BMJ

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Effectiveness of yearly, register based screening for chlamydia in the Netherlands: controlled trial with randomised stepped wedge implementation

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Abstract

Objective To evaluate the effectiveness of register based, yearly chlamydia screening.

Design Controlled trial with randomised stepped wedge implementation in three blocks.

Setting Three regions of the Netherlands: Amsterdam, Rotterdam, and South Limburg.

Participants 317 304 women and men aged 16-29 years listed on municipal registers at start of trial.

Intervention From March 2008 to February 2011, the Chlamydia Screening Implementation programme offered yearly chlamydia screening tests. Postal invitations asked people to use an internet site to request a kit for self collection of samples, which would then be sent to regional laboratories for testing. Treatment and partner notification were done by the general practitioner or at a sexually transmitted infection clinic.

Main outcome measures Primary outcomes were the percentage of chlamydia tests positive (positivity), percentage of invitees returning a specimen (uptake), and estimated chlamydia prevalence. Secondary outcomes were positivity according to sex, age, region, and sociodemographic factors; adherence to screening invitations; and incidence of self reported pelvic inflammatory disease.

Results The participation rate was 16.1% (43 358/269 273) after the first invitation, 10.8% after the second, and 9.5% after the third, compared with 13.0% (6223/48 031) in the control block invited at the end of round two of the intervention. Chlamydia positivity in the intervention blocks at the first invitation was the same as in the control block (4.3%) and 0.2% lower at the third invitation (odds ratio 0.96 (95% confidence interval 0.83 to 1.10)). No substantial decreases in positivity were seen after three screening rounds in any region or sociodemographic group. Among the people who participated three times (2.8% of all invitees), positivity fell from 5.9% to 2.9% (odds ratio 0.49 (0.47 to 0.50)).

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Conclusions There was no statistical evidence of an impact on chlamydia positivity rates or estimated population prevalence from the Chlamydia Screening Implementation programme after three years at the participation levels obtained. The current evidence does not support a national roll out of this register based chlamydia screening programme.

Trial registration NTR 3071 (Netherlands Trial Register, www. trialregister.nl).

Introduction

Chlamydia screening has been promoted as a means of controlling sexual transmission of *Chlamydia trachomatis* (chlamydia),[1-3] which is the most common notifiable infection in some high income countries.[1] Before introducing a screening programme there should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity.[4] The goals of chlamydia screening are to detect and treat asymptomatic infections, to limit ongoing transmission in the community, and to reduce the incidence of pelvic inflammatory disease.[5] Pelvic inflammatory disease results from microorganisms, including *C trachomatis*, ascending to the upper genital tract and is a strong risk factor for tubal factor infertility and ectopic pregnancy.[6] The efficacy of a one-off offer of screening in preventing pelvic inflammatory disease has been shown in three randomised trials (in the US, Denmark, and UK), all of which reported a reduction in incidence in the intervention group after one year of follow-up.[7-9] The most recent trial, with methods with the lowest risk of bias, showed the smallest effect (risk ratio 0.65 (95% confidence interval 0.34 to 1.22)).[9]

We lack evidence from randomised controlled trials that either opportunistic or register based repeated chlamydia screening reduces the prevalence of chlamydia in the population.[10] Nevertheless, opportunistic chlamydia screening is widely practised.[11 12] The National Chlamydia Screening Programme in England recommends chlamydia screening for sexually active women and men under 25 years of age every year and after a change of sexual partner.[2 5] The number of chlamydia tests in England has increased since the start of the programme in 2003 to cover 33% of all 15-24 year olds in 2010-11, when tests from both the programme and all other sources are included.[13] The population impact of the programme is not known, however, because population chlamydia prevalence has never been measured as an end point.[14] To evaluate the effect of screening on chlamydia transmission, multiple screening rounds and implementation of screening in geographically defined clusters are needed because repeated infection after treatment is common,[15] and sexual partners need to be invited at the same time.[16] This is because screening of a population in clusters is more likely to reduce immediate re-infection within sexual partnerships or transmission in local sexual networks than allocation of individuals to intervention and control groups and helps prevent "Why me?" questions that would arise if people in the same neighbourhoods received invitations at different times.

The feasibility of a single round of register based chlamydia screening has been examined in uncontrolled studies in the UK and the Netherlands.[17-19] In the Netherlands, in 2002-03 kits for self sampling were sent to a selection of 21 000 15-29 year old adults: 41% returned a sample, and 2.0% (95% confidence interval 1.7% to 2.3%) were chlamydia positive.[19] On the basis of these results, the Dutch Ministry of Health decided to consider a national chlamydia screening programme if there was evidence of feasibility, effectiveness, and cost effectiveness.[3] The objectives of this study were to investigate the effects of yearly invitations for chlamydia screening on the percentage of positive chlamydia test results (positivity), uptake of chlamydia screening, and estimated chlamydia prevalence among sexually active women and men in the Netherlands.

Methods

The intervention[20] and evaluation[21] of the Chlamydia Screening Implementation project have been described in detail. Results from the first year of screening,[20-22] process evaluations,[23 24] and experiences of participants and non-responders[25] have been published. The main features of the trial are summarised here.

