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**Impact of intensified testing for urogenital *Chlamydia trachomatis* infections:
A randomized study with nine year of follow-up**

by

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Abstract

Background

DNA amplification assays are increasingly being used to facilitate testing of asymptomatic individuals for urogenital *Chlamydia trachomatis*. The long-term clinical benefit in terms of avoided infertility and ectopic pregnancy is unknown.

Methods

In 1997, a total of 15,459 women and 14,980 men aged 21–23 were living in Aarhus County, Denmark. A random sample of 4,000 women and 5,000 men were contacted by mail and offered the opportunity to be tested for *C. trachomatis* by means of a sample obtained at home and mailed directly to the laboratory. The remaining 11,459 women and 9,980 men received usual care and constituted the control population. All men and women were subsequently followed for nine years by use of Danish health registers. We collected data on pelvic inflammatory disease (PID), ectopic pregnancy (EP), infertility diagnoses, in-vitro fertilization (IVF) treatment, and births in women, and on epididymitis in men. The intervention and control groups were compared using Cox regression analyses and the intention-to-screen principle.

Results

Among women, we found no differences between the intervention group and the control group: hazard ratios (95% confidence interval) for: PID, 1.12 (0.70–1.79); EP, 0.97 (0.63–1.51); infertility, 0.87 (0.71–1.07); IVF treatment, 0.88 (0.62–1.26); and births, 1.02 (0.95–1.10). In men, the hazard ratio for epididymitis was 1.25 (0.70–2.24).

Conclusions

A population based offer to be tested for urogenital *C. trachomatis* infection by use of non-invasive samples and DNA-amplification did not reduce the long-term risk of reproductive complications in women or epididymitis in men.

Trial registration number – in www.clinicaltrials.gov: NCT 00827970

Introduction

C. trachomatis can cause urogenital infections, and might cause pelvic inflammatory disease (PID), ectopic pregnancy (EP), and infertility in women.¹⁻³ The organism is frequently asymptomatic, and the United States Centre for Disease Control and Prevention,⁴ Australia,⁵ The Netherlands,⁶ and England⁷ all recommend regular testing of young women using sensitive DNA amplification assays. However, only sparse scientific evidence supports the hypothesis that widespread testing of asymptomatic individuals for *C. trachomatis* DNA will reduce the risk of later reproductive complications⁸

Two randomized trials reported fewer PID cases after one year of follow-up in high-risk women and high-school women tested once for *C. trachomatis*.^{9,10} However, the benefit of widespread testing - in terms of avoidance of long-term reproductive complications such as EP and infertility - has not been studied in controlled intervention trials; nor has the benefit of widespread testing of men. The major obstacle for conducting such studies is that the damage to reproductive organs caused by a *C. trachomatis*, i.e. EP or infertility, may be noted only several years later, when the woman wants to conceive. This obstacle can be overcome by performing randomized studies in communities with unique personal identification numbers and high-validity registers of discharge diagnoses. The Danish health care system provides this scenario¹¹.

In 1997 we performed a population-based intervention trial in which young men and women were randomized to either an offer to be tested for *C. trachomatis* by use of a home obtained and mailed sample or usual care¹². In the present paper we report the effect of this intervention after nine years of follow-up in terms of PID, EP or infertility in women and epididymitis in men.

Methods

Study population

The study was carried out in the county of Aarhus, which in 1997 had a population of approximately 650,000 inhabitants (12% of the Danish population). In Denmark, all inhabitants are registered in the county health service register by use of their personal identification number (CPR number). This number, which is unique to every Danish citizen, incorporates sex and date of birth, and permits accurate linkage of information between registers. In the county health service register, we identified the CPR numbers of all women and men who were born in 1974, 1975, or 1976 and were living in the County of Aarhus by 13 October 1997 (aged 21 to 24 at initiation of the study). This age-group was chosen as it had the highest prevalence of infection according to the local register at the Department of Microbiology, Aarhus University Hospital. A total of 15,459 women and 14,980 men fulfilled these inclusion criteria and were included in the study.

