|----------------------|
| Composite            | 0·116                                       | 0·109                                         | 0·110                                       | 0·082                                         | −0·030                                          | −0·026              | 0·24    | 0·77 (0·61–0·96) |
| Chlamydia trachomatis | 0·071                                       | 0·060                                         | 0·075                                       | 0·055                                         | −0·022                                          | −0·015              | 0·12    | 0·79 (0·62–1·00) |
| Neisseria gonorrhoeae | 0·002                                       | 0·000                                         | 0·002                                       | 0·002                                         | −0·0004                                         | −0·0006             | 0·56    | 0·62 (0·17–2·28) |
| Trichomonas vaginalis | 0·051                                       | 0·057                                         | 0·041                                       | 0·029                                         | −0·013                                          | −0·013              | 0·35    | 0·66 (0·48–0·92) |
| Syphilis seroreactive (titre ≥1:8) | 0·004                                       | 0·004                                         | 0·002                                       | 0·002                                         | −0·001                                          | −0·001              | 0·44    | 0·72 (0·32–1·63) |
| Syphilis seroreactive (titre ≥1:16) | 0·001                                       | 0·002                                         | 0·002                                       | 0·001                                         | −0·001                                          | −0·001              | 0·43    | 0·43 (0·10–1·81) |
| HIV            | 0·000                                       | 0·001                                         | 0·002                                       | 0·002                                         | −0·0004                                         | −0·0002             | 0·26    | 1·10 (0·29–3·98) |

| Young men (n=6374) |
|---------------------|
| Composite            | 0·050                                       | 0·042                                         | 0·051                                       | 0·044                                         | −0·006                                          | −0·004              | 0·58    | 1·00 (0·77–1·31) |
| Chlamydia trachomatis | 0·044                                       | 0·037                                         | 0·048                                       | 0·040                                         | −0·008                                          | −0·002              | 0·71    | 0·94 (0·72–1·23) |
| Neisseria gonorrhoeae | 0·001                                       | 0·002                                         | 0·003                                       | 0·002                                         | +0·001                                          | +0·001              | 0·33    | 3·65 (0·16–81·2) |
| Trichomonas vaginalis | 0·003                                       | 0·003                                         | 0·004                                       | 0·003                                         | −0·001                                          | −0·001              | 0·63    | 0·82 (0·36–1·69) |
| Syphilis seroreactive (titre ≥1:8) | 0·006                                       | 0·005                                         | 0·003                                       | 0·003                                         | −0·001                                          | −0·001              | 0·66    | 1·39 (0·50–3·86) |
| Syphilis seroreactive (titre ≥1:16) | 0·005                                       | 0·003                                         | 0·002                                       | 0·003                                         | −0·001                                          | −0·001              | 0·50    | 1·72 (0·45–6·55) |
| HIV            | 0·003                                       | 0·004                                         | 0·006                                       | 0·005                                         | −0·001                                          | −0·002              | 0·22    | 0·74 (0·38–1·42) |

| Female sex workers (n=4130) |
|-----------------------------|
| Composite                   | 0·215                                       | 0·212                                         | 0·221                                       | 0·145                                         | −0·075                                          | −0·074              | 0·023   | 0·66 (0·47–0·94) |
| Chlamydia trachomatis       | 0·155                                       | 0·138                                         | 0·145                                       | 0·099                                         | −0·045                                          | −0·037              | 0·82    | 0·72 (0·54–0·98) |
| Neisseria gonorrhoeae       | 0·024                                       | 0·012                                         | 0·010                                       | 0·007                                         | −0·003                                          | −0·007              | 0·026   | 1·44 (0·02–122)  |
| Trichomonas vaginalis       | 0·074                                       | 0·097                                         | 0·086                                       | 0·045                                         | −0·042                                          | −0·053              | 0·048   | 0·49 (0·32–0·75) |
| Syphilis seroreactive (titre ≥1:8) | 0·016                                       | 0·012                                         | 0·011                                       | 0·014                                         | +0·003                                          | +0·003              | 0·32    | 1·32 (0·79–2·00) |
| Syphilis seroreactive (titre ≥1:16) | 0·007                                       | 0·006                                         | 0·007                                       | 0·008                                         | +0·001                                          | +0·001              | 0·72    | 1·12 (0·67–1·89) |
| HIV            | 0·007                                       | 0·008                                         | 0·005                                       | 0·003                                         | −0·002                                          | −0·002              | 0·51    | 0·49 (0·10–2·54) |