Study setting and participants

The study took place in three regions of the Netherlands—the urban areas of Amsterdam and Rotterdam and a defined suburban area of South Limburg (Parkstad). All women and men aged 16-29 years old who were listed on the municipal population register from March 2008 to February 2011 were eligible to participate. Clusters were geographical and administrative units that included about 2000 people in the target age group in the cities and 1000 in South Limburg, resulting in 82 clusters (158 545 people) in Amsterdam, 62 clusters (119 868 people) in Rotterdam, and 46 clusters (38 891 people) in South Limburg.

Interventions and blinding

The intervention was a register based programme with personalised yearly invitations to be screened for *C trachomatis* infection sent to the target population. The letter included the address of the programme website (www.chlamydiatest.nl) and a secure login code through which eligible participants could request a kit for self sampling (urine for men, vaginal swab or urine for women).[20] Samples could be posted in prepaid secure packaging for testing by means of nucleic acid amplification tests. A single reminder letter was sent to anyone who did not access the website within four weeks, and email reminders were sent to individuals who requested a kit but did not return a specimen within two weeks.[24] Test results, with a referral letter for those with positive results, were provided online, with an email or text message reminder after 14 and 28 days and a letter by post after six weeks for those who did not access it. Treatment and partner notification were provided by the person's general practitioner or at a local sexually transmitted infections clinic. People with a positive test were sent a retest kit six months after treatment. In Amsterdam and Rotterdam, all people who reported that they ever had sex were asked to request a test kit. In South Limburg, chlamydia prevalence was expected to be lower than in the cities, and test kits were only sent to people completing a risk assessment form that had been developed previously.[26] A risk score of ≥6 with the form was compatible with a positivity of 4-5% and excluded 20-30% of potential participants.[27] Participants provided informed consent online.

The control condition was usual care. Testing for chlamydia is available from general practitioners and at sexually transmitted infections clinics. There was no specific promotion of chlamydia testing during the trial period. Investigators, participants, and laboratory staff could not be blinded to allocation to intervention or control care.

Comparison groups and randomised stepped wedge implementation

The intervention was implemented by means of a stepped wedge design, with sequential roll out to clusters in a randomly determined order over time so that, by the end of the three year

study period, each cluster had been invited at least once.[21] The original study design encompassed 26 months of screening. To allow the evaluation of up to three screening rounds, clusters in the three regions were divided into three groups, called blocks A, B, and C (blocks were not geographically contiguous). Block A was smaller in the cities (one sixth of the population; invited three times); block B included two thirds of the population (invited twice); and block C (one sixth of the population, invited once after the second invitation was sent to blocks A and B) was the control group. The programme was subsequently prolonged by six months, allowing a third invitation in block B. In the smaller rural area, clusters were divided into three blocks of the same size to maximise statistical power.

Allocation of clusters—Clusters were allocated by two members of the evaluation team (ELMOdC and IVFvdB) who were blinded to the identity of clusters. Before allocation, clusters were stratified into three levels of community risk for chlamydia infection (high, medium, or low) based on demographic factors associated with chlamydia test positivity in the Netherlands (that is, proportions of 16-29 year olds, of Surinamese and Antillean residents, and of residents in the lowest income category; also level of urbanisation in the South Limburg region).[19] For each region, cluster names were replaced by numbers and listed by cluster size and risk level. The investigators allocated de-identified clusters so that the required block sizes for A, B, and C were achieved and similar proportions of high, medium, and low risk target population per block were obtained. The results of the allocation and geographical distribution of clusters have been reported elsewhere.[21]

Randomised stepped wedge roll out—The order of invitation of clusters was randomised by assigning computer generated random numbers to clusters and then sorting clusters within one block using these numbers (using Microsoft Excel 2002). The order of clusters was then used to generate daily lists of 600 invitees from each of the regional municipal registers and forward these to the logistics company for mailing.

Sample size calculation

The sample size and numbers of clusters were determined by the actual size of the target population (16-29 year old women and men) in the three regions. The size of the control group blocks (one sixth of the population in the cities and one third in South Limburg) was determined to obtain maximum statistical power. Power calculations were based on the pilot feasibility study, which found participation of 30% and 3% of chlamydia tests positive in urban areas.[19]

Monte Carlo simulations of chlamydia positivity before and after screening in hypothetical clusters (assuming that positivity ranged from 0 to 10% with an average of 4%, 5%, or 6% before screening) were run to determine the minimum detectable decline with given population numbers for the three regions and for each block.[21] The trial had sufficient power (80%, α 0.05) to detect an absolute overall reduction of 1% in prevalence after one or two screening rounds if participation rates were at least 10% in Amsterdam and Rotterdam and 25% in South Limburg with the baseline assumptions. After the first screening round, revised simulations resulted in a minimal detectable decline of 0.5% in positivity rate for Amsterdam, 0.8% in Rotterdam, and 1.2% in Limburg, whereas, for comparisons with the control block, the declines would need to exceed 1.2% to 1.5% if participation rates in the second and third rounds were similar.

Outcomes

The effectiveness of chlamydia screening was planned to be based on three primary outcomes; chlamydia test positivity, percentage participating, and estimated chlamydia prevalence in all regions. The main aim of the intervention was to reduce chlamydia prevalence in intervention areas, but prevalence could not be measured directly because, at the expected levels of screening uptake, the percentage of positive chlamydia tests is not a reliable estimate of population prevalence. The power calculation was therefore based on chlamydia positivity, and this is the primary outcome reported. Secondary outcomes were chlamydia test positivity and test uptake by sex, age, ethnic group, and region; estimated chlamydia prevalence; and incidence of self reported pelvic inflammatory disease.