Intervention

The intervention was described in an earlier publication¹² and is only briefly described here (Figure 1). In October 1997, a group of 4,000 women and 5,000 men were randomly selected from the study population. The 9,000 individuals were all offered a test for *C. trachomatis* by use of samples obtained at home. The remaining 11,459 women and 9,980 men constituted the control group. In the period between 31 October 1997 and 6 December 1997, all 9,000 participants in the intervention group received an invitation by direct mail to be tested for *C. trachomatis* by taking a sample at home and mailing it directly to the diagnostic laboratory. The intervention group was further subdivided into two randomly assigned groups (group 1 and group 2), each containing 2,000 women and 2,500 men. The difference between intervention groups 1 and 2 was that group 1 participants received the test package together with the invitation, whereas group 2 participants had to return a prestamped, preaddressed reply card to the study centre to receive the test package. The participation rates and number of detected

infections due to our intervention are described in Figure 1. A total of 1,175 women (29.4%) and 1,033 men (20.7%) were tested as part of the intervention and 84 *C. trachomatis* infections in women and 60 *C. trachomatis* infections in men were identified (prevalence 7.1% and 5.8 %, respectively).

Usual care

Individuals in the intervention groups as well as those in the control group had the opportunity of usual care consisting of an endocervical and/or urethral swab sample taken by a physician in his/her office. Free testing is available in Denmark. In the study period of three months 9.4 % of women in the control group and 9.0 % of women in the intervention group were tested as part of usual care. For men the corresponding figures were 1.4 % and 1.5 % for the two groups, respectively (for details see reference 12).

Randomization

A computer-based randomization was performed by administration personnel of Aarhus County. To check that the randomization of individuals was successful, we collected data on important social characteristics by use of the CPR numbers (both intervention groups and control group). Data regarding living status, occupation, and country of origin were collected from the governmental agency Statistics Denmark.

Treatment of infected individuals

In the present study infected individuals should contact a general practitioner (GP) for medical treatment and partner notification. In a previous study¹³ this procedure facilitated treatment of at least 95% of individuals (unpublished data). From a previous study we also know that more than 85% of *C. trachomatis* infected individuals seen by a GP in our area receive either medical treatment to current partner immediately (patient expedited partner therapy) or test of current partner is facilitated (by patient referral)¹⁴.

In the present study all *C. trachomatis* positive individuals also received a second offer to be tested for the infection by use of a home-obtained and mailed sample 24 weeks after

the initial test. A total of 59 women were tested and three were *C. trachomatis* positive for the second time. The corresponding number in males was that 32 submitted a second sample and one was *C. trachomatis* positive for the second time¹⁵.

Outcomes: PID and epididymitis

The entire study population (comprising individuals who accepted the test offer, those who did not, and the control group) was followed in central governmental registers during the first year after the test offer to assess the rates of PID (women) or epididymitis (men). In Denmark, these patients are treated either in hospitals or in general practices.

Treatment in hospital. All patients admitted to a hospital in Denmark are registered by their CPR number in the Danish Hospital Discharge Registry and classified according to the Danish versions of the ICD-10 (since 1994). The discharge registry was evaluated previously, and it was found that 87% of the codes for diagnoses were in accordance with the hospital case records for paediatrics, general surgery and gynaecology/obstetrics¹¹. In our study the codes used for PID were: N700, N709, N710, N719, N730, N733, N735, N738, O030, O035, O040, O045, O070, and the codes used for epididymitis were: N450 and N459.

Outpatient treatment – Patients receiving antibiotic treatment outside of hospitals in Denmark are registered by use of the CPR number in Statistics Denmark, according to the type of medication prescribed by the doctor. Outpatient treatment of PID and epididymitis caused by *C. trachomatis* is mainly handled in general practices. From a minor study performed in our community, we knew that one-tenth of the general practitioners (GPs) would refer a suspected case of PID or epididymitis for treatment in a hospital, and one-third of GPs would treat a PID in their practice by use of doxycycline (an antibiotic that is not used to treat many other conditions in Denmark) (B. Andersen, personal communication). Therefore, we collected data on the use of doxycycline from Statistics Denmark.

For the purposes of this study, we defined PID in women and epididymitis in men as being registered with one of the relevant ICD-10 codes in the Danish Hospital Discharge Registry or receiving doxycycline after having consulted a GP.

Outcomes: in vitro fertilization treatment

Women in Denmark receiving fertility treatment, whether it is in a public or private hospital, are registered in a central registry at the National Board of Health using their CPR number. In this registry, the type of treatment received and the date, place, and results of treatment are registered. All women were followed in this register until the end of 2004 (the latest year of complete data) or until they underwent an in vitro fertilization (IVF) procedure.

