Title: The population effectiveness of opportunistic chlamydia testing in primary care: a cluster randomised controlled trial.

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Abstract

Background

Screening young sexually active adults for genital *Chlamydia trachomatis* is promoted, but its population effectiveness is debated. The Australian Chlamydia Control Effectiveness Pilot (ACCEPt) investigated the effects of opportunistic chlamydia testing in primary care on chlamydia prevalence, pelvic inflammatory disease (PID) and epididymitis in the population. Our hypothesis was that if chlamydia testing rates increased sufficiently, the prevalence of chlamydia in the population would decrease.

Methods

We conducted a cluster randomised controlled trial. Clusters were rural towns with a minimum of 500 women and men aged 16-29 years resident and no more than six primary care clinics. We randomly allocated each cluster using a computer-generated-minimisation algorithm to receive a clinic-based chlamydia testing intervention or continue usual care. Clinic staff were aware of the allocation, and posters and information cards in the waiting room informed patients that the clinic was in a trial of chlamydia testing but did not specify whether the clinic was intervention or control. The intervention included computerised reminders, an education package, payments for chlamydia testing and feedback on testing rates. The primary outcome was chlamydia prevalence, estimated before randomisation and at trial end in patients aged 16-29 years attending clinics. Secondary outcomes included chlamydia testing and the incidence of PID (diagnosed in clinics and hospitals) and epididymitis (in clinics). Analyses were intention to treat. (Australian Clinical Trial Register ACTRN12610000297022).

Findings

Between July 2010 and December 2012, we randomly assigned 26 clusters (63 clinics) to receive a chlamydia testing intervention and 26 clusters (67 clinics) to continue with usual care. Overall, 93,828 16 to 29 year olds attended intervention and 86,527 attended control clinics over a mean of 3·1 years. We collected data for the final outcome measurements between July 2014 and December 2015. The estimated chlamydia prevalence in intervention clusters decreased from 5·0% (92/1833) to 3·4% (76/2237, difference −1·6%; 95%CI −2·9 to −0·3), and in control, from 4·6% (88/1925) to 3·4% (589/1716, difference

−1·1%; 95%CI –2·7 to 0·5). The odds ratio for the difference between intervention and control clusters was 0·9 (95%CI 0·5 to 1·5). No adverse events were reported by clinics, clinic staff or patients.

Interpretation

The ACCEPt results, in conjunction with evidence about the feasibility of sustained uptake of opportunistic testing in primary care, indicate that sizeable reductions in chlamydia prevalence or chlamydia-associated complications might not be achievable.

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Research in context

Evidence before this study

A systematic review of chlamydia screening interventions identified six RCTs published up to the 14th February 2016, four of which investigated the effect on the incidence of PID of a single offer of a chlamydia screening test and two which investigated the effect of multiple rounds of chlamydia screening on chlamydia prevalence. In a meta-analysis, the incidence of PID was lower in intervention than control groups (risk ratio, RR 0·68; 95%CI 0·49 to 0·94; I^2=8%). However, methodological limitations of the trials could have resulted in an over-estimation of the protective effects of a single chlamydia screening test. A cluster-RCT in women and men in the general population in the Netherlands found no change in chlamydia positivity among those tested after three rounds of screening (RR 0·96, 95% CI 0·84 to 1·09). However, screening uptake was low, with only 16% screened in the first round, falling to 10% in the third round. A cluster RCT of a multifaceted intervention that included syndromic management for sexually transmitted infections (STIs) among young adults in the community and STI screening in female sex workers in Peru found no difference in chlamydia prevalence after four years among young adults but in secondary analyses, found a reduction among female sex workers (adjusted RR 0·72; 95% CI 0·54 to 0·98). None of the trials investigated the impact of multiple rounds of testing on both chlamydia prevalence and the incidence of PID. We searched PubMed from January 1 2016 to February 28 2018 with the terms “chlamydia” and (“randomised controlled trial” or “randomised clinical trial” or “trial” or “randomly”) and restricted the search to clinical trials in English only. No further completed trials were identified.

Added value of this study

The Australian Chlamydia Control Effectiveness Pilot (ACCEPt) is, to our knowledge, the first RCT to investigate the impact of repeated rounds of testing on the multiple biological outcomes of chlamydia prevalence, PID and epididymitis. It was a pragmatic trial that reflected the situation that would occur if an opportunistic chlamydia screening programme was rolled out. Our chlamydia testing intervention was successfully implemented in 63 clinics, reaching over 90,000 men and women aged 16 to 29 years and increasing absolute testing rates by 11.9% (from 8.2% to 20.1%), double that achieved in the only other trial of

multiple rounds of testing in a high-income country. While it did not have a measurable effect on estimated prevalence of chlamydia in the population, the incidence of PID requiring hospitalisation decreased by 13·7 per 10,000 (95%CI: −26·9 to −0·5). However, there was no change in the incidence of PID or epididymitis diagnosed in the clinic.

Implications of all the available evidence

In high-income countries, the ACCEPt trial results, in conjunction with evidence about the feasibility of sustained uptake of opportunistic testing in primary care clinics and evidence from previous trials, indicate that sizeable reductions in chlamydia prevalence or chlamydia-associated complications might not be achievable.

Introduction

Screening among young sexually active adults is widely promoted to control transmission of *Chlamydia trachomatis*,[1-3] which causes chlamydia, the most commonly diagnosed bacterial sexually transmitted infection (STI) in high income countries.[1,3,4] Chlamydia is usually asymptomatic and common in young sexually active women and men, with an estimated population-based prevalence of 3·1% among women and 2·3% among men aged 16 to 24 years in the UK[5] and 4.7% among women aged 14 to 24 years in the USA.[6] Screening for asymptomatic infection aims to prevent pelvic inflammatory disease (PID), which can cause tubal factor infertility and ectopic pregnancy. Treatment of a sufficiently large number of infections should limit transmission and reduce prevalence.

The effectiveness and cost-effectiveness of chlamydia screening interventions are debated.[7,8] In randomised controlled trials (RCTs), a single round of screening and treatment reduced the incidence of PID, although the effect might have been overestimated.[7] Multiple rounds of screening did not reduce population chlamydia prevalence in young adults, but screening coverage in one trial was very low.[9] Given the uncertainty about the effects of multiple rounds of screening on both PID and on chlamydia prevalence, additional evidence is needed. The objective of the Australian Chlamydia Control Effectiveness Pilot (ACCEPt) was to investigate the effect of opportunistic testing in primary care clinics on *C trachomatis* prevalence, PID and epididymitis in the population. Our hypothesis was that if chlamydia testing rates increased sufficiently, the population-based prevalence of chlamydia would decrease.

Methods

The trial protocol trial can be found at http://www.thelancet.com/protocol-reviews/12PRT-9010.[10] We report the trial according to the CONSORT extension for cluster RCTs.

Study design

ACCEPt was a pragmatic cluster RCT targeting sexually active women and men aged 16 to 29 years for annual chlamydia testing at primary care clinics in the Australian states of New South Wales, Victoria, South Australia and Queensland. Rural towns were chosen as clusters because they are geographically separated to minimise contamination and all clinics in a

town could be enrolled. About 25% of Australia's population lives in rural areas. Primary care clinics included general practices and Aboriginal medical services. General practitioners (GPs) in Australia provide most primary care, including over 80% of testing for STIs. Most general practices in Australia are businesses with varying numbers of GPs, nurses and support staff. About 5% of towns in ACCEPt had an Aboriginal medical service. We enrolled clinics between July 2010 and December 2012 for baseline measurements, and collected final outcome data between July 2014 and December 2015.

The Royal Australian College of General Practitioners (RACGP) National Research and Evaluation Ethics Committee and the Aboriginal Medical Research Council approved the trial. The trial is registered with the Australian Clinical Trial Register (http://www.anzctr.org.au), number ACTRN12610000297022.

Clusters, primary care clinics, GPs and patients

Clusters were rural towns, defined by postcode boundaries (remoteness area 2-5 in the Australian Statistical Geography Standard), with a minimum of 500 men and women aged 16 to 29 years old at the 2006 census and no more than six clinics. Towns were ineligible if their primary economic activity was mining, military or tourism.

Within each cluster we invited all primary care clinics. If a clinic refused to participate, the cluster was ineligible. GPs gave written consent to implement the intervention or control at the clinic level and to provide access to their consultation and chlamydia testing data. New clinics in each cluster and new GPs during the trial were recruited.

Men and women attending clinics for any consultation during the intervention period were eligible for one chlamydia test per year, regardless of symptoms or contact history, if they were aged 16 to 29 years and had ever had vaginal or anal intercourse. We collected de-identified data about consultations from electronic patient records.

Randomisation and masking

A statistician, located at a site away from the clusters, generated the randomisation sequence using a computer-generated minimisation algorithm. The algorithm aimed to

achieve balance for three pre-specified variables: i) estimated chlamydia prevalence (<3% vs. ≥3%, based on an earlier study);[11] ii) chlamydia testing rate (<6% vs. ≥6% based on data from rural primary care clinics in 2008);[12] and iii) number of 16 to 29 year olds in the town (<2000 vs. ≥2000, the 75th percentile of population size in eligible postcodes). The statistician ran the randomisation algorithm after the baseline estimation of chlamydia prevalence in each cluster and informed research staff of the allocation who in turn notified clinics. GPs and clinic staff were aware of the allocation. Posters and information cards in waiting rooms informed patients that the clinic was taking part in a trial of chlamydia testing but did not specify whether the clinic was in the intervention or control. Pathology laboratories conducting the testing were not informed of the allocation.

Procedures

We developed a multifaceted intervention package to encourage staff to offer annual chlamydia testing to all eligible patients, based on evidence from systematic reviews and considerations of long-term feasibility in Australian primary care.[13] Guided by normalisation process theory, the research team worked with each clinic to tailor the intervention to the clinic and embed it into routine practice.[14] The intervention package (see protocol) included:[10] an education package for GPs and nurses about strategies for offering testing for chlamydia, management of infection and partner notification; clinical criteria for PID and epididymitis diagnosis; payments for GPs (AUD$5, $7 or $8 per test where <20%, 20-40% or >40% of eligible patients were tested, respectively); payments for nurses (AUD$10 for each test); quarterly written feedback to GPs on their testing rates discussed in a face-to-face meeting between a research staff member and GPs; a computer alert prompting testing with eligible patients; support to develop a reminder system to recall patients after 12 months if chlamydia negative or after three months if treated for chlamydia; and partner notification information and resources, including access to www.letthemknow.org.au.

Research staff instructed control clinics to test for and manage chlamydia according to their usual practice. GPs received a minimal education package with clinical criteria for PID and epididymitis diagnosis to minimise measurement bias for these conditions, but they did not receive any other elements of the intervention package.