Statistical analysis

We calculated absolute differences and odds ratios comparing chlamydia test positivity in intervention blocks and control blocks and, within intervention blocks, changes between the first and third rounds. Cluster effects for participation and positivity rates were calculated for round one using multivariable logistic regression with the variable "cluster" added as a second level. Clustering had a modest impact on participation rates (adjusted median odds ratio for cluster 1.14 (95% confidence interval 1.11 to 1.16), P<0.001) and no impact on positivity (median odds ratio 1.03 (1.0 to 1.14)) so we report participation rates adjusted for clustering and positivity rates at the individual level. To account for baseline differences that might bias the estimate of impact on chlamydia positivity we included block allocation, community risk level, and cluster size as covariates and estimated the adjusted odds ratio.

The prevalence of chlamydia in the whole target population was estimated by extrapolation from positivity rates among participants by weighting based on demographic data available for all invitees and an estimate of people being sexually active. Therefore, cross tabulations of gender, age, ethnicity, and community risk in participants and invited populations were used to calculate survey weights for each invitation round (demographic data for the whole target population were obtained from the municipal register at the time of invitation). Weights were calculated by dividing the proportion of participants with a specified profile by the proportion of invitees with the same profile (for example, the profile "<20 year old, Dutch, male" represents 2% of the participant population but 4% of those invited, so the weight assigned is 2). Firstly, the crude prevalence in the invited population was estimated as the weighted positivity rate. Estimates were then further adjusted for sexual experience (assuming those who had never had sexual intercourse to be uninfected) by multiplying these crude prevalence rates by the fractions of sexually experienced women and men by one year age bands using data from the National Sexual Health Survey 2009.[28] For South Limburg the estimates were also adjusted for the exclusion of people with lower levels of sexual risk behaviour by calculating a range of prevalence estimates with maximum values based on the assumption that the group excluded from participation because of a low score in the risk assessment had the same positivity rate as the lowest risk group included (with cut off score) and minimum values assuming this group had zero positivity.

Estimated chlamydia prevalence was a pre-specified outcome, but the results should be interpreted cautiously because probable differences between participants and non-participants in sexual risk level could not be taken into account (the information about sexual behaviour was not available for non-participants and for

55% of participants who did not fill in the online questionnaire at baseline). We considered multiple imputation of data but rejected it because the main parameters were systematically missing for all non-participants and not scattered throughout the dataset.

Secondary analyses compared changes in chlamydia positivity in each region and in demographic subgroups (age, gender, and ethnic group (based on participant's country of birth and that of his or her parents)). An indicator of socioeconomic status based on income, education level, and employment was available for the lowest level postcode areas (parts of streets) (Netherlands Institute for Social Research). An additional, voluntary set of questions about self reported pelvic inflammatory disease in the preceding year was offered to female participants after they had completed the general questionnaire (main question: "Have you been diagnosed with a pelvic infection (an infection in the ovaries or the uterus, not the bladder) in the past 12 months?"). We used SPSS version 18 (IBM Corporation, Somers, New York, USA) and SAS version 9.2 (SAS Institute, USA) for statistical analyses.

Results

Population

From March 2008 to February 2011 a total of 834 971 invitations were sent to 421 820 individuals aged 16-29 years in the three regions (table 1⇓). Of these, 162 096 received an invitation in each of three consecutive years, showing the mobility of the target population. Altogether, 102 283 samples were returned by 79 173 people, and 4252 cases of chlamydia infection were detected. At the time of analysis, 2661 of these cases were retested after six months (uptake 65%). See the figure⇓ for an overview of the study population in different stages of the trial.

Participation

After the first invitation, 16.1% (43 358/269 273) of invitees in blocks A and B returned a specimen; 10.8% (28 803/265 979) returned one after the second invitation; and 9.5% (23 899/251 688) after the third invitation. The participation rate in the control block C (invited after the second invitation in blocks A and B) was 13.0% (6223/48 031). Similar trends in participation rate per round were seen in each region (table 2⇓). Participation in South Limburg was lower than in the cities because of the use of the risk assessment. The downward trend in participation over time was consistent across blocks when stratified by community risk level and cluster size.

Women were more likely to take part than men in all three invitation rounds (odds ratio, 2.34 (95% confidence interval 2.31 to 2.38)). Participation rates were higher among older age groups (odds ratio 1.89 (1.85 to 1.92) for 25-29 year olds *v* 16-19 year olds), Dutch invitees versus invitees of non-Dutch background (odds ratio 1.90 (1.87 to 1.92)), in people living in clusters of low community risk (odds ratio 1.57 (1.54 to 1.61) for low *v* high risk areas), and for people living in postcode areas with high socioeconomic status scores (odds ratio 1.28 (1.24 to 1.33) for high *v* low socioeconomic status). These differences were similar in consecutive screening rounds.