Outcomes: EP, female infertility, and births

All of the women in the study population were followed-up via the Danish Hospital Discharge Registry for nine years after randomization. The following outcomes were considered: discharge diagnosis of EP, infertility, or childbirth. The codes used were O00 (all sub-codes) for EP; N97 (all sub-codes) for female infertility; and O80, O81, O82, O83, or O84 (all sub-codes) for childbirth. Women were followed in this register until the end of 2006.

Power calculation

We used a power of 80% and an alpha of 5% to calculate the statistical power. We considered the risk of PID for women in the control group to be 3%¹⁶, and we wanted to be able to detect a 1% minimum reduction in the number of PID cases in the intervention group compared with the control group (intention-to-screen analysis). These assumptions required inclusion of 3,607 women in the intervention group and 10,821 women in the control group, which was less than the total actual number included in our study.

Statistical analyses

For the intention-to-screen analyses, we compared the occurrence of outcomes between those who received no intervention (control group) at baseline and those who received the intervention (intervention group). For this purpose, data regarding the two types of approach strategies were

merged. In the Cox regression analysis, individuals were followed from the time of randomization (October 31, 1997) to the first date of an event. If no event occurred, the follow-up ended on February 5, 1999 for PID and epididymitis (one year after the last test was performed as part of the intervention), by the end of 2004 for the outcome of IVF treatment, and by the end of 2006 for all other outcomes.

First, we calculated the number of events per 100 person-years at risk for the total population and for individuals in the intervention group and the control group. The corresponding hazard ratio (control group compared with intervention group) and 95% confidence interval (CI) was calculated for each event. Second, we performed a subanalysis within the intervention group by calculating the events per 100 person-years at risk and the corresponding hazard ratios for participants and nonparticipants. Separate analyses were not conducted for *C. trachomatis*-positive test results compared with *C. trachomatis*-negative results, because the numbers of events in each subgroup were too low to allow calculation of hazard ratios.

Stata 9 was used for statistical analysis of data.

Approval

The study was approved by the local Ethical Committee in the County of Aarhus and by the Danish Data Protection Agency.

Results

As seen from Table 1, approximately one fourth of the study population lived alone, one fourth lived with a partner without being married, and one fifth were married. The remaining participants lived with their parents or had other arrangements. The majority were employed, while about 12% were students and 12% received welfare payments. Only 5% were immigrants. These characteristics were well balanced between the intervention and the control group after randomization.

Table 1: Living status, occupation and country of origin for all randomised individuals. Data are extracted from Danish registers.

	Intervention <i>n</i> = 9,000		Control <i>n</i> = 21,439		All participants <i>n</i> = 30,439	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
Living status*						
- Living alone	2,457	27.3%	5,718	26.7%	8,175	26.8%
- Married	1,644	18.3%	3,759	17.7%	5,403	17.8%
- Living with partner [†]	2,218	24.7%	5,493	25.6%	7,711	25.3%
Occupation*						
- student	1,150	12.8%	2,896	13.5%	4,046	13.3%
- employed	6,323	70.3%	14,935	69.6%	21,258	69.8%
- unemployed	354	3.9%	831	3.8%	1,185	3.9%
- welfare payment [‡]	1,104	12.3%	2,647	12.3%	3,751	12.3%
Origin*						
- Danish	8,411	93.5%	20,067	93.6%	28,478	93.5%
- Immigrant	467	5.1%	1,122	5.2%	1,589	5.2%
- Descendant	53	0.6%	120	0.6%	173	0.6%

*The numbers do not add up to 100% because of other possible categories and missing data.

[†]Living with partner but not married.

‡Not including students.

Among the entire population of 15,459 women, 97 had a diagnosis of PID within the first year (6.3 cases per 1,000 women). Twenty-three of these women were admitted to hospital and 74 were treated in general practice. During the entire nine-year study period, a total of 102 women were hospitalized with EP (0.73 cases per 1,000 women), 451 had a diagnosis of infertility (3.2 cases per 1,000 women), and 3,800 gave birth to at least one child (27.3 birth per 1,000 women). During the seven-years follow-up for IVF treatment, 152 received this procedure (1.4 per 1,000 women). During one year of follow-up for the 14,980 men, seven were discharged from a hospital with a diagnosis of epididymitis and 49 received treatment in general practice (3.9 per 1,000 men) (Figure 1).