In both intervention and control clinics, we instructed staff to test for chlamydia using patient-collected urine specimens or vaginal swabs. Diagnosis was based on nucleic acid amplification tests (NAAT) conducted by the clinic's usual pathology provider. Clinics were instructed to treat and manage chlamydia according to Australian guidelines,[15] with a single one gram dose of azithromycin, and to initiate partner notification.

Trial outcomes

The primary outcome was chlamydia prevalence in the population served by the clinics in each cluster. We assumed that the proportion of positive chlamydia tests among people attending the clinic would provide an estimate of the population prevalence. We used the same method to estimate the prevalence of *C trachomatis* before randomisation (survey 1) and at the end of the intervention period (survey 2). See Yeung et al. for further detail on prevalence survey methods,[16] but in brief, a member of the research team invited consecutive patients in the clinic waiting room to participate, assessed eligibility, and obtained written consent. People attending clinics for a consultation were eligible if they were aged 16 to 29 years and had ever had vaginal or anal intercourse. The research member was based at each clinic for up to six weeks to enrol the target number of participants. Researchers recorded non-participants' age and gender. Participants provided a self-collected specimen for testing.

Outcome definitions are described in the protocol.[10] The primary outcome, *C trachomatis* prevalence, was estimated as the proportion of women and men aged 16 to 29 years in the surveys with a positive chlamydia test result. Secondary outcomes were measured at the cluster level: incidence of PID in clinics or hospitals or epididymitis in clinics, yearly chlamydia test uptake, chlamydia positivity among those tested, chlamydia re-testing 10-15 months after a negative test or re-testing six weeks to six months after a positive test, and repeat chlamydia diagnosis. We installed data extraction software (GRHANITE™ www.grhanite.com) on computers, which extracted anonymised patient information from 12 months before recruitment until trial end.

We collected PID data from two sources: participating clinics and hospitals. These data could not be combined because they were measured in different ways. At clinics, we measured

the incidence proportion (cumulative incidence) of PID diagnosed among women aged 16 to 33 years over the intervention period. The denominator was the number of female patients aged 16 to 33 years with at least one consultation during the intervention period. Given the uncertainty about when PID occurs following chlamydia infection,[17] the upper age limit allowed for infection among women aged 26 to 29 years at start of the trial, who might have developed PID during the intervention period. GPs were advised to use the United States Centers for Disease Control and Prevention clinical criteria to diagnose PID.[18] In hospitals, we used ICD10 codes to measure the incidence proportion of PID among women living in each cluster,[19] obtained from each State health department, based on primary diagnoses of PID. The age range for the numerator and denominator for hospitalisation data was 15 to 34 years because these data were only available aggregated in 5-year age groups.

We measured the incidence proportion of epididymitis among men aged 16 to 29 years attending clinics during the intervention. The denominator was the number of male patients aged 16 to 29 years with at least one consultation at the clinic during the intervention period. The upper age limit was 29 years because epididymitis is usually an acute condition associated with a current chlamydia infection.[20] The diagnosis of epididymitis was based on signs and symptoms as defined in Australian guidelines.[15]

Definitions of all other secondary outcomes are listed in the protocol.[10]

Statistical analysis

We based the sample size on an assumption of an absolute difference of 2% in estimated chlamydia prevalence at the end of the trial (4% in control and 2% intervention clusters).[11,21] We needed 52 clusters with an average of 80 women and men aged 16 to 29 years tested for chlamydia per cluster to detect a difference of this size with 80% power and 5% significance, based on an intra-class correlation coefficient (ICC) of 0·009.[11] The number of patients enrolled at each clinic was proportional to the number of 16 to 29 year olds in the clinic database. This sample size allowed us to estimate chlamydia prevalence with precision of ±0.5%.

We analysed trial results according to intention to treat. We used generalised linear models that accounted for clustering using the generalised estimating equation approach, with robust standard errors. We fitted an unadjusted model as the initial analysis for each outcome. For the primary outcome, estimated chlamydia prevalence, we also fitted a multivariable model to control for imbalances in cluster-level baseline covariates (socioeconomic status) and potential individual level confounding factors such as gender, age group, number of sex partners in the last 12 months, condom use last encounter, clinic attendance for a sexual health reason and antibiotic use in the last three months. For secondary outcomes, the multivariable models included gender, age group, and socioeconomic status of the area served by the clinic.

We calculated the absolute difference in chlamydia prevalence between survey 1 and survey 2 with 95% confidence intervals (CI) for intervention and control clusters using the binomial error distribution with the identity link function. We calculated the absolute difference for the prevalence treatment effect, PID, and epididymitis using the identity link function. The relative difference between intervention and control clusters was estimated as an odds ratio (OR, prevalence, testing, retesting, repeat infection) using the binomial error distribution with the logit link function or risk ratio (PID, epididymitis) using the Poisson error distribution with the log link function, with 95% CI and p-values from the corresponding hypothesis tests. Statistical significance was taken as a two-sided p-value less than 0.05, with no adjustment for multiple comparisons. Specific models for each secondary outcome are described in the protocol.[10]

We pre-specified exploratory analyses of the effect of the intervention in different subgroups for the primary outcome (gender, age group, estimated baseline chlamydia prevalence and baseline testing rate) and secondary outcomes (gender and age group). We used tests for interaction to examine evidence for heterogeneity of effects between intervention allocation and each subgroup. In addition, we conducted a pre-specified secondary analysis of the primary outcome to explore the effect of adherence to the intervention by excluding intervention clinics that had testing rates below the 25% percentile in the final year (10.7%) and control clinics that had testing rates above this cutpoint.

We used SAS Version 9.1 for most analyses. We used STATA/SE Version 14.2 to analyse PID hospitalisation data and R Version 3.3.1 to obtain the intra-cluster-correlation coefficient.

Deviations from the protocol

There were no deviations in trial implementation. Our statistical analysis plan did not explicitly state the reporting of absolute differences but these are included as good reporting practice.

Role of the funding source

Australian Government Department of Health, National Health and Medical Research Council, Victorian Department of Health and New South Wales Ministry of Health funded ACCEPt. The RACGP and Australian Primary Care Nurse Association provided additional in-kind support. The funding bodies had no role in study design, data collection, data analysis, data interpretation or writing of this paper. The corresponding author had access to all data and responsibility for the decision to submit for publication.

Results

We enrolled 130 clinics in 54 postcode areas and 87% of clinics approached agreed to participate. We merged four neighbouring towns into two clusters because of close proximity (<40 kms) and randomised 52 clusters to intervention or control (Figure 1). The mean distance by road between an intervention and a control cluster was 830 kms (SD 513; range 40 to 2136 km). The intervention period in each cluster ranged from 2·5 to 4·2 years with a mean of 3·1 years (SD 0·3). Three clinics in different control clusters (2·3%) withdrew from the trial.

Baseline characteristics of clusters and GPs in intervention and control clusters were comparable (Table 1). The response rates and characteristics of participants in surveys 1 and 2 were comparable between intervention and control and between the two surveys. Given the comparability at cluster, clinic and individual level, we report results from the unadjusted models. Findings from the adjusted models are shown in the tables.

We enrolled 3,758 patients into survey 1 and 3,953 into survey 2. In each survey, women were more likely to participate: survey 1, 72·5% women vs 65·7% of men; survey 2, 72·4% of women vs 63·7% of men. The median ages of those who refused and those who participated was 23 years in both surveys. The intra-class correlation for chlamydia prevalence was 0·004 (SE 0·002) for survey 1 and 0.001 (SE 0·002) for survey 2.

Between surveys 1 and 2, the estimated chlamydia prevalence in intervention clusters decreased from 5·0% (92/1833) to 3·4% (76/2237) (difference −1·6%, 95% CI −2·9% to −0·3%) and, in control, from 4·6% (88/1925) to 3·4% (59/1716) (difference −1·1% 95% CI −2·7% to 0·5%) (Table 2, Figure S1). The absolute difference in treatment effect between intervention and control was estimated as –0·5 (95% CI −2·6 to 1·5; relative difference OR 0·9; 95%CI 0·5 to 1·5). In subgroup analyses, there was no evidence of differences in the treatment effect between the intervention and control when stratified by gender, age, Aboriginal status, baseline chlamydia prevalence or baseline chlamydia testing rate (Supplementary Table S2). In a secondary analysis of adherence to the intervention, we estimated an OR of 0·7 (95% CI 0·3 to 1·6) for the relative difference in the treatment effect between intervention and control (Supplementary Table S3).

For PID diagnosed in clinics, the incidence estimates in intervention and control clusters were similar, difference 5·5 per 10,000 (95% CI −13·4 to 24·3) (Table 2, Figure S2). For PID diagnosed in hospitals, the incidence was lower in intervention (24·2 per 10,000 over 3 years follow-up) than control clusters (37·9 per 10,000 over 3 years follow-up; difference −13·7 per 10,000, 95% CI −26·9 to −0·5). For epididymitis diagnosed in clinics, the incidence was similar in intervention and control clusters (difference −1·6 per 10,000, 95% CI −12·4 to 9·1) (Table 2, Figure S2).

Among 93,828 patients aged 16 to 29 years who attended intervention clinics at least once during the trial, 22,769 had at least one chlamydia test (67·8% had one, 20·7% had two and 11·5% had three or more tests). Among 86,527 patients attending control clinics, 14,774 had at least one chlamydia test (70·7% had one, 19·6% had two and 9·7% had three or more tests). The proportion of patients tested increased each year: in intervention clusters from 8·2% (95% CI 7·0 to 9.4) to 20·1% (95% CI 18·4 to 21·8; difference 11·9%, 95%CI 10·3 to 13·4)

and in control from 8·2% (95% CI 7·2 to 9·2) to 12·9% (95% CI 11·2 to 14·5; difference 4·6%; 95% CI 3·3 to 6·0). The increase was greater in intervention than control clusters (OR 1·7, 95% CI 1·4 to 2·1, in the final year) (Figure 2A, Supplementary Table S1). Chlamydia testing uptake increased in both sexes and across age groups (Figure 2B, 2C and Supplementary Table S4). Chlamydia positivity decreased in both intervention and control clusters and, in the final year, was lower in intervention clusters (6·8%, 95% CI 5·6 to 8·0) than control (8·8%, 95% CI 7·7 to 9·9; OR 0·8; 95%CI 0·6 to 1·0) (Supplementary Table S1). Chlamydia positivity was higher in men than women at all time points and highest among 16 to 19 year olds (Supplementary Table S5).

The proportion of patients who had a repeat test within 10 to 15 months of a negative chlamydia test result was higher in intervention than control clusters throughout the intervention period (Supplementary Table S1). The highest proportion was 10·4% (95% CI 8·7 to 12·1) after year one in intervention clusters and declined to below 4·0% in both groups by the final year. Among patients with a positive chlamydia test, the proportion with a repeat test within six weeks to six months was higher in intervention than control throughout the intervention period (Supplementary Table S1). The odds of a repeat positive chlamydia test after retesting was similar in intervention and control clusters during the intervention period (Supplementary Table S1).