Overall numbers are from the 2006 surveys. Proportions calculated on the basis of how many individuals provided biological specimens that were adequate for testing. Individuals aged 18–29 years are classed as young adults. *From linear regression on differences between paired cities in 2006, adjusted for differences in 2002. †Adjusted for 2002 prevalences, but not for pairing. CIs computed with method of Pan and Wall.‡Includes T vaginalis in women only, per original analysis plan. §Adjusted results for N gonorrhoeae in female sex workers are very sensitive to the model used.

Table 3: Prevalence of sexually transmitted infections in control and intervention cities
In intervention cities, we trained and certified workers at 623 (80.6%) of 773 pharmacies, and 701 (69.6%) of 1007 physicians and midwives in private practice. We continued training new pharmacy workers and clinicians coming to these cities. Pharmacies in intervention cities reported 290,440 visits for STI-related symptoms in 2004–06; clinicians reported 184,208. Substantial, sustained improvements in syndromic management in intervention cities were noted after 7280 simulated-patient visits to pharmacies in the 20 cities at baseline and at 3, 6, and 18 months thereafter (data not shown).

Mobile teams in ten intervention cities interviewed FSWs 48,207 times during 20 8-week cycles. Numbers of venues and FSWs visited per cycle increased by more than 50% in the first year, but then stabilised (data not shown). In the 2005 surveys, young adult survey participants in intervention cities reported exposure to the campaign messages about STIs and condoms more and reported unprotected sex with a casual partner less often than did those in control cities (data not shown). Women in intervention cities sought appropriate care for STI-related symptoms more often than those in control cities (data not shown).

In 2006, data for the composite primary outcome were available for 12,930 (98.7%) of 13,104 young adults providing samples (6374 men and 6556 women). The adjusted composite STI prevalence in young men and women was an absolute 1.1% lower, adjusted for baseline prevalence, in intervention cities than in control cities (p=0.0046; table 3). For young men, by contrast, 141 (4.4%) of 3297 in control cities had any STI compared with 364 (11.0%) of 3185 in intervention cities (p=0.024; table 3). For young women, 268 (8.2%) of 3259 women had any STI in intervention cities compared with 318 (9.9%) of 3501 in control cities (p=0.096; table 3). In ancillary analysis limited to the 451 (22.1%) of 2045 in control cities (table 3).

In 2006, the prevalence of C trachomatis in men who had sex with FSWs in the past year was 7.2% in control cities and 3.5% in intervention cities (adjusted RR 0.68, 95% CI 0.28–1.68). The (unmatched) intraclass correlation for the composite STI prevalence in intervention FSW communities was 0.046 (95% CI 0.00–0.092), and in control communities 0.012 (95% CI 0.00–0.050). In young women and FSW, any differences in rates of infection with C trachomatis in each population were 0.00–0.018).

Discussion

After 3 years of interventions, the prevalence of any of four curable STIs in young adults was lower in intervention cities than in control cities, although this difference was not significant. The difference was significant in young women, but not in young men. Additionally, FSWs in intervention cities had significantly lower prevalence of STIs. As far as we are aware, this is the first urban community randomised trial to show an intervention might reduce prevalences of curable STIs in young women and FSWs (panel).

Although the effect in FSWs was consistent with projections, results in young adults were not as expected. We anticipated that FSW screening and treatment could help to lower STI prevalences in young men, because data have implicated that unprotected sex with FSWs is the major risk factor for STIs in men in Lima.2 We predicted that prevalence of STIs would fall in young women because of reduced prevalence in male clients. We observed no overall reduction of STIs in young men, although our 2006 survey did show that prevalence of C trachomatis was lower in those who reported sex with FSWs in the past year in intervention than in control cities. The effect of interventions in women, especially on trichomoniasis, could be because they sought appropriate care for STI-related symptoms more than did men. For example, many more women were treated for vaginal discharge in 2004–06 in intervention cities than were men for urethral discharge.