The intention-to-treat analysis (Table 2) of women revealed no differences between the intervention group and the control group with regard to all outcome measures (hazard ratio [95% CI]): PID, 1.12 (0.70–1.79); EP: 0.97 (0.63–1.51); infertility, 0.87 (0.71–1.07); IVF treatment 0.88 (0.62–1.26); and births, 1.02 (0.95–1.10). In the analysis of men, we found no significant reduction in epididymitis, with a hazard ratio of 1.25 (95% CI: 0.70–2.24).

Table 2

Comparison of long-term effects of *C. trachomatis* testing in the intervention group vs. the control group (intention-to-screen analysis).

	Control group <i>n</i> = 21,439		Intervention group <i>n</i> = 9,000		HR	95% Confidence intervals
	IR	<i>n</i>	IR	<i>n</i>		
Women		11,459		4,000		
PID	0.51	74	0.45	23	1.12	0.70 to 1.79
EP	0.072	75	0.074	27	0.97	0.63 to 1.51
Infertility	0.31	322	0.36	129	0.87	0.71 to 1.07
IVF treatment	0.13	109	0.15	43	0.88	0.62 to 1.26
Births	3.03	2833	2.97	967	1.02	0.95 to 1.10
Men		9,980		5,000		
Epididymitis	0.32	40	0.25	16	1.25	0.70 to 2.24

For the PID and epididymitis diagnoses, the follow-up time was one year. For IVF treatment, the follow-up time was seven years, and for all other outcomes, the follow-up time was nine years. Cox regression analyses were performed.

HR, hazard ratio; IR, incidence rate per 100 person-years at risk.

A subanalysis of those who accepted the test offer and those who did not is shown in Table 3. No statistically significant differences were found for any of the outcomes among women or men.

Table 3

Comparison of long-term effects of *C. trachomatis* testing for participating and non participating individuals in the intervention group.

	Nonparticipants <i>n</i> = 6,792		Participants <i>n</i> = 2,208		HR	95% Confidence intervals
	IR	<i>n</i>	IR	N		
Women		2,825		1,175		
PID	0.45	16	0.47	7	0.96	0.40 to 2.34
EP	0.07	19	0.07	8	1.00	0.44 to 2.28
Infertility	0.33	85	0.41	44	0.81	0.56 to 1.17
IVF-treatment	0.15	31	0.14	12	1.09	0.56 to 2.12
Births	2.87	659	3.19	308	0.90	0.79 to 1.03
Men		3,967		1,033		
Epididymitis	0.20	10	0.46	6	0.44	0.14 to 1.20

For the PID and epididymitis diagnoses, the follow-up time was one year. For IVF treatment, the follow-up time was seven years, and for all other outcomes, the follow-up time was nine years. Cox regression analyses were performed.

HR, hazard ratio; IR, incidence rate per 100 person-years at risk.

Discussion

In this randomized study we included more than 30,000 individuals and offered 9,000 of these the opportunity to be tested for *C. trachomatis* by use of a non-invasive sample. We found no impact of this intervention on PID, EP, or fertility complications in women or epididymitis in men.

The three major strengths of this study were its randomized design, its long-term follow-up, and the unique Danish citizen numbers that allowed for complete follow-up of the entire study population in high validity national registers¹¹. Population-based randomized studies with long follow up at the level of the individual level is a unique possibility in countries with a registration system as in the Scandinavian countries.

A weakness in our study was the lack of a precise diagnosis for PID. Most PID diagnoses are obtained by clinical examination only, rather than by laparoscopy. There is no doubt that we were not able to include all diagnoses in our study, not even all correct PID diagnoses because the proxy doxycycline was the only measure we had for this diagnosis in general practice. This is also reflected in the fact that an incidence of PID on 3% was not reached in the study as we expected from the power-calculation, which may wrongly result in rejection of the hypothesis that widespread testing prevents PID. However, as this was a randomized study, the impact of this possible lack of consistency probably had an equal effect in both groups. There is a tendency towards a slightly lower incidence of PID in the intervention group compared to the control-group but this was not significant and would not have been significant if the expected incidence was actually reached in the same proportion of individuals. In contrast, the outcome measures of EP, IVF treatment, and delivery were precise, but the relatively short follow-up period for these conditions may result in underestimation of the effect of the intervention .