No adverse events were reported by clinics, clinic staff or patients

Discussion

We implemented a pragmatic multifaceted chlamydia testing intervention in 63 primary care clinics, reaching over 90,000 men and women aged 16 to 29 years, with an absolute increase in testing of 11·9% (to 20.1%) over a mean of 3·1 years follow-up. The estimated prevalence of chlamydia declined in both intervention (absolute difference −1·6%) and control clusters (absolute difference −1·1%). The incidence of PID-related hospitalisations was 40% lower (absolute difference −13·7 per 10,000) in intervention than control clusters, but the incidence of PID and epididymitis diagnosed in clinics were similar.

ACCEPt has several strengths. First, it is the only RCT to have evaluated the effects of several rounds of opportunistic chlamydia screening on multiple outcomes of chlamydia prevalence, PID and epididymitis. Second, ACCEPt shows the value of randomisation. In a before-and-after design, without a control arm, the reduction in estimated chlamydia prevalence would have been assumed to have resulted from increased testing. Third, the pragmatic implementation and evaluation reflect the situation that would occur if a chlamydia screening programme was rolled out, with the addition of theory-based implementation into routine practice.[14] Fourth, cluster randomisation meant that all clinics in a town were offered the same intervention package. Measurement of an infectious disease outcome at the cluster level also captured the effects on transmission within social and sexual networks. To our knowledge, this trial provides the least biased estimate to date of the effectiveness of an intervention to increase opportunistic chlamydia testing. Measures to minimise bias included enrolment of all clinics in a cluster to reduce contamination, allocation concealment, use of routine data to minimise measurement bias and blinding of the statistician in the analysis.

The trial also had limitations. First, we estimated chlamydia prevalence in the population by conducting a survey in attenders at clinics, and only about 30% of those who took part were men, reflecting clinic attendance patterns. To increase external validity, we enrolled consecutive patients, irrespective of the reason for consultation; response rates were high, about 70% in each survey and measured characteristics of participants in both surveys were similar. Second, our sample size assumed an absolute reduction in estimated chlamydia prevalence of 2% in the intervention and no change in the control. We did not anticipate a decrease in both groups. Nevertheless, we can rule out baseline differences as a source of uncertainty because we estimated chlamydia prevalence at the start and end of the trial and there were no important baseline imbalances between groups. Third, the trial was conducted in rural towns so the results might not be generalisable to more ethnically and socio-economically diverse urban areas. However, we accounted for area level socio-economic factors in our analysis. Fourth, we could not eliminate ascertainment bias from the diagnosis of PID within clinics because clinical judgment can be influenced by knowledge of a woman's chlamydia test status. Fifth, we were unable to collect data on partner notification nor confirm treatment of all diagnosed cases, but, data from primary care in

Australia suggest nearly all cases are treated.[22] Finally, as our intervention was pragmatic and modified as clinics' needs changed, we could not determine which intervention components were the most effective at increasing test uptake.

ACCEPt is one of the few controlled trials to have evaluated the effects of chlamydia testing on prevalence. The Dutch Chlamydia Screening Implementation (CSI) trial evaluated yearly register-based invitations to 16 to 29 year old women and men using self-collected specimens.[9] Uptake was too low to estimate chlamydia prevalence in the population, so the investigators reported the proportion of chlamydia tests with a positive result (chlamydia positivity) and found no difference between intervention and control areas, with poor uptake as a possible explanation. Baseline chlamydia positivity in ACCEPt (4·8%, 180/3758) and the first CSI screening round (4·3%, 1851/43358) were similar. Unlike CSI, chlamydia positivity in ACCEPt declined over time. This was not unexpected because, as testing rates increase, the inclusion of lower risk individuals will decrease chlamydia positivity. The reduction in the incidence of PID hospitalisation (RR 0·6, 95% CI 0·4 to 1·0) in ACCEPt was compatible with the relative risk in a meta-analysis of previous trials.[7] However, the incidence of PID was low and the absolute difference was small (13·7 per 10,000 after a mean of 3.1 years). One trial in Denmark that used routine data to estimate PID incidence from hospital and community records, found comparably low rates of PID (around 50 per 10,000 women) but no difference between control and intervention (hazard ratio 1·12, 95% CI 0·7 to 1·8).[23] Neither ACCEPt nor the Danish trial found an effect of chlamydia testing on epididymitis in men.

The ACCEPt intervention did not result in a clinically relevant difference in estimated chlamydia prevalence between intervention and control clusters after three years. An important reason might be that testing uptake needed to be sustained at higher levels for longer, with higher levels of repeat testing. Our mathematical modelling suggested that uptake of 20% by women and men under 30 years could reduce population prevalence by 65% in 10 years.[21] Our intervention increased uptake to an average of 20%, which may have increased further over time. Larger financial incentives might have increased testing rates more, but at the time of the trial, our incentive payments were based on what was offered for immunisation and other similar preventive activities in general practice. A one-year pilot

for the National Chlamydia Screening Programme in England achieved uptake of 45% with GP incentives of up to £25 per test.[24] These payments were not sustained during the roll-out with testing rates in general practice falling to below 10%.[25] The effects of higher levels of test uptake on population prevalence of chlamydia remain unclear. In Great Britain, population chlamydia prevalence in women aged 18 to 24 years was 3·1% in 1999 to 2000 and 3·2% in 2010 to 2011,[5] during which testing coverage increased from 8% in 2008 to about 30% in 2011.[25] In the United States of America, population chlamydia prevalence among women aged 15 to 24 years was 4·1% (95% CI 2·4 to 6·8) in 1999 to 2000 and 3·8% (95% CI 2·4 to 6.0) in 2007 to 2008,[26] when testing coverage among women aged 15 to 24 years was reported to be more than 35% per year.[27]

Reasons for the reduction in estimated chlamydia prevalence in both intervention and control clusters, despite marked differences in test uptake, are unclear. We do not think that awareness about the intervention or information given to control clusters contributed to the reduction in prevalence for two reasons. First, only GPs in intervention clusters received education about chlamydia testing and management and the PID and epididymitis package included only information about criteria for diagnosis. Second, testing uptake did not increase after survey 1. It is possible that treatment of chlamydia detected during the first survey removed prevalent infections from the population, with insufficient time between the surveys for rebound. The geographical separation of rural towns in Australia might have reduced the opportunity for new infections to be introduced and, in survey 2, 78% of participants reported that their most recent sexual partner came from within the same postcode. However, the surveys only included about 10% of all patients registered at the clinics, so a marked reduction in *C trachomatis* transmission at the population level is unlikely. Background antibiotic use may have affected both intervention and control, particularly as the second survey took place during a severe influenza season.[28] We think that antibiotic use is an unlikely explanation because prescribing increased by only 5·6% across Australia between surveys,[29] chlamydia notifications in the population as a whole did not decline,[4] and statistical adjustment for reported antibiotic use in both surveys did not affect our results. Regression to the mean, affecting both intervention and control, is the most likely explanation. It is also possible that participants in survey 1 were at higher risk of

chlamydia than those in survey 2, even though participation rates and measured characteristics were similar.

The ACCEPt intervention was an intensive but highly pragmatic package that can be adapted to different primary care clinics. Although it increased levels of opportunistic chlamydia testing, it is likely that substantial investment would be required to increase and maintain test coverage at higher levels. An ongoing economic evaluation will determine its cost-effectiveness. In high income countries with a low general population chlamydia prevalence, public health specialists and policy makers should decide on an acceptable level for chlamydia control and focus on the reduction of social and ethnic inequalities in chlamydia and its associated complications.[30] The ACCEPt results, in conjunction with evidence about the feasibility of sustained uptake of opportunistic testing in primary care clinics, indicate that substantial reductions in chlamydia prevalence or chlamydia-associated complications might not be achievable.

ACCEPt Consortium:

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Author contributions:

JSH, MTS, RG, BD, ML, JG, DR, JK, CF, NL secured the funding for the trial. JSH was involved in the conception and design of the study, data analysis and data interpretation and for monitoring any reported adverse events or breaches of protocol. MTS, RG, BD, JG, JK, CKF

and NL were involved in the conception and design of the study and data interpretation. ML was involved in the conception and design of the study, data analysis and data interpretation. SB was involved in the data analysis and interpretation. AV was involved in data collection and enrolment of clinics, GPs and patients. LB and DR were involved in study design and data collection. All authors contributed to the writing of this manuscript and approved the final version for submission.

Declaration of interests:

All authors declare no competing interests.

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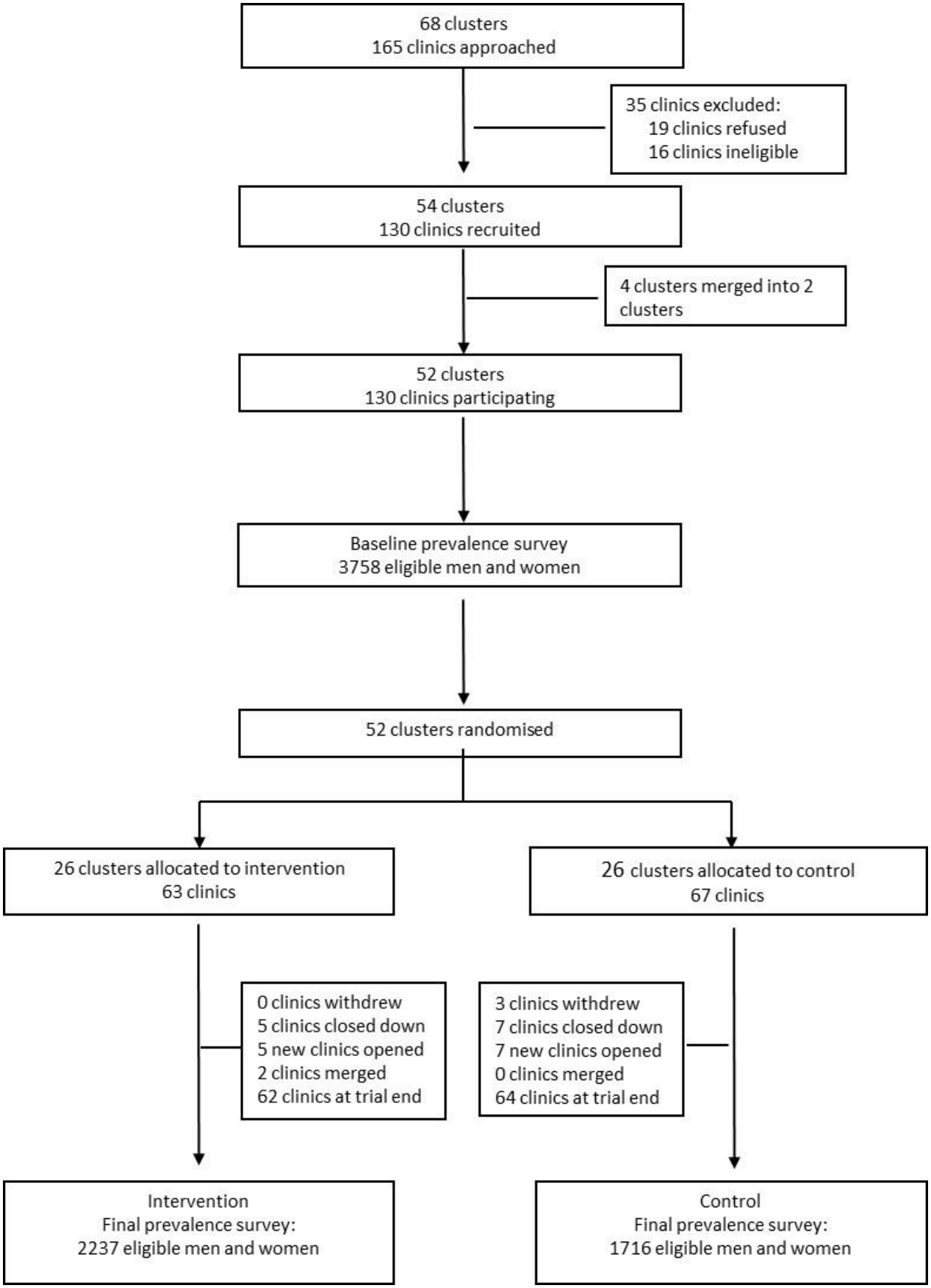