Percentage of positive chlamydia test results (positivity)

The overall chlamydia positivity rate was 4.3% (1851/43 358) among participants in the intervention blocks at the first invitation, 4.0% (1153/28 803) at the second, and 4.1% (981/23 899) at the third invitation (table 3⇓). Chlamydia positivity in the intervention blocks at the first invitation was the same as in the control block (4.3%, table 1⇓) and 0.2% lower at the third invitation than in the control block (odds ratio 0.96 (0.83 to 1.10)). The positivity rates in the control blocks in each region were not all similar with those of the intervention blocks at the start (table 3⇓). The difference between chlamydia positivity in the intervention blocks at the third invitation and in the control block was 0.05% in Amsterdam (3.4% *v* 3.4%, odds ratio 1.01 (0.81 to 1.26)), −0.27% in Rotterdam (5.3% *v* 5.5%, odds ratio 0.95 (0.77 to1.16)), and −1.02% in South Limburg (3.1% *v* 4.1%, odds ratio 0.74 (0.45 to 1.21)) (table 3⇓). In South Limburg the difference reached the minimum level detectable in power calculations, but statistical evidence for a difference was weak because of low participation rates. There were some differences in changes in positivity between blocks A and B but these were not systematically related to community risk level or cluster size. The odds for chlamydia positivity in the first compared with the third invitation in all regions combined, controlling for block allocation, community risk level, and cluster size, was 0.97 (0.90 to 1.05), similar to the unadjusted odds ratio.

Overall, women were more often chlamydia positive than men (4.2% *v* 3.8%, odds ratio 1.12 (1.04 to 1.21)). Chlamydia positivity rates were higher in young people under 20 years old than among older invitees in all three rounds: at the first invitation, 7.1% in <20 year olds, 4.9% in 20-24 year olds, and 2.7% in 25-29 year olds (odds ratio 2.70 (2.47 to 2.95)). There were no marked differences in the change in positivity after two or three invitations according to age. The positivity rate was generally higher in clusters categorised as being at high risk than low risk (6.7% *v* 3.0%, odds ratio 2.30 (2.10 to 2.52)), in postcode areas with low socioeconomic status scores compared with areas with high scores (4.6% *v* 2.4%, odds ratio 1.91 (1.54 to 2.37)) and among participants with non-Dutch background compared with a Dutch background (5.6% *v* 3.4%, odds ratio 1.63 (1.53 to 1.74)). Declines in positivity were slightly greater in high risk clusters than low risk clusters (−0.3% *v* 0.0%), in low socioeconomic status postcodes than high status postcodes (−0.8% *v* −0.1%), and in non-Dutch ethnic groups than Dutch groups (−0.5% *v* −0.1%).

Repeated participation

People who had participated in a previous screening round were more likely to participate again: 28-30% of initial participants responded again when re-invited (round two n=10 474, round three n=8298); 51% of people who participated twice did so again at the third invitation (n=6001), but only 5% of those who had not participated earlier did so on a following invitation. Over three screening rounds, 25% of people who were invited three times participated at least once (39 854), 8.3% participated twice (13 441/162 096), and 2.8% participated three times (4510/162 096). Among the people who participated in all three rounds, the percentage with a positive chlamydia test fell from 5.9% in round one (264/4510) to 2.9% (131/4510) in round three (difference −3.0%, odds ratio 0.49 (0.47 to 0.50)).

Incidence of self reported pelvic inflammatory disease

The question on pelvic inflammatory disease was answered by about 20% of female participants who completed the general questionnaire (n=6420). Of these, 103 (1.6%) answered "Yes" to having been diagnosed with a pelvic infection in the previous year, while 300 women (4.8%) answered "I don't know for sure." Among these "unsure" respondents there were 20 cases

of potential pelvic inflammatory disease, comprising ovarian infections diagnosed by ultrasound or other related medical procedures or reporting symptoms consistent with infection. The incidence of pelvic inflammatory disease among respondents, including these possible cases, would be 1.9%. The self reported incidence did not change over the three invitations: 1.8% (19/1072) at the first invitation, 2.1% (47/2261) at the second, and 1.9% (44/2340) at the third (odds ratio 1.06 (0.62 to 1.83) comparing first with third invite).

Estimated population prevalence

The estimated population prevalence was lower than positivity rates among the screening participants: 2.6% in Amsterdam, 3.7% in Rotterdam, and 3.2% in South Limburg in round one (table 3⇓). The estimated prevalence in the third invitation round was lower than in the control area in Amsterdam (2.5% *v* 3.0%) and South Limburg (1.8% *v* 2.5%), but not in Rotterdam (both 3.9%). Prevalence estimates were generally higher in men than in women; the decline in prevalence was strongest in women aged >20 years.

Discussion

Main findings

In this controlled trial the participation rate was lower than expected from an earlier pilot study and declined over the three screening rounds. The chlamydia positivity rate in the intervention blocks was 4.3% at baseline and 4.1% at the third invitation, compared with 4.3% in the control block. There was no statistical evidence of a reduction in chlamydia positivity in the whole target population from systematic population based screening, although results in South Limburg, where a risk based selection was added, were more promising than in Amsterdam and Rotterdam. Among the people taking part in all three years (2.8% of all participants), chlamydia positivity declined from 6% at the first test to 3% at the third (difference −3.0%, odds ratio 0.49 (0.47 to 0.50)).

Strengths and weaknesses of study

The main strengths of this trial were the evaluation of three yearly rounds of chlamydia screening invitations in different geographical settings in the Netherlands and the use of population registers that showed who had and had not taken part in screening. The stepped wedge design allowed comparisons between screened and non-screened areas in a logistically feasible way.