Partner notification (PN) is important in STI control and lack of PN can possibly eliminate the effect of testing for *C. trachomatis* since index-patients can very quickly be re-infected. In our study PN was not measured, but only few infected individuals were *C.*

trachomatis positive six months later. This indicates that lack of PN was not a major problem in our study, but we cannot completely ignore a dilution of a positive effect of the intervention.

This is the first study to report the effect of intensified testing for *C. trachomatis* on long-term reproductive complications EP, infertility, IVF-treatment and birth in women and epididymitis in men. Two earlier studies reported the effect of a single test offer on PID in women within one year after the intervention^{9, 10, 13} and both studies reported a reduction in PID incidence in contrary to our study. The study by Scholes et al⁹ was performed in a high-risk population which, therefore, does not permit its direct comparison with the present study. The study by Ostergaard et al¹⁰ was in high-schools, which is also a low low-risk population, but this study experienced considerable drop-out before follow-up (a drop-out that differed between the intervention group and the control group), and the outcome measures were based on self-reports. The use of a registry-based design allowed us to overcome these types of bias.

Negative results should always prompt considerations of study design. In our study such a consideration could be that the power of the study was not strong enough, but in comparison with comparable randomised studies^{9, 10} (645 tested women with 44 detected infections and 867 tested women with 43 detected infections), the strength of our study should be sufficient to show an effect for the outcome PID. It could also be argued that only one fourth of the invited individuals in our study participated in the intervention and as in cancer screening studies nonparticipants could be at a higher risk for a complication than participants. However, a comparison of different *C. trachomatis* screening studies shows that the prevalence tends to decline the higher the participation rate indicating that some kind of self-selection takes place¹⁷. Also in our analysis of nonparticipants¹² we found that those who declined the invitation to be tested probably had a lower infection risk than those who accepted the invitation. Testing of asymptomatic individuals may give rise to psychosocial problems for the tested individuals^{18, 19} and the positive predictive value of a test decreases as the prevalence decreases. Testing asymptomatic individuals for *C. trachomatis*, benefits and harms should be balanced.

Evidence for the natural history of asymptomatic *C. trachomatis* infections is clearly not strong²⁰. Our knowledge of the association between *C. trachomatis* infections and PID, EP, and infertility stems from important landmark studies by Weström et al.^{1, 21}. These studies showed that PID was often followed by fertility complications later in life. However, the studied populations were not divided into patients with *C. trachomatis* infection and other urogenital tract infections. Subsequently, numerous seroepidemiological studies²²⁻²⁷ have supported the idea that asymptomatic infections facilitate fertility complications. However, these studies have a retrospective design and are based on serology, which may have invited erroneous conclusions.²⁸ On the contrary, in a small study by Morré et al,²⁹ 30 women with an untreated, asymptomatic *C. trachomatis* infection were followed for a year and none of them developed PID. In a very recent study by Oakeshott et al³⁰ 2529 women were randomised to either immediately test and treatment or no intervention. Within one year 9.5% of control women compared to 1.6% of women in the intervention group developed PID. This difference seemed apparent but was not statistically significant and the authors conclude that the effectiveness of a single Chlamydia test in preventing PID may have been overestimated. This conclusion corresponds with the findings of our study. It can be suggested that a major study will show an effect of an intervention, but the overall effect of *C. trachomatis* testing on the development of PID has earlier been overestimated. It may be that the natural history of *C. trachomatis* infection has changed over time or that the highly sensitive DNA-amplification methods to detect *C. trachomatis* also detects potentially harmless asymptomatic infections and even dead organisms.

In conclusion, our study found that a single round of testing for *C. trachomatis* by DNA amplification assay was not associated with clinical benefit in terms of fewer later reproductive complications. This may be so because the new DNA amplification tests are too sensitive and detect infections that would not lead to later complications, or because the natural history of *C. trachomatis* infections has changed. A major study or several rounds of screening may change the conclusion but based on existing evidence and the results of this study we

suggest that the rationale for widespread *C. trachomatis* testing should be re-evaluated. Possible benefits should be weighed against harms. When screening interventions are considered a key question should be how to evaluate the intended outcomes in order to obtain more answers and add to the evidence base within this field.

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Contributions of authors:

All authors participated in design of the study, interpretation of data and editing of the manuscript. BA also ran the intervention and wrote the paper, and IS also performed the statistical analyses.