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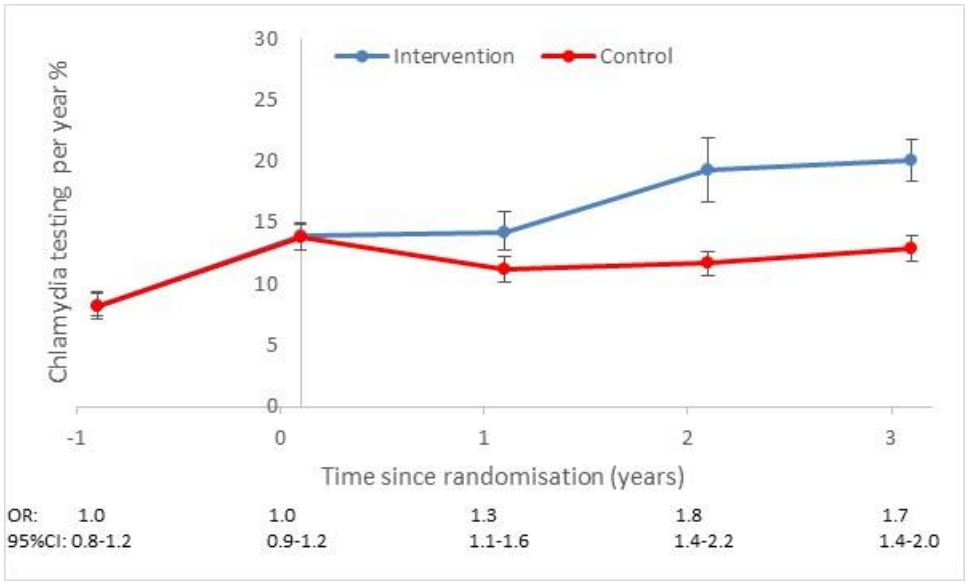
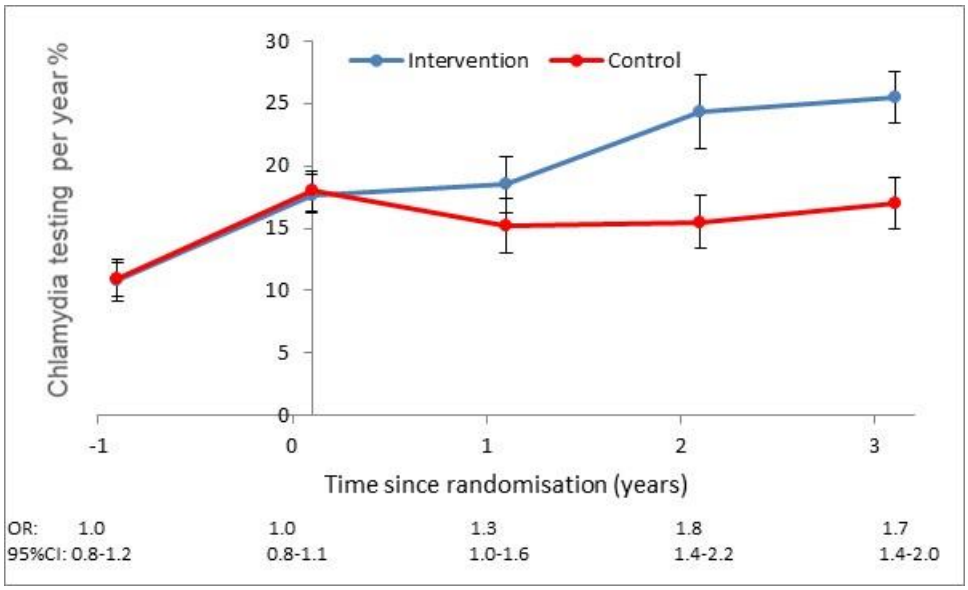
642 **Figure 1: Flow chart**


Intervention
Control
Chlamydia testing per year %
30
25
20
15
10
5
0
-1
0
1
2
3
Time since randomisation (years)
OR: 1.0 1.0 1.3 1.8 1.7
95%CI: 0.8-1.2 0.9-1.2 1.1-1.6 1.4-2.2 1.4-2.0

A)


Intervention
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30
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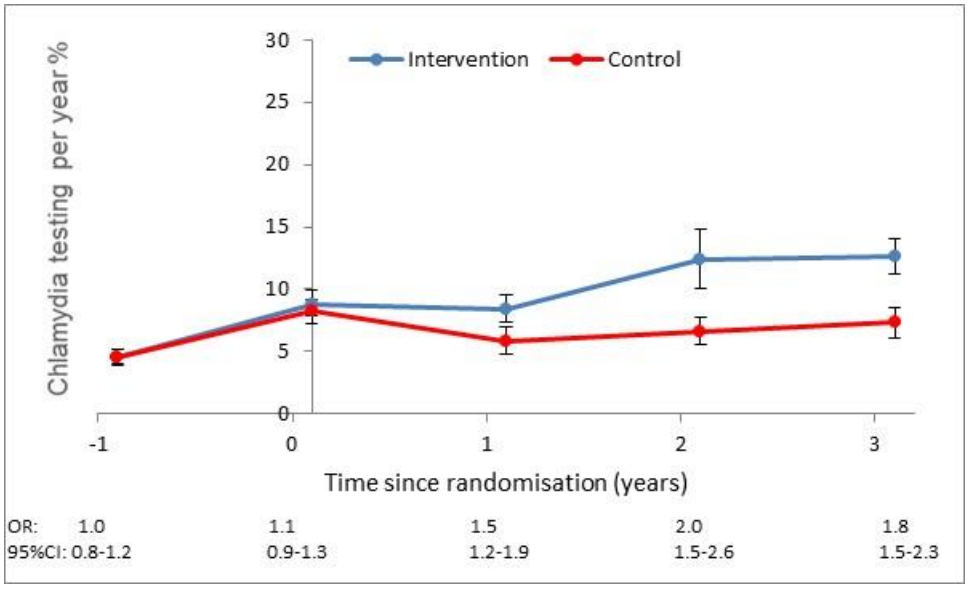
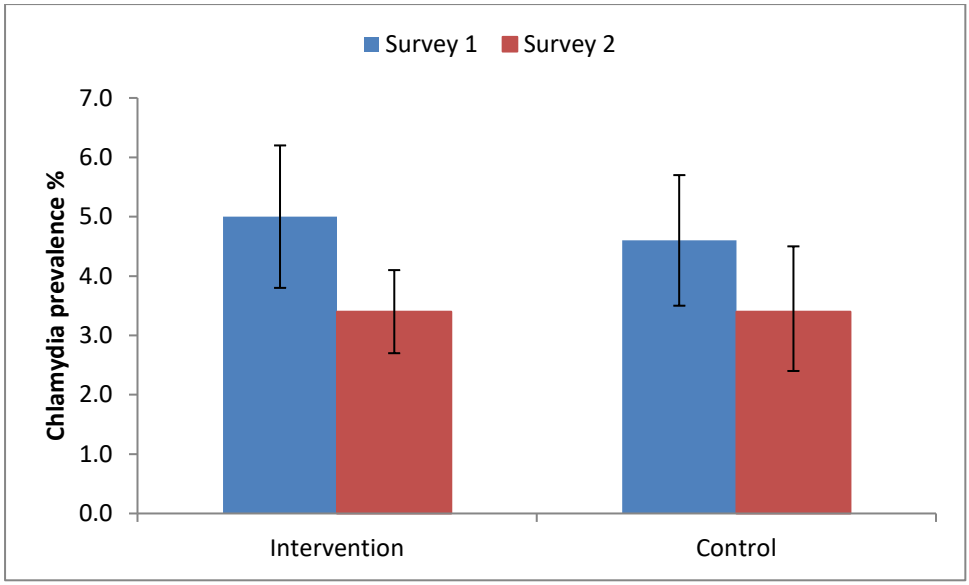
3
Time since randomisation (years)
OR: 1.0 1.0 1.3 1.8 1.7
95%CI: 0.8-1.2 0.8-1.1 1.0-1.6 1.4-2.2 1.4-2.0

B)

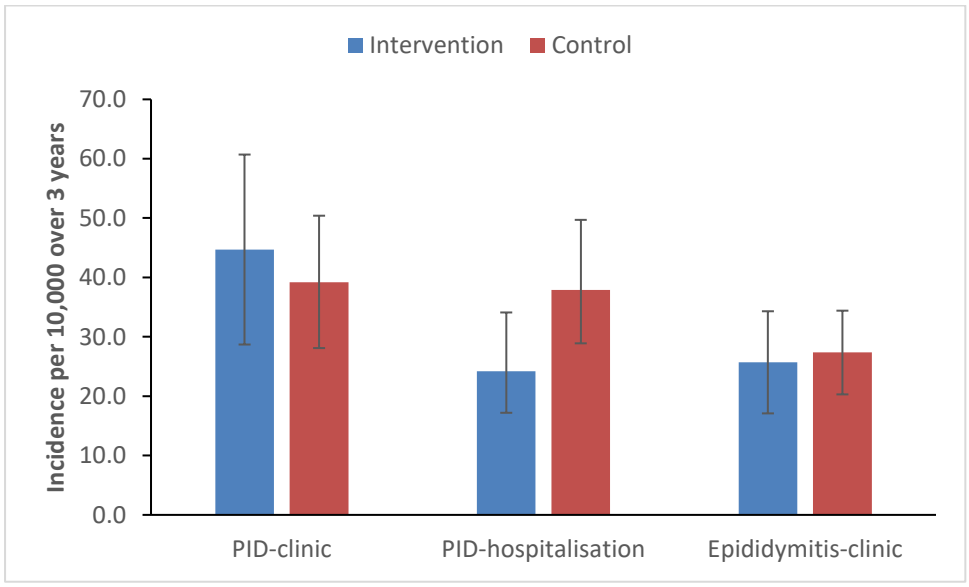


C)

Figure 2: Chlamydia testing per 100 per year by time since randomisation – A) Overall, B) Females, C) Males. (Time since randomisation refers to time since the start of the intervention period in each cluster and is defined as: -1 is defined as the (24-13) months before randomisation; 0 is defined as (12-1) months before randomisation, prevalence survey 1 was conducted during this time; 1 as (1-12) months after randomisation; 2 as (13-24) months after randomisation; 3 as (25-36) months after randomisation.