A limitation to the design of the trial was the non-random allocation of clusters to intervention and control blocks. This might have introduced selection bias if investigators deliberately allocated specific clusters to block A, which was planned to have the most screening rounds. We do not think this happened because the investigators were blinded to the identity of clusters and did not know whether the intervention effect might differ by risk level or cluster size. The subsequent randomisation of the order of implementation within blocks and addition of a third round of screening in block B would also reduce the risk of bias in the results.

The allocation achieved blocks of the required size, and the magnitude of baseline imbalances according to level of chlamydia risk could also have arisen by chance with random allocation, which is acknowledged as a limitation of group level interventions when the number of clusters is limited.[29] Although we stratified the clusters according to community risk level, the intervention and control block were not completely comparable

in all three regions. In addition, cluster allocation could have reduced, but not eliminated, transmission of chlamydia within clusters. Sexual networks do not strictly follow geographical boundaries and the blocks for implementation were not contiguous. Opportunities for chlamydia transmission between clusters receiving screening invitations at different times would dilute the effect of the intervention.

Of note, the participation rate in the control block C was not completely comparable to that achieved after the first invitation in the intervention blocks A and B, but was in between the participation rates in rounds 1 and 2. Invitees in the control group received their first invitation only in the second year of the programme. It is conceivable that the initial uptake was stimulated by the novelty and the boost of the publicity generated at the start of the screening, the effect of which would have waned by the time the control group got the invitation.

In practice, low uptake was probably the greatest barrier to interrupting transmission. The low uptake also made it impossible to estimate chlamydia prevalence reliably using multiple imputation methods. Because of the lower than expected participation, the estimates were extrapolated from a small proportion of the target population. In addition, the weights were based on demographics and proportion of people who are sexually experienced but not other behavioural data. The inverse probability weighting method assumed that prevalence in the unscreened population was the same as in participants with the same demographic profile. This is unlikely because people accepting an offer to be screened for chlamydia had higher levels of sexual risk behaviour and risk of chlamydia infection than the general population, especially at the second and third invitation.[22 28 30] Therefore, we expect that the true prevalence will be lower and the decline steeper.

Comparison with other studies

The results of this randomised trial give new information about the effects of register based chlamydia screening over multiple screening rounds on chlamydia prevalence at modest levels of uptake. To our knowledge, these are the least biased estimates available to date. Previous evidence came from ecological time trend studies showing declines in rates of diagnosed chlamydia or chlamydia positivity from countries conducting opportunistic chlamydia screening from the late 1980s to mid 1990s.[31-33] It is difficult to know how much of the declines in these studies were attributable to screening efforts because this time period coincided with the early phase of the HIV epidemic, when there were major publicity campaigns to encourage safer sexual practices and reductions in sexual risk behaviour.[11]

Participation rates in this trial decreased after each round, which was unexpected. However, this pattern has also been observed for bowel cancer screening in the UK.[34] The uptake of opportunistic chlamydia screening in England has increased over time with coverage of 33% in 2010-11.[14] The studies that examined the feasibility of one-off chlamydia screening invitations showed higher uptake rates. The Dutch Ct-Pilot Screening project achieved 30% participation in highly urbanised areas.[19] The Chlamydia Screening Studies (ClaSS) project in England resulted in a 35% participation rate.[17 18] In those studies, the kits for home collection of specimens were sent to the invitees (which is very costly to sustain), whereas in our trial people had to log in to an internet website to request the kit. In the United States, an internet based project offering chlamydia screening has reported increasing numbers of participants over time but does not actively offer regular

screening, and numbers of test requests are low when related to population size.[35-37]

Interpretation

The aim of the Chlamydia Screening Implementation programme using home collected specimens was to supplement the coverage of existing, clinic based, opportunistic chlamydia testing to reduce the prevalence of chlamydia infection. However, in spite of a personal invitation letter, easy online home based procedures, and the use of text messaging and email reminders to increase response rates, participation was too low to reduce chlamydia transmission in the target population over the three years of the intervention. The impact on self reported pelvic inflammatory disease could not be assessed reliably. It is still possible that register based chlamydia screening could reduce chlamydia prevalence at the population level given more time or in a different population, but we have observed that the coverage and frequency of regular testing needed to achieve this goal were not easy to reach.

There are several possible reasons for the lack of observed effectiveness of chlamydia screening in this trial. First, the intervention might not have been intensive enough to achieve an effect. Second, any effect in the intervention blocks might have been diluted by contamination from unscreened clusters or areas outside the intervention regions. Third, the effective difference in screening coverage between intervention and control blocks was reduced by ongoing opportunistic testing activity.

There are two lines of evidence suggesting that the intensity of the intervention played a role. First, the percentage of positive chlamydia tests fell markedly among people who were screened in all three rounds. This effect was limited to only 3% of all eligible participants, however. The low uptake of yearly screening was in line with reports from Sweden, where, in a 10 year period, only 1.1% of women had 10 tests or more,[38] and the US, which found that in a five year period 0.1% of women aged 15-25 years had a test every year.[39] Second, in South Limburg the positivity and prevalence estimates declined more than in the cities. Here, a risk selection tool made screening more efficient,[27] but it did not reach more people and the findings in this rural area cannot be extrapolated to urban populations directly.