Movement of FSWs between cities, and infrequent use of condoms with non-client partners, probably restricted the effect of interventions in this population. The high rate of condom use reported by FSWs in control cities in 2006 meant further improvement in intervention cities would be difficult. In 2005, surveys reached 2–10% of young adults (dependent on city size) but higher proportions of FSWs. Treatment of infected FSWs in 2005 surveys could have attenuated 2006 survey differences in FSWs in control and intervention cities.

Our study had several strengths: detailed preliminary studies; widespread community engagement; cluster-randomised design with pair-wise matching and adjustment for baseline prevalences; inclusion of three disparate geographic regions in Latin America, (a neglected area); many evidence-based intervention components, with structural and technical components
A systematic review had previously identified 74 late-phase randomised controlled trials of interventions to prevent sexually transmitted infections (STIs) other than HIV reported before the end of 2009. Of these studies, three cluster randomised trials used syndromic management and measured STI rates and HIV incidence. The multicomponent community randomised trial in Masaka, Uganda, compared a control group with a behaviour-change intervention, with or without improved STI syndromic management. The behaviour-change intervention significantly lowered incidence of infection with herpes simplex virus 2, and the combined intervention significantly reduced incidence of syphilis (rapid-plasma-reagin titre ≥1:8) and gonorrhoea prevalence. Prevalence of Chlamydia trachomatis was not affected, and Trichomonas vaginalis was not assessed. In the Tanzanian trial of improved STI syndromic management, the adjusted relative risk in intervention versus control cities for syphilis seroprevalence (rapid-plasma-reagin titre ≥1:8) in adult cohorts was 0·71 (95% CI 0·54–0·93) after 2 years. Prevalence of urethral infection with Neisseria gonorrhoeae or C trachomatis was not significantly lowered. After 2 years, prevalences of any curable STI in antenatal women (N gonorrhoeae, C trachomatis, T vaginalis, or active syphilis) were similar in intervention and control communities. The Zimbabwean trial showed no effect on STIs.

A 2008 review of HIV and STI prevention interventions in female sex workers (FSWs) in resource-poor settings identified 28 interventions with follow-ups of more than 6 months and externally measurable outcomes. Overall, evidence suggested that multicomponent interventions can reduce HIV and STI acquisition in FSWs, as can structural interventions (eg, required condom use in Thai brothels). However, only two cluster randomised trials showed STI outcomes. Of those, one unpublished study with two cycles of presumptive antimicrobial treatment showed no significant effect on gonorrhoea or chlamydial infection. A second showed that when FSWs were given the option of female condoms, aggregate STI risk was not significantly affected.

India’s Avahan project is an important non-randomised multicomponent prevention programme targeting high-risk populations to decrease population-level spread of HIV and other STIs. Although reductions in HIV prevalence were associated with intervention intensity in three of six states, a separate commentary concluded that only with a prospective, robust assessment of the programme’s implementation could the investigators have convincingly proven effectiveness.

How few cluster-randomised controlled trials of multicomponent interventions to reduce transmission of curable STIs exist, especially in urban settings, is remarkable. None have shown an effect on C trachomatis or T vaginalis, the two most common curable STIs. This study used a multicomponent intervention adapted to high-risk and general-population groups. Our primary outcome analysis provided weak evidence at best for a reduction in curable STIs in young adults. However, secondary and ancillary analyses did show significant reductions in young women and FSWs, largely due to reductions in C trachomatis and T vaginalis infection. The trial revealed important context-specific challenges and opportunities, such as FSW mobility, potential for interventions for male sex workers, potential of pharmacy-based interventions, and effects of condom social marketing and of health-communication campaigns.

Contributors
PJG was one of the principal investigators in the Peruvian research team, and did the pharmacy and the health-communication-campaign interventions. CPC did the general population surveys to measure outcomes. FEC designed and supervised the surveys and interventions for FSWs. PJG, CPC, and KKH designed the parent study. JPH supervised biostatistical aspects of the study design and analysis. WLHW contributed to laboratory quality control. All listed authors contributed significantly to the trial, and participated in preparation of the report.

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Implementation partners
The Peruvian STD and AIDS Control Program, Ministry of Health, National Institute of Health, and National Institute of Statistics and Informatics, the US Naval Medical Research Center Detachment, APROPO, Roche Molecular Systems, Focus Technologies, and Gen-Probe.

Conflicts of interest
We declare that we have no conflicts of interest.

Panel: Research in context

Systematic review
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