Supplementary Figure S1: Primary outcome – chlamydia prevalence



Supplementary Figure S2: Secondary morbidity outcomes (PID-clinic – incidence of PID diagnosed at participating clinics; PID-hospitalisation – incidence of PID associated hospitalisations; Epididymitis-clinic – incidence of epididymitis diagnosed at participating clinics)

Table 1: Baseline characteristics of clusters and clinics and characteristics of those participating in each prevalence survey

Variable	Intervention	Control	Australian average§
Number of clusters	26	26	-
Number of clinics at randomisation	63	67	-
Number of GPs*	305	281	-
GPs who are female n (%)*	120 (39)	112 (40)	41%
GP age group (n, %)*			
≤44 yrs.	149 (49)	145 (52)	33%
45-59 yrs.	131 (43)	110 (39)	45%
≥60 yrs.	25 (8)	26 (9)	22%
Socioeconomic status of clusters n (%)†			
Relatively most disadvantaged Q1	9 (35)	7 (27)	
Q2	14 (54)	14 (54)	-
Q3	2 (8)	5 (19)	
Q4	1 (4)	0 (0)	
Relatively least disadvantaged Q5	0 (0)	0 (0)	
Remoteness area of clusters n (%)‡			
Inner Regional	14 (54)	12 (46)	-
Outer Regional	11 (42)	12 (46)	
Remote	1 (9)	2 (8)	
Total population 16 to 29 year olds§			
16-19 yrs n(%)	10288 (34)	11924 (36)	
20-24 yrs n(%)	9912 (32)	10407 (32)	
25-29 yrs n(%)	10327 (34)	10480 (32)	
Females n(%)	14798 (49)	15961 (49)	
Chlamydia testing in the 12 months prior to recruitment n/N, % (95%CI)‖	2802/34143 8·2 (7·0 to 9·4)	3107/37775 8·2 (7·2 to 9·2)	-
Chlamydia prevalence prior to randomisation n/N, % (95%CI) ¶	92/1833 5·0 (3·8 to 6·2)	88/1925 4·6 (3·5 to 5·7)	-
Prevalence survey 1			
No· of participants in the analysis	1833	1925	-
Response rate % (95%CI)	68·8 (61·7 to 75·1)	71·8 (66·9 to 76·3)	
Females n (%)	1276 (70)	1394 (72)	-
Age group n (%)			
16-19 yrs.	432 (24)	521 (27)	-
20-24 yrs.	714 (39)	697 (36)	
25-29 yrs.	687 (37)	707 (37)	
No· of partners last 12 months n (%)			
Missing	199 (11)	166 (9)	-
0/1	1109 (68)	1201 (68)	
2	253 (15)	267 (15)	
3+	272 (17)	291 (17)	
Prevalence survey 2			
No· of participants in the analysis	2237	1716	-
Response rate % (95%CI)	72 (67·4 to 76·5)	67 (61·0 to 72·0)	
Females n (%)	1616 (72)	1229 (72)	-
Age group n (%)			
16-19 yrs.	570 (25)	424 (25)	-
20-24 yrs.	834 (37)	696 (41)	
25-29 yrs.	833 (37)	596 (35)	
No· of partners last 12 months n (%)			
Missing	182 (8)	119 (7)	-
0/1	1458 (71)	1104 (69)	
2	255 (12)	204 (13)	
3+	342 (17)	289 (18)	

CI = confidence interval. NB: Not all percentages add up to 100% because of rounding.
* Based on the number of GPs recruited at baseline. General practice is dynamic with GPs departing and/or joining clinics throughout the trial. Over 1200 GPs were recruited during the trial. † Socioeconomic status based on quintiles (Q) of each cluster's index of relative socio-economic disadvantage Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA) (2011). ‡ Remoteness area is based on the Australian Statistical Geography Standard Remoteness Structure of each cluster. Australian Bureau of Statistics. Australian Statistical Geography Standard (ASGS): Remoteness Structure, (2011). § Population of 16 to 29 year old men and women in the cluster. Australian Bureau of Statistics. Population by Age and Sex, Australian States and Territories. (2006). It includes people who have never been sexually active. ‖ n= number of patients aged 16 to 29 years who had at least one chlamydia test in the 12 months prior to the clinic's recruitment. ¶ Based on prevalence survey 1 results: n=number of people who test NAAT positive for chlamydia; N=number of people tested. § Australian National GP Workforce Statistics 2010-2011. Department of Health. GP Workforce Statistics –

2001-02 to 2016-17. 2017.
http://health.gov.au/internet/main/publishing.nsf/Content/General+Practice+Statistics-1

Table 2: Primary and morbidity secondary outcomes

	Intervention		Control		Unadjusted Treatment effect		Adjusted Treatment effect	
Primary outcome	**n/N**	**Prevalence (%) (95%CI)**	**n/N**	**Prevalence (%) (95%CI)**	**OR* (95% CI)**	**P value**	**OR* (95% CI)**	**P value**
Chlamydia prevalence								
Survey 1	92/1833	5·0 (3·8 to 6·2)	88/1925	4·6 (3·5 to 5·7)				
Survey 2	76/2237	3·4 (2·7 to 4·1)	59/1716	3·4 (2·4 to 4·5)	0·9 (0·5 to 1·5)	0·6522	0·9 (0·5 to 1·6)†	0·6727
Difference: survey 2-survey 1		–1·6 (–2·9 to –0·3)		–1·1 (–2·7 to 0·5)				
Treatment effect: difference (intervention-control)		–0·5 (95%CI: –2·6 to 1·5 p=0·6097)‡						
Secondary outcomes – morbidity	**n/N**	**Incidence (95%CI)**	**n/N**	**Incidence (95%CI)**	**RR‖ (95% CI)**	**P value**	**RR‖ (95% CI)**	**P value**
PID incidence per 10,000 over 3 years- clinic§	239/65519	44·7 (28·7 to 60·7)	237/60384	39·2 (28·1 to 50·4)	1·1 (0·7 to 1·8)	0·5622	1·2 (0·8 to 1·9)**	0·4553
Difference (intervention-control)		5·5 per 10,000 (95%CI: –13·4 to 24·3 p=0·5693)§§						
PID incidence per 10,000 over 3 years– hospital¶	57/23527	24·2 (17·2 to 34·1)	88/23219	37·9 (28·9 to 49·7)	0·6 (0·4 to 1·0)	0·0444	0·6 (0·4 to 1·0)††	0·0407
Difference (intervention-control)		–13·7 per 10,000 (95%CI: –26·9 to –0·5 p=0·0423)§§						
Epididymitis incidence per 10,000 over 3 years-clinic‡‡	106/41168	25·7 (17·2 to 34·3)	106/38717	27·4 (20·3 to 34·4)	0·9 (0·6 to 1·4)	0·7676	0·9 (0·6 to 1·4)**	0·6790
Difference (intervention-control)		–1·6 per 10,000 (95%CI: –12·4 to 9·1 p=0·7660)§§						

OR = Odds Ratio; RR = Risk Ratio; CI = Confidence Interval

* OR is for the interaction between randomisation group and survey 1 versus 2. † The adjusted model includes gender, age group, number of opposite lifetime partners, number of opposite sex partners in the last 12 months, condom use last encounter, sexual health related concerns, any antibiotic use last 3 months, and socioeconomic status of clusters. ‡ Unadjusted treatment effect calculated as the difference between survey2 – survey1 for intervention clusters and survey 2 – survey 1 for control clusters.. **§** Based on diagnoses recorded in the medical records software at each clinic. Incidence is a measure of the incidence proportion among women attending the clinic during a 3 year intervention period. Age group is limited to those aged 16 to 33 years. ¶ Any hospital admission for a primary diagnosis based on the following ICD-10 codes: ICD10 codes N70.0, N70.1, N70.9, N71.0, N71.1, N71.9, N73.0, N73.1, N73.2, N73.3, N73.4, N73.5, N73.8, N73.9, A56.1, N74.4. Age group is limited to those aged 15 to 34 years. Incidence is a measure of the incidence proportion among those attending the hospital during a 3 year intervention period. || RR is for intervention versus control. ** The adjusted model contains age group and socioeconomic status of cluster. †† The adjusted model contains age group only. ‡‡ Based on diagnoses recorded in the medical records software at each clinic. Incidence is a measure of the incidence proportion among men attending the clinic during a 3 year intervention period. Age group is limited to those aged 16 to 29 years. **§§**Unadjusted absolute difference between intervention and control incidence.