People in both intervention and control blocks had access to chlamydia testing; the average self reported testing rate for the trial age group (16-29 years) in the Netherlands is estimated to be 10-12% per year.[28] The level of regular screening by people tested opportunistically is not known. In the intervention blocks the response rate, restricting the denominator to the sexually active population, was 20% in the first year (25% in women and 13% in men).[22 40] Overall chlamydia test coverage in the first year was therefore about 30% of sexually active 16-29 year olds in the intervention blocks and 10% in the control block. It is not known whether home based sampling replaced testing in existing sexual health services, but visitor numbers at local sexually transmitted infection clinics did not fall during the study period.[41] The positivity rates for chlamydia in sexually transmitted infections clinics (12-13% for 16-29 year olds)[41] and general practice (16% positive of tested[42]) are higher than among those invited for screening, and people tested in sexually transmitted infection clinics report higher numbers of partners in the previous six months, more symptoms of infection, and lower levels of condom use.[41] The behavioural risk profile of the participants in the Chlamydia Screening Implementation programme was higher than that of adults of the same age in the general population.[22] On the other hand, non-responders seemed to be at lower risk of infection and chose not to participate for reasons such as not yet being sexually active, self perceived low risk, or having had a recent test.[22] Participants who tested more than once tended to have higher risk sexual behaviour.[27 43] Self selection should have increased the yield of prevalent infections detected.

Implications for research, practice and policy

The results of this study provide unique data that can be used for future research.[44 45] A dynamic network simulation model, adapted from a previous model[45] and using data from the programme, suggests a proportional decrease of 20-30% in positivity rates for chlamydia after 10 years if register based screening was added to current opportunistic testing.[46] Cost effectiveness analysis indicates that this effect would be too small to reach acceptable incremental cost effectiveness ratios based on either major outcomes averted or quality adjusted life years gained.[47] For clinical practice, the high levels of repeat infections after treatment (9% at six months[48]) suggest that improvements in case management and partner notification would benefit the infected individual.

The findings of the Chlamydia Screening Implementation programme provide valuable practice based evidence showing the limitations of the systematic screening approach in daily reality. This contradicts the suggestion from a modelling study that home based screening could have an impact on chlamydia prevalence within a few years,[49] but supports an earlier UK expert opinion that register based chlamydia screening would not be effective.[50] There is, however, still no evidence of effectiveness for the opportunistic approach chosen for the English National Chlamydia Screening Programme either.[11] The results of the Australian Chlamydia Control and Effectiveness Pilot trial of multiple rounds of opportunistic chlamydia screening in general practice could fill this evidence gap by 2014.[51]

There might be other settings where systematic screening would work, for example in countries with higher prevalence or lower levels of opportunistic testing. Evaluation of interventions in cluster randomised trials with biological end points would be valuable. The register based Chlamydia Screening Implementation programme showed that yearly individual invitations for three years and internet based home sampling were logistically feasible but did not achieve sufficient or sustained levels of uptake and did not reduce chlamydia prevalence when compared with the control population. The results of this trial do not support the national roll out of a register based chlamydia screening programme.

> **What is already known on this topic**
>
> Chlamydia infection is the most common treatable sexually transmitted infection in many industrialised countries
>
> Randomised controlled trials have examined the effect of chlamydia screening on the incidence of pelvic inflammatory disease but not on chlamydia prevalence
>
> All published intervention studies have been limited to a single round of screening. Evidence of the impact of annual chlamydia screening has been limited to ecological and mathematical modelling studies
>
> **What this study adds**
>
> Three yearly rounds of register based chlamydia screening did not achieve a marked reduction in the percentage of people testing positive at each round
>
> Participation rates were low and decreased with each successive round
>
> The results of this trial do not support the national roll out of this register based chlamydia screening programme

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Cite this as: *BMJ* 2012;345:e4316

Tables

Table 1| Baseline characteristics of clusters and individuals in the Chlamydia Screening Implementation programme, by block at enrolment (see text for details)

	Block A			Block B			Block C			Total		
	No of clusters (n=39)	No of individuals (n=55 776)	% of total per block	No of clusters (n=114)	No of individuals (n=213 497)	% of total per block	No of clusters (n=37)	No of individuals (n=48 031)	% of total per block	No of clusters (n=190)	No of individuals (n=317 304)	% of total
Community risk:												
High	7	10 569	18.9	21	36 732	17.2	6	11 331	23.6	34	58 632	18.5
Medium	19	30 401	54.5	54	113 141	53.0	18	23 625	49.2	91	167 167	52.7
Low	13	14 806	26.5	39	63 624	29.8	13	13 075	27.2	65	91 505	28.8
Cluster size (quarters):												
197-1596	26	23 619	42.3	45	45 078	21.1	25	20 702	43.1	96	89 399	28.2
1597-2209	5	9080	16.3	29	55 063	25.8	7	13 324	27.7	41	77 467	24.4
2210-2825	5	12 257	22.0	24	60 219	28.2	2	4484	9.3	31	76 960	24.3
2826-4538	3	10 820	19.4	16	53 137	24.9	3	9521	19.8	22	73 478	23.2
Region:												
Amsterdam	13	25 072	45.0	56	114 847	53.8	13	18 626	38.8	82	158 545	50.0
Rotterdam	10	17 543	31.5	42	85 792	40.2	10	16 533	34.4	62	119 868	37.8
South Limburg	16	13 161	23.6	16	12 858	6.0	14	12 872	26.8	46	38 891	12.3
Gender:												
Male	—	26 928	48.3	—	102 534	48.0	—	23 884	49.7	—	153 346	48.3
Female	—	28 848	51.7	—	110 963	52.0	—	24 147	50.3	—	163 958	51.7
Age (years):												
16-19	—	12 406	22.2	—	45 667	21.4	—	9574	19.9	—	67 647	21.3
20-24	—	20 569	36.9	—	77 599	36.3	—	18 581	38.7	—	116 749	36.8
25-29	—	22 801	40.9	—	90 231	42.3	—	19 876	41.4	—	132 908	41.9
Ethnic origin†:												
Dutch	—	29 670	53.2	—	105 018	49.2	—	24 692	51.4	—	159 380	50.2
Surinamese/Antillean	—	4210	7.5	—	24 195	11.3	—	4315	9.0	—	32 720	10.3
Turkish/Moroccan	—	9293	16.7	—	33 593	15.7	—	7801	16.2	—	50 687	16.0
Sub-Saharan African	—	1727	3.1	—	7804	3.7	—	1814	3.8	—	11 345	3.6
Other	—	10 876	19.5	—	42 887	20.1	—	9409	19.6	—	63 172	19.9
Participation and chlamydia test positivity												
Participation (%)	15.5			16.3			13.0			15.6		
Chlamydia positivity (%)	4.31			4.27			4.30			4.28		