Supplementary Table S1: Secondary outcomes – chlamydia testing, positivity, re-testing and repeat infection

	Intervention		Control		Unadjusted Treatment effect		Adjusted Treatment effect	
	n/N	Proportion (%) (95%CI)	n/N	Proportion (%) (95%CI)	OR* (95% CI)	P value	OR* (95% CI)	P value
Chlamydia testing by time since randomisation †								
–1	2802/34143	8·2 (7·0 to 9·4)	3107/37775	8·2 (7·2 to 9·2)	1·0 (0·8 to 1·2)	0·9810	1·0 (0·9 to 1·3)¶	0·6733
0	5893/42418	13·9 (12·8 to 15·0)	6115/44262	13·8 (12·5 to 15·2)	1·0 (0·9 to 1·2)	0·9277	1·0 (0·9 to 1·2)¶	0·7109
1	6264/43968	14·2 (12·6 to 15·9)	5005/44666	11·2 (9·5 to 12·9)	1·3 (1·1 to 1·6)	0·0093	1·4 (1·1 to 1·7)¶	0·0045
2	8494/44005	19·3 (16·7 to 21·9)	5090/43438	11·7 (10·1 to 13·3)	1·8 (1·4 to 2·2)	<·0001	2·0 (1·6 to 2·5)¶	<·0001
3	8779/43676	20·1 (18·4 to 21·8)	5168/40156	12·9 (11·2 to 14·5)	1·7 (1·4 to 2·0)	<·0001	1·8 (1·5 to 2·1)¶	<·0001
Absolute difference‡		11·9 (10·3 to 13·4)		4·6 (3·3 to 6·0)				
Relative change in testing: year 3 vs year –1		2·8 (2·4 to 3·2)§		1·6 (1·4 to 1·9) §	1·7 (1·4 to 2·1)‖	<·0001	1·7 (1·4 to 2·1)‖¶	<·0001
Chlamydia positivity by time since randomisation †								
–1	250/2364**	10·6 (9·0 to 12·2)	310/2704**	11·5 (8·6 to 14·3)	0·9 (0·7 to 1·3)	0·5720	0·9 (0·6 to 1·2)¶	0·4812
0	535/5071**	10·6 (9·6 to 11·5)	485/5309**	9·1 (8·0 to 10·3)	1·2 (1·0 to 1·4)	0·0605	1·2 (1·0 to 1·4)¶	0·0756
1	573/5230**	11·0 (9·7 to 12·2)	457/4152**	11·0 (9·1 to 12·9)	1·0 (0·8 to 1·2)	0·9638	0·9 (0·8 to 1·2)¶	0·5993
2	634/7084**	8·9 (7·7 to 10·2)	438/4341**	10·1 (8·7 to 11·5)	0·9 (0·7 to 1·1)	0·2310	0·9 (0·7 to 1·1)¶	0·2077
3	498/7316**	6·8 (5·6 to 8·0)	394/4478**	8·8 (7·7 to 9·9)	0·8 (0·6 to 1·0)	0·0173	0·7 (0·6 to 0·9)¶	0·0151
Absolute difference‡		–3·8 (-6·0 to –1·5)		–2·7 (–5·1 to –0·2)				
Relative change in positivity: year 3 vs year –1		0·6 (0·5 to 0·8) §		0·7 (0·5 to 1·0) §	0·8 (0·6 to 1·2)‖	0·3271	0·8 (0·5 to 1·2)‖¶	0·3304
Chlamydia retesting (10-15 months) after a negative test result by time since randomisation†								
–1	167/2193	7·6 (6·3 to 8·9)	189/2489	7·6 (6·3 to 8·8)	1·0 (0·8 to 1·3)	0·9804	1·0 (0·8 to 1·3)¶	0·8220
0	397/4716	8·4 (7·1 to 9·7)	272/5000	5·4 (4·6 to 6·3)	1·6 (1·3 to 2·0)	<·0001	1·7 (1·3 to 2·1)¶	<·0001
1	506/4880	10·4 (8·7 to 12·1)	269/3862	7·0 (6·1 to 7·9)	1·5 (1·2 to 1·9)	<·0001	1·6 (1·3 to 2·0)¶	<·0001
2	610/6690	9·1 (8·3 to 9·9)	310/4075	7·6 (6·3 to 8·9)	1·2 (1·0 to 1·5)	0·0603	1·3 (1·1 to 1·6)¶	0·0130
3	260/7010	3·7 (2·2 to 5·2)	81/4236	1·9 (1·2 to 2·7)	2·0 (1·1 to 3·5)	0·0182	2·1 (1·2 to 3·8)¶	0·0147
Absolute difference‡		–3·9 (–5·6 to –2·3)		–5·7 (–7·0 to –4·4)				
Relative change in retesting: year 3 vs year –1		0·5 (0·3 to 0·7) §		0·2 (0·2 to 0·4) §	2·0 (1·1 to 3·5)‖	0·0196	2·0 (1·1 to 3·6)‖¶	0·0149
Chlamydia retesting (6 weeks - 6 months) after a positive test result by time since randomisation†								
–1	46/250	18·4 (13·6 to 23·2)	49/310	15·8 (10·7 to 20·9)	1·2 (0·7 to 1·9)	0·4543	1·2 (0·7 to 1·9)††	0·4673
0	118/535	22·1 (18·2 to 25·9)	93/485	19·2 (15·2 to 23·2)	1·2 (0·9 to 1·7)	0·2976	1·2 (0·9 to 1·7)¶	0·2572
1	159/573	27·7 (23·9 to 31·6)	90/457	19·7 (16·2 to 23·2)	1·6 (1·2 to 2·1)	0·0017	1·6 (1·2 to 2·2)¶	0·0015
2	158/634	24·9 (22·2 to 27·7)	84/438	19·2 (14·0 to 24·3)	1·4 (1·0 to 2·0)	0·0608	1·4 (1·0 to 2·0)††	0·0611
3	113/498	22·7 (18·9 to 26·5)	68/394	17·3 (13·1 to 21·4)	1·4 (1·0 to 2·0)	0·0537	1·6 (1·1 to 2·2)¶	0·0103
Absolute difference‡		4·3 (–1·5 to 10·0)		1·5 (–5·8 to 8·7)				
Relative change in retesting: year 3 vs year –1		1·3 (0·9 to 1·9) §		1·1 (0·7 to 1·9) §	1·2 (0·6 to 2·2)‖	0·6284	1·2 (0·6 to 2·3)‖¶	0·5277
Repeat chlamydia infection (6 weeks – 6 months) after a positive test result by by time since randomisation†								
–1	5/46	10·9 (1·3 to 20·5)	10/49	20·4 (6·2 to 34·7)	0·5 (0·1 to 1·7)	0·2470	0·3 (0·1 to 1·0)¶	0·0515
0	15/118	12·7 (7·0 to 18·4)	12/93	12·9 (7·0 to 18·8)	1·0 (0·5 to 2·0)	0·9621	1·0 (0·5 to 2·0)‡‡	0·9680
1	22/159	13·8 (9·5 to 18·2)	10/90	11·1 (6·5 to 15·7)	1·3 (0·7 to 2·3)	0·3871	1·3 (0·7 to 2·3)††	0·4378
2	20/158	12·7 (6·3 to 19·0)	13/84	15·5 (7·1 to 23·8)	0·8 (0·3 to 1·8)	0·5770	0·8 (0·3 to 1·7)¶	0·4837
3	12/113	10·6 (4·4 to 16·9)	5/68	7·4 (0·0 to 14·8)	1·5 (0·4 to 5·1)	0·5187	1·4 (0·4 to 5·1)¶	0·5650
Absolute difference‡		–0·3 (–12·3 to 11·8)		–13·1(–23·3to –2·8)				
Relative change in repeat infection: year 3 vs year –1		1·0 (0·3 to 3·4) §		0·3 (0·1 to 0·7) §	3·1 (0·7 to 13·8)‖	0·1287	3·6(0·9 to 14·2)‖¶	0·0724

OR = Odds Ratio; CI = Confidence Interval
* OR is for intervention versus control. † Time since randomisation refers to time since the start of the intervention period in each cluster and is defined as : -1 is defined as the (24-13) months before randomisation; 0 is defined as (12-1) months before randomisation, prevalence survey 1 was conducted during this time; 1 as (1-12) months after randomisation; 2 as (13-24) months after randomisation; 3 as (25-36) months after randomisation. ‡ Absolute difference between relative year 3 and year –1. § Odds ratio for relative year 3 vs year –1. ‖Odds ratio for intervention vs control for year 3 vs year –1. ** The denominator for chlamydia positivity is not equivalent to the number of chlamydia tests undertaken because chlamydia test results are not always stored electronically in the medical records at each clinic. Positivity is calculated based on the number of tests for which test results were stored electronically. ¶ Adjusted for gender, age group and socioeconomic status of clusters. †† Adjusted for age and gender. ‡‡ Adjusted for gender only.

Supplementary Table S2: Subgroup analyses of primary outcome – chlamydia prevalence

Subgroup		Intervention		Control		Unadjusted Treatment effect		Interaction test
		n/N	Prevalence (%) (95%CI)	n/N	Prevalence (%) (95%CI)	OR* (95% CI)	P value	P value†
Male	Survey 1	33/557	5·9 (4·0 to 7·8)	27/531	5·1 (3·5 to 6·7)	0·7		
	Survey 2	19/621	3·1 (1·8 to 4·4)	18/487	3·7 (2·0 to 5·4)	(0·3 to 1·6)	0·3814	0·4547
Female	Survey 1	59/1276	4·6 (3·3 to 5·9)	61/1394	4·4 (3·1 to 5·6)	1·0		
	Survey 2	57/1616	3·5 (2·5 to 4·6)	41/1229	3·3 (2·1 to 4·5)	(0·5 to 1·8)	0·9732	
Age [16-19 years]	Survey 1	35/432	8·1 (5·3 to 10·9)	35/521	6·7 (4·4 to 9·1)	0·9		
	Survey 2	34/570	6·0 (3·9 to 8·1)	23/424	5·4 (3·0 to 7·9)	(0·4 to 2·1)	0·8028	
Age [20-24 years]	Survey 1	43/714	6·0 (4·0 to 8·0)	41/697	5·9 (3·9 to 7·9)	0·7		
	Survey 2	26/834	3·1 (1·9 to 4·3)	28/696	4·0 (2·6 to 5·4)	(0·4 to 1·4)	0·3341	0·7352
Age [25-29 years]	Survey 1	14/687	2·0 (1·0 to 3·1)	12/707	1·7 (1·0 to 2·4)	1·2		
	Survey 2	16/833	1·9 (1·0 to 2·9)	8/596	1·3 (0·2 to 2·5)	(0·4 to 4·0)	0·7834	
Aboriginal/Torres Strait Islander	Survey 1	8/103	7·8 (2·5 to 13·0)	6/124	4·8 (2·1 to 7·6)	0·9		
	Survey 2	8/164	4·9 (1·4 to 8·3)	4/128	3·1 (0·9 to 5·3)	(0·2 to 4·0)	0·9373	
Not (Aboriginal/Torres Strait Islander)	Survey 1	77/1578	4·9 (3·6 to 6·1)	75/1662	4·5 (3·3 to 5·7)	0·9		0·9295
	Survey 2	68/2015	3·4 (2·7 to 4·0)	54/1562	3·5 (2·3 to 4·6)	(0·5 to 1·5)	0·6546	
Cluster chlamydia prevalence prior to randomisation < 3%‡	Survey 1	11/590	1·9 (1·0 to 2·7)	7/487	1·4 (0·6 to 2·3)	0·7		
	Survey 2	24/729	3·3 (2·1 to 4·5)	20/531	3·8 (1·8 to 5·8)	(0·3 to 1·8)	0·4159	
Cluster chlamydia prevalence prior to randomisation ≥ 3%‡	Survey 1	81/1243	6·5 (5·3 to 7·7)	81/1438	5·6 (4·6 to 6·6)	0·9		0·5813
	Survey 2	52/1508	3·4 (2·6 to 4·3)	39/1185	3·3 (1·9 to 4·6)	(0·5 to 1·6)	0·7559	
Cluster chlamydia testing in the 12 months prior to randomisation < 6%§	Survey 1	14/299	4·7 (1·9 to 7·4)	13/281	4·6 (2·4 to 6·8)	1·0		
	Survey 2	14/322	4·3 (2·4 to 6·3)	11/262	4·2 (0·2 to 8·2)	(0·3 to 3·7)	0·9604	
Cluster chlamydia testing in the 12 months prior to randomisation ≥ 6%§	Survey 1	78/1534	5·1 (3·7 to 6·5)	75/1644	4·6 (3·3 to 5·8)	0·9		0·7964
	Survey 2	62/1915	3·2 (2·5 to 4·0)	48/1454	3·3 (2·2 to 4·4)	(0·5 to 1·5)	0·6052	

OR = Odds Ratio; CI = Confidence Interval

* OR is for the interaction between randomisation group and survey 1 versus 2. † Interaction test between study group and variable of interest. ‡ Based on survey 1 prevalence cut-point of 3% used in the randomisation algorithm. § Based on chlamydia testing cut-point of 6% used in the randomisation algorithm.

Supplementary Table S3: Secondary analysis of primary outcome chlamydia prevalence, in clinics that adhered to their randomisation allocation*

	Intervention		Control		Unadjusted Treatment effect		Adjusted Treatment effect	
Primary outcome	**n/N**	**Prevalence (%) (95%CI)**	**n/N**	**Prevalence (%) (95%CI)**	**OR† (95% CI)**	**P value**	**OR†‡ (95% CI)**	**P value**
Chlamydia prevalence								
Survey 1	78/1623	4·8 (3·5 to 6·1)	33/793	4·2 (2·5 to 5·8)	0·7	0·3990	0·7	0·4342
Survey 2	67/2009	3·3 (2·6 to 4·1)	27/669	4·0 (1·6 to 6·5)	(0·3 to 1·6)		(0·3 to 1·7)	
Difference: survey 2-survey 1		–1·5 (–2·9 to –0·1)		–0·1 (–3·1 to 3·0)				
Treatment effect: difference (intervention-control)		–1·4 (95% CI –4·7 to 1·9 p=0·4096)§						

OR = Odds Ratio; CI = Confidence Interval

* Analysis is limited to intervention clinics testing ≥10·7% and control clinics testing <10·7% in the 12 months prior to survey 2, irrespective of the cluster's testing performance before the start of the trial. A total of 23 intervention and 11 control clusters were included in the analysis. †OR is for the interaction between randomisation group and survey 1 versus 2. ‡ Adjusted for gender, age group, socioeconomic status of clusters. § Unadjusted treatment effect calculated as the difference between survey2–survey1 for intervention clusters and survey 2 – survey 1 for control clusters.

Supplementary Table S4: Subgroup analyses of secondary outcomes – chlamydia testing

		Intervention		Control		Unadjusted Treatment effect		Interaction test
Subgroup	**Chlamydia testing by time since randomisation***	**n/N**	**Proportion (%) (95%CI)**	**n/N**	**Proportion (%) (95%CI)**	**OR (95% CI)**	**P value**	**P value†**
Males	–1	636/14061	4·5 (3·9 to 5·2)	711/15731	4·5 (4·0 to 5·1)	1·0 (0·8 to 1·2)	0·9936	0·9058
	0	1560/17998	8·7 (7·8 to 9·5)	1532/18780	8·2 (7·2 to 9·1)	1·1 (0·9 to 1·3)	0·4201	0·2040
	1	1560/18490	8·4 (7·4 to 9·5)	1115/19061	5·8 (4·7 to 7·0)	1·5 (1·2 to 1·9)	0·0015	0·0792
	2	2304/18552	12·4 (10·1 to 14·8)	1216/18465	6·6 (5·5 to 7·7)	2·0 (1·5 to 2·6)	<·0001	0·1225
	3	2296/18212	12·6 (11·2 to 14·0)	1230/16952	7·3 (6·1 to 8·5)	1·8 (1·5 to 2·3)	<·0001	0·1748
Females	–1	2166/20082	10·8 (9·1 to 12·5)	2396/22044	10·9 (9·5 to 12·2)	1·0 (0·8 to 1·2)	0·9380	
	0	4333/24420	17·7 (16·2 to 19·3)	4583/25482	18·0 (16·4 to 19·6)	1·0 (0·8 to 1·1)	0·8253	
	1	4704/25478	18·5 (16·2 to 20·8)	3890/25605	15·2 (13·0 to 17·4)	1·3 (1·0 to 1·6)	0·0373	
	2	6190/25453	24·3 (21·4 to 27·3)	3874/24973	15·5 (13·4 to 17·6)	1·8 (1·4 to 2·2)	<·0001	
	3	6483/25464	25·5 (23·5 to 27·5)	3938/23204	17·0 (14·9 to 19·1)	1·7 (1·4 to 2·0)	<·0001	
Age [16-19 years]	–1	1016/11834	8·6 (7·4 to 9·7)	1121/13267	8·4 (7·4 to 9·5)	1·0 (0·8 to 1·2)	0·8607	0·8203
	0	1925/14282	13·5 (12·0 to 14·9)	1994/15522	12·8 (11·5 to 14·2)	1·1 (0·9 to 1·2)	0·5143	0·4995
	1	2114/14463	14·6 (12·6 to 16·6)	1721/15287	11·3 (9·5 to 13·0)	1·3 (1·1 to 1·7)	0·0097	0·3212
	2	2798/14145	19·8 (17·2 to 22·3)	1741/14781	11·8 (10·0 to 13·6)	1·8 (1·5 to 2·3)	<·0001	0·8235
	3	2738/13744	19·9 (18·1 to 21·7)	1713/13576	12·6 (10·5 to 14·7)	1·7 (1·4 to 2·1)	<·0001	0·9613
Age [20-24 years]	–1	1136/11675	9·7 (8·2 to 11·3)	1224/12499	9·8 (8·5 to 11·1)	1·0 (0·8 to 1·2)	0·9498	
	0	2349/14786	15·9 (14·6 to 17·2)	2362/14608	16·2 (14·5 to 17·9)	1·0 (0·8 to 1·1)	0·7884	
	1	2572/15283	16·8 (14·9 to 18·7)	1957/15076	13·0 (10·9 to 15·0)	1·4 (1·1 to 1·7)	0·0063	
	2	3412/15416	22·1 (19·3 to 25·0)	1999/14697	13·6 (11·6 to 15·7)	1·8 (1·4 to 2·3)	<·0001	
	3	3542/15311	23·1 (21·2 to 25·1)	2073/13754	15·1 (13·2 to 16·9)	1·7 (1·4 to 2·0)	<·0001	
Age [25-29 years]	–1	650/10634	6·1 (5·1 to 7·2)	762/12009	6·3 (5·3 to 7·4)	1·0 (0·8 to 1·2)	0·7493	
	0	1619/13350	12·1 (11·0 to 13·2)	1759/14132	12·4 (11·1 to 13·8)	1·0 (0·8 to 1·1)	0·7072	
	1	1578/14222	11·1 (9·6 to 12·6)	1327/14303	9·3 (7·9 to 10·7)	1·2 (1·0 to 1·5)	0·0700	
	2	2284/14444	15·8 (13·1 to 18·5)	1350/13960	9·7 (8·3 to 11·0)	1·8 (1·4 to 2·2)	<·0001	
	3	2499/14621	17·1 (15·5 to 18·7)	1382/12826	10·8 (9·4 to 12·1)	1·7 (1·4 to 2·0)	<·0001	

OR = Odds Ratio; CI = Confidence Interval

* Time since randomisation refers to time since the start of the intervention period in each cluster and is defined as : 1 is defined as the (24-13) months before randomisation; 0 is defined as (12-1) months before randomisation, prevalence survey 1 was conducted during this time; 1 as (1-12) months after randomisation; 2 as (13-24) months after randomisation; 3 as (25-36) months after randomisation. † Interaction test between study group and variable of interest (gender or age).

Supplementary Table S5: Subgroup analyses of secondary outcomes – chlamydia positivity

		Intervention		Control		Unadjusted Treatment effect		Interaction test
Subgroup	**Chlamydia positivity by time since randomisation*†**	**n/N**	**Proportion (%) (95%CI)**	**n/N**	**Proportion (%) (95%CI)**	**OR (95% CI)**	**P value**	**P value‡**
Male	–1	98/519	18·9 (15·6 to 22·1)	107/602	17·8 (14·1 to 21·5)	1·1 (0·8 to 1·5)	0·6482	0·2450
	0	174/1288	13·5 (11·4 to 15·6)	167/1322	12·6 (10·9 to 14·4)	1·1 (0·9 to 1·4)	0·5135	0·4224
	1	190/1228	15·5 (13·6 to 17·3)	148/882	16·8 (14·1 to 19·4)	0·9 (0·7 to 1·1)	0·4059	0·4472
	2	225/1821	12·4 (10·1 to 14·6)	151/994	15·2 (12·9 to 17·5)	0·8 (0·6 to 1·0)	0·0776	0·2773
	3	179/1827	9·8 (7·3 to 12·3)	133/1044	12·7 (10·4 to 15·1)	0·7 (0·5 to 1·0)	0·0865	0·9583
Female	–1	152/1845	8·2 (6·9 to 9·6)	203/2102	9·7 (6·5 to 12·8)	0·8 (0·6 to 1·2)	0·3796	
	0	361/3783	9·5 (8·6 to 10·5)	318/3987	8·0 (6·6 to 9·3)	1·2 (1·0 to 1·5)	0·0659	
	1	383/4002	9·6 (8·2 to 10·9)	309/3270	9·4 (7·5 to 11·4)	1·0 (0·8 to 1·3)	0·9185	
	2	409/5263	7·8 (6·6 to 9·0)	287/3347	8·6 (7·2 to 9·9)	0·9 (0·7 to 1·1)	0·3643	
	3	319/5489	5·8 (4·9 to 6·8)	261/3434	7·6 (6·4 to 8·8)	0·8 (0·6 to 0·9)	0·0160	
Age [16-19 years]	–1	118/842	14·0 (12·0 to 16·0)	125/967	12·9 (9·6 to 16·2)	1·1 (0·8 to 1·5)	0·5746	0·1410
	0	256/1642	15·6 (13·3 to 17·9)	190/1704	11·2 (8·8 to 13·5)	1·5 (1·1 to 1·9)	0·0071	0·0082
	1	253/1764	14·3 (12·1 to 16·5)	197/1402	14·1 (11·2 to 16·9)	1·0 (0·8 to 1·4)	0·8699	0·1486
	2	277/2291	12·1 (10·0 to 14·2)	179/1477	12·1 (9·6 to 14·6)	1·0 (0·7 to 1·3)	0·9860	0·2613
	3	203/2251	9·0 (6·7 to 11·4)	161/1460	11·0 (9·4 to 12·7)	0·8 (0·6 to 1·1)	0·1717	0·2522
Age [20-24 years]	–1	107/974	11·0 (8·4 to 13·5)	147/1087	13·5 (10·5 to 16·6)	0·8 (0·6 to 1·1)	0·1927	
	0	220/2023	10·9 (9·8 to 12·0)	208/2050	10·1 (8·8 to 11·5)	1·1 (0·9 to 1·3)	0·3978	
	1	228/2142	10·6 (8·9 to 12·4)	201/1637	12·3 (9·8 to 14·7)	0·9 (0·6 to 1·1)	0·2609	
	2	267/2867	9·3 (7·8 to 10·8)	187/1708	10·9 (9·3 to 12·6)	0·8 (0·7 to 1·1)	0·1380	
	3	201/2939	6·8 (5·7 to 7·9)	173/1802	9·6 (8·4 to 10·8)	0·7 (0·6 to 0·9)	0·0007	
Age [25-29 years]	–1	25/548	4·6 (2·8 to 6·3)	38/650	5·8 (2·7 to 9·0)	0·8 (0·4 to 1·5)	0·4437	
	0	59/1406	4·2 (3·1 to 5·3)	87/1555	5·6 (4·6 to 6·6)	0·7 (0·5 to 1·0)	0·0582	
	1	92/1324	6·9 (5·1 to 8·8)	59/1113	5·3 (4·1 to 6·5)	1·3 (0·9 to 1·9)	0·1105	
	2	90/1926	4·7 (3·6 to 5·8)	72/1156	6·2 (4·9 to 7·6)	0·7 (0·5 to 1·0)	0·0701	
	3	94/2126	4·4 (3·5 to 5·3)	60/1216	4·9 (3·6 to 6·3)	0·9 (0·6 to 1·3)	0·5213	