Table 2| **Participation in chlamydia screening, by region, sex, and screening invitation**

	No of people invited	No of people participated	Participation rate (% (95% CI))*
Total:	834 971	102 283	12.2 (11.7 to 12.8)
1st invitation	269 273	43 358	16.1 (15.3 to 16.9)
2nd invitation	265 979	28 803	10.8 (10.3 to 11.4)
3rd invitation	251 688	23 899	9.5 (9.0 to 10.0)
Control	48 031	6223	13.0 (11.4 to 14.7)
Region			
Amsterdam:			
1st invitation	139 919	24 059	17.2 (16.4 to 18.3)
2nd invitation	136 689	16 355	12.0 (11.2 to 12.8)
3rd invitation	133 736	13 866	10.4 (9.6 to 11.3)
Control	18 626	2899	15.6 (12.5 to 19.3)
Rotterdam:			
1st invitation	103 335	16 414	15.8 (14.6 to 17.1)
2nd invitation	104 692	10 753	10.2 (9.5 to 11.0)
3rd invitation	104 885	9057	8.7 (8.0 to 9.4)
Control	16 533	2254	13.6 (11.8 to 15.6)
South Limburg:			
1st invitation	26 019	2885	11.1 (10.1 to 12.3)
2nd invitation	24 598	1687	6.9 (6.2 to 7.6)
3rd invitation	13 067	874	6.7 (5.8 to 7.6)
Control	12 872	1070	8.3 (7.1 to 9.8)
Gender			
Male:			
1st invitation	129 462	13 617	10.5 (10.0 to 11.0)
2nd invitation	128 299	8616	6.7 (6.4 to 7.0)
3rd invitation	121 156	6970	5.8 (5.5 to 6.0)
Control	23 884	2025	8.5 (7.6 to 9.5)
Female:			
1st invitation	142 419	29 831	21.3 (20.3 to 22.3)
2nd invitation	141 078	20 246	14.7 (13.9 to 15.4)
3rd invitation	131 010	16 853	13.0 (12.2 to 13.8)
Control	24 172	4199	17.4 (15.1 to 19.9)

*Confidence intervals are corrected for cluster effect (inter-cluster effect on participation was significant).

Table 3| Chlamydia test positivity and estimated population prevalence, by region, sex and screening invitation

	No of people who participated	No (%) positive for chlamydia	Change in positivity from 1st invite (%)	Change in positivity compared with control block		Estimated prevalence (% (95% CI))*
				Change (%)	Odd ratio (95% CI); P value	
Total:	102 283	4252 (4.2)				2.7
1st invitation	43 358	1851 (4.3)	—	−0.02	1.00 (0.87 to 1.13); 0.94	2.6
2nd invitation	28 803	1153 (4.0)	−0.3	−0.29	0.93 (0.81 to 1.07); 0.30	2.6
3rd invitation	23 899	981 (4.1)	−0.2	−0.19	0.96 (0.83 to 1.10); 0.52	2.6
Control	6223	267 (4.3)	—	—	1.00 (reference)	3.0
Region						
Amsterdam:						
1st invitation	24 059	871 (3.6)	—	0.24	1.07 (0.87 to 1.33); 0.51	2.6 (2.4 to 2.8)
2nd invitation	16 355	565 (3.5)	−0.2	0.07	1.02 (0.82 to 1.27); 0.84	2.5 (2.3 to 2.7)
3rd invitation	13 866	476 (3.4)	−0.2	0.05	1.01 (0.81 to 1.26); 0.92	2.5 (2.2 to 2.7)
Control	2899	98 (3.4)	—	—	1.00 (reference)	3.0 (2.1 to 3.9)
Rotterdam:						
1st invitation	16 414	834 (5.1)	—	−0.46	1.06 (0.95 to 1.19); 0.30	3.7 (3.4 to 3.9)
2nd invitation	10 753	519 (4.8)	−0.3	−0.72	0.91 (0.75 to 1.11); 0.36	3.5 (3.2 to 3.8)
3rd invitation	9057	478 (5.3)	0.2	−0.27	0.95 (0.77 to 1.16); 0.60	3.9 (3.6 to 4.3)
Control	2254	125 (5.5)	—	—	1.00 (reference)	3.9 (3.2 to 4.6)
South Limburg:						
1st invitation	2885	146 (5.1)	—	0.95	1.24 (0.88 to 1.75); 0.22	3.2 (2.7–3.6)†
2nd invitation	1687	69 (4.1)	−1.0	−0.02	0.99 (0.67 to 1.46); 0.96	2.6 (2.4–2.8)†
3rd invitation	874	27 (3.1)	−2.0	−1.02	0.74 (0.45 to 1.21); 0.23	1.8 (1.7–1.9)†
Control	1070	44 (4.1)	—	—	1.00 (reference)	2.5 (2.3–2.6)†
Gender						
Male:						
1st invitation	13 617	522 (3.8)	—	−0.22	0.94 (0.74 to 1.20); 0.64	3.5
2nd invitation	8616	318 (3.7)	−0.1	−0.36	0.91 (0.71 to 1.16); 0.45	3.3
3rd invitation	6970	283 (4.1)	0.2	0.01	1.00 (0.78 to 1.29); 0.98	3.6
Control	2025	82 (4.0)	—	—	1.00 (reference)	3.8
Female:						
1st invitation	29 831	1329 (4.5)	—	0.05	1.02 (0.87 to 1.19); 0.85	3.1
2nd invitation	20 246	835 (4.1)	−0.3	−0.28	0.94 (0.80 to 1.10); 0.43	2.7
3rd invitation	16 853	698 (4.1)	−0.3	−0.26	0.93 (0.79 to 1.10); 0.42	2.9
Control	4199	185 (4.4)	—	—	1.00 (reference)	3.1

*Confidence intervals are not corrected for cluster effect (inter-cluster effect on positivity was not significant). Confidence intervals could not be calculated for South Limburg, so they are also unavailable for the total population and estimates by gender.

†Values are intermediates with high and low estimates rather than confidence intervals.
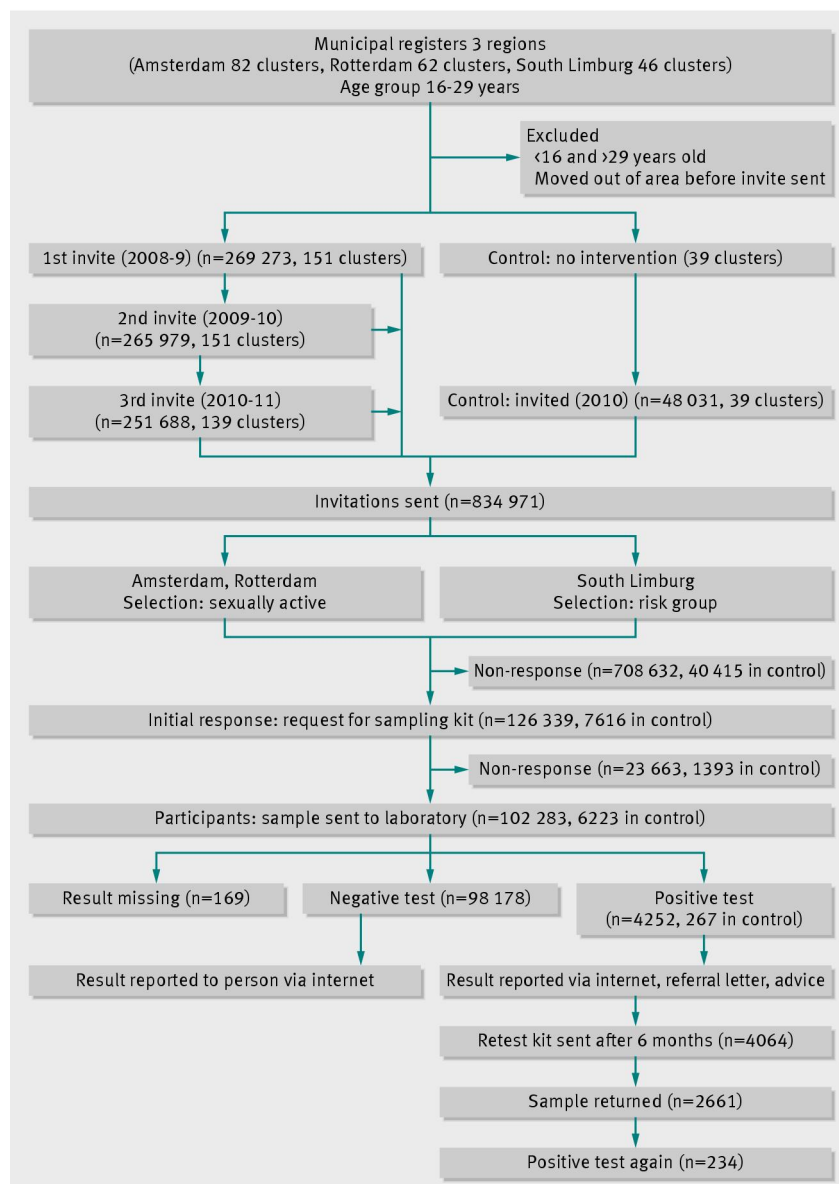
Figure

Fig Flow chart of the Chlamydia Screening Implementation programme