OR = Odds Ratio; CI = Confidence Interval

* Time since randomisation refers to time since the start of the intervention period in each cluster and is defined as : -1 is defined as the (24-13) months before randomisation; 0 is defined as (12-1) months before randomisation, prevalence survey 1 was conducted during this time; 1 as (1-12) months after randomisation; 2 as (13-24) months after randomisation; 3 as (25-36) months after randomisation. †The denominator for chlamydia positivity is not equivalent to the number of chlamydia tests undertaken because chlamydia test results are not always stored electronically in the medical records at each clinic. Positivity is calculated based on the number of tests for which test results were stored electronically. ‡ Interaction test between study group and variable of interest (gender or age).

Supplementary Table S6: Subgroup analysis of secondary outcomes – retesting within 10 to 15 months after a negative test

		Intervention		Control		Unadjusted Treatment effect		Interaction test
Subgroup	**Chlamydia retesting by time since randomisation***	**n/N**	**Proportion (%) (95%CI)**	**n/N**	**Proportion (%) (95%CI)**	**OR (95% CI)**	**P value**	**P value†**
Male	–1	22/443	5·0 (2·7 to 7·2)	22/513	4·3 (2·9 to 5·7)	1·2 (0·7 to 2·1)	0·5964	0·5895
	0	56/1158	4·8 (3·2 to 6·5)	29/1206	2·4 (1·2 to 3·6)	2·1(1·1 to 3·8)	0·0179	0·3697
	1	62/1087	5·7 (4·1 to 7·3)	31/770	4·0 (2·0 to 6·0)	1·4 (0·8 to 2·6)	0·2142	0·7525
	2	85/1653	5·1 (4·1 to 6·2)	40/879	4·6 (3·1 to 6·0)	1·1 (0·8 to 1·7)	0·5160	0·6263
	3	48/1693	2·8 (1·4 to 4·3)	9/950	0·9 (0·4 to 1·5)	3·1 (1·4 to 6·6)	0·0044	0·1735
Female	–1	145/1750	8·3 (6·7 to 9·9)	167/1976	8·5 (7·0 to 9·9)	1·0 (0·7 to 1·3)	0·8768	
	0	341/3558	9·6 (7·9 to 11·2)	243/3794	6·4 (5·4 to 7·4)	1·5 (1·2 to 2·0)	0·0004	
	1	444/3793	11·7 (9·7 to 13·7)	238/3092	7·7 (6·7 to 8·7)	1·6 (1·3 to 2·0)	<·0001	
	2	525/5037	10·4 (9·4 to 11·5)	270/3196	8·4 (6·9 to 10·0)	1·3 (1·0 to 1·6)	0·0374	
	3	212/5317	4·0 (2·4 to 5·6)	72/3286	2·2 (1·3 to 3·1)	1·9 (1·0 to 3·3)	0·0372	
Age [16-19 years]	–1	78/760	10·3 (8·1 to 12·5)	88/883	10·0 (7·8 to 12·1)	1·0 (0·7 to 1·4)	0·8449	0·5510
	0	164/1523	10·8 (8·6 to 12·9)	116/1644	7·1 (5·9 to 8·2)	1·6 (1·2 to 2·1)	0·0009	0·7790
	1	251/1822	13·8 (11·4 to 16·2)	123/1411	8·7 (7·2 to 10·2)	1·7 (1·3 to 2·2)	0·0001	0·3541
	2	302/2515	12·0 (10·3 to 13·7)	160/1610	9·9 (8·1 to 11·7)	1·2 (1·0 to 1·6)	0·0937	0·9964
	3	112/2723	4·1 (2·5 to 5·7)	46/1752	2·6 (1·5 to 3·8)	1·6 (0·9 to 2·8)	0·1173	0·1092
Age [20-24 years]	–1	67/899	7·5 (5·9 to 9·1)	68/983	6·9 (5·2 to 8·7)	1·1 (0·8 to 1·5)	0·6490	
	0	166/1856	8·9 (7·7 to 10·2)	105/1892	5·5 (4·4 to 6·7)	1·7 (1·3 to 2·2)	<·0001	
	1	182/1890	9·6 (7·9 to 11·4)	110/1438	7·6 (5·8 to 9·5)	1·3 (0·9 to 1·8)	0·1232	
	2	211/2529	8·3 (6·9 to 9·8)	103/1485	6·9 (5·3 to 8·6)	1·2 (0·9 to 1·7)	0·1970	
	3	105/2583	4·1 (2·0 to 6·2)	28/1530	1·8 (0·9 to 2·7)	2·3 (1·1 to 4·7)	0·0248	
Age [25 to 29 years]	–1	22/534	4·1 (2·6 to 5·6)	33/623	5·3 (3·2 to 7·3)	0·8 (0·4 to 1·3)	0·3360	
	0	67/1337	5·0 (3·7 to 6·3)	51/1464	3·5 (2·4 to 4·6)	1·5 (1·0 to 2·2)	0·0696	
	1	73/1168	6·3 (4·8 to 7·7)	36/1013	3·6 (2·5 to 4·6)	1·8 (1·2 to 2·6)	0·0019	
	2	97/1646	5·9 (4·8 to 7·0)	47/980	4·8 (3·3 to 6·3)	1·2 (0·9 to 1·8)	0·2538	
	3	43/1704	2·5 (1·5 to 3·5)	7/954	0·7 (0·2 to 1·3)	3·5 (1·6 to 7·8)	0·0020	

OR = Odds Ratio; CI = Confidence Interval

* Time since randomisation refers to time since the start of the intervention period in each cluster and is defined as : -1 is defined as the (24-13) months before randomisation; 0 is defined as (12-1) months before randomisation, prevalence survey 1 was conducted during this time; 1 as (1-12) months after randomisation; 2 as (13-24) months after randomisation; 3 as (25-36) months after randomisation. † Interaction test between study group and variable of interest (gender or age).

Supplementary Table S7: Secondary outcomes – alternative definitions of retesting after a positive test

		Intervention		Control		Unadjusted Treatment effect		Adjusted Treatment effect	
Retesting after a positive test		**n/N**	**Proportion (%) (95%CI)**	**n/N**	**Proportion (%) (95%CI)**	**OR* (95% CI)**	**P value**	**OR* (95% CI)**	**P value**
Chlamydia retesting (< 3 weeks) after a positive test result by time since randomisation†									
	–1	30/250	12·0 (6·3 to 17·7)	38/310	12·3 (6·9 to 17·6)	1·0 (0·5 to 2·0)	0·9469	1·0 (0·5 to 2·2)‖	0·9252
	0	50/535	9·3 (6·3 to 12·4)	70/485	14·1 (11·2 to 17·6)	0·6 (0·4 to 0·9)	0·0232	0·7 (0·4 to 1·0)¶	0·0749
	1	57/573	9·9 (5·9 to 14·0)	71/457	15·5 (11·9 to 19·2)	0·6 (0·4 to 1·0)	0·0502	0·6 (0·4 to 1·0)‖	0·0464
	2	61/634	9·6 (7·3 to 11·9)	66/438	15·1 (11·0 to 19·2)	0·6 (0·4 to 0·9)	0·0131	0·6 (0·4 to 0·9)¶	0·0101
	3	48/498	9·6 (6·6 to 12·7)	44/394	11·2 (7·5 to 14·9)	0·8 (0·5 to 1·4)	0·5135	0·9 (0·6 to 1·5)¶	0·7375
Chlamydia retesting (6 weeks – 4 months) after a positive test result by time since randomisation†									
	–1	36/250	14·4 (10·4 to 18·4)	34/310	11·0 (6·8 to 15·1)	1·4 (0·8 to 2·3)	0·2367	1·3 (0·8 to 2·3)‖	0·2737
	0	93/535	17·4 (14·4 to 20·4)	73/485	15·1 (11·1 to 19·0)	1·2 (0·8 to 1·7)	0·3510	1·2 (0·8 to 1·7)¶	0·2914
	1	108/573	18·8 (15·7 to 22·0)	62/457	13·6 (9·4 to 17·7)	1·5 (1·0 to 2·2)	0·0516	1·5 (1·0 to 2·3)¶	0·0544
	2	117/634	18·5 (15·7 to 21·2)	61/438	13·9 (10·3 to 17·5)	1·4 (1·0 to 2·0)	0·0523	1·4 (1·0 to 2·0)‖	0·0531
	3	92/498	18·5 (14·6 to 22·3)	49/394	12·4 (9·1 to 15·8)	1·6 (1·1 to 2·3)	0·0177	1·7 (1·1 to 2·6)¶	0·0086

OR = Odds Ratio; CI = Confidence Interval

* OR is for intervention versus control. † Time since randomisation refers to time since the start of the intervention period in each cluster and is defined as : to 1 is defined as the (24-13) months before randomisation; 0 is defined as (12-1) months before randomisation, prevalence survey 1 was conducted during this time; 1 as (1-12) months after randomisation; 2 as (13-24) months after randomisation; 3 as (25-36) months after randomisation‖ Adjusted for age and gender. ¶ Adjusted for gender, age group and socioeconomic status of clusters.