Statement:

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Key messages:

- A widespread offer in a Danish population aged 21 to 24 years to be tested for *C. trachomatis* infection by use of a home-obtained and mailed sample was successful in terms of number of tested individuals and detected infections.
- After one to nine years of follow-up the intervention could not be shown to have any impact on pelvic inflammatory disease, ectopic pregnancy or infertility in women or epididymitis in men.
- Long term effect of widespread testing for *C. trachomatis* is still unknown.

Reference List

1. Westrom L. Effect of acute pelvic inflammatory disease on fertility. *Am J Obstet Gynecol.* 1975;121:707-713.
2. Mardh PA, Ripa T, Svensson L et al. *Chlamydia trachomatis* infection in patients with acute salpingitis. *N Engl J Med.* 1977;296:1377-1379.
3. Hillis SD, Joesoef R, Marchbanks PA et al. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. *Am J Obstet Gynecol.* 1993;168:1503-1509.
4. Chlamydia screening among sexually active young female enrollees of health plans-United States, 1999-2001. *MMWR Morb Mortal Wkly Rep.* 2004;53(42):983-985.
5. Hocking JS, Walker J, Regan D. Chlamydia screening - Australia should strive to achieve what others have not. *Med J Aust.* 2008;188(2):106-108.
6. Sheldon T. Holland plans chlamydia screening in 300,000 young people. *BMJ.* 2007;335(7631):1177.
7. LaMontagne DS, Fenton KA, Randall S et al. Establishing the National Chlamydia Screening Programme in England: results from the first full year of screening. *Sex Transm Infect.* 2004;80:335-341.
8. Low N, Bender N, Nartey L et al. Effectiveness of chlamydia screening: systematic review. *Int J Epidemiol.* 2009;38:435-48.
9. Scholes D, Stergachis A, Heidrich FE et al. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. *N Engl J Med.* 1996;334:1362-1366.
10. Ostergaard L, Andersen B, Moller JK et al. Home sampling versus conventional swab sampling for screening of *Chlamydia trachomatis* in women: a cluster-randomized 1-year follow-up study. *Clin Infect Dis.* 2000;31(4):951-957.
11. Andersen TF, Madsen M, Jorgensen J et al. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull.* 1999;46:263-268.
12. Andersen B, Olesen F, Møller JK et al. Population-Based Strategies for Outreach Screening of Urogenital *Chlamydia trachomatis* infections: A Randomised Controlled Trial. *J Infect Dis.* 2002;185:252-258.
13. Østergaard L, Andersen B, Olesen F et al. Efficacy of home sampling for universal screening of *Chlamydia trachomatis*. *BMJ.* 1998;317:26-27.
14. Andersen B, Østergaard L, Nygård B et al. Urogenital *Chlamydia trachomatis* infections in general practice: diagnosis, treatment, follow-up and contact tracing. *Fam Pract.* 1998;15(3):223-228.
15. Andersen B, Kjaer HO, Møller JK et al. Follow-up after asymptomatic urogenital *Chlamydia trachomatis* infection. Comparative cohorte study. In: Schachter Jeal, editor.

Proceedings of the Tenth International Symposium on Human Chlamydial Infections. 2002:161-164.

16. Land JA, Van Bergen JE, Morre SA et al. Epidemiology of *Chlamydia trachomatis* infection in women and the cost-effectiveness of screening. *Hum Reprod Update*. 2010;16(2):189-204.
17. European Centre for Disease Prevention and Control. Technical report: Review of Chlamydia control activities in EU countries. 2008.
18. Kangas I, Andersen B, Olesen F et al. Psychosocial impact of *Chlamydia trachomatis* testing in general practice. *Br J Gen Pract*. 2006;56 (529):587-593.
19. Duncan B, Hart G, Scoular A et al. Qualitative analysis of psychosocial impact of diagnosis of *Chlamydia trachomatis*: implications for screening. *BMJ*. 2001;322(7280):195-199.
20. Wallace LA, Scoular A, Hart G et al. What is the excess risk of infertility in women after genital chlamydia infection? A systematic review of the evidence. *Sex Transm Infect*. 2008;84(3):171-175.
21. Westrom L, Joesoef R, Reynolds G et al. Thompson SE. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. *Sex Transm Dis*. 1992;19(4):185-192.
22. Hawes LA, Gilbert GL. Seroepidemiology of *Chlamydia trachomatis* infection in infertile women in Melbourne. *Med J Aust*. 1986;145(10):497-499.
23. Mehanna MT, Rizk MA, Eweiss NY et al. Chlamydial serology among patients with tubal factor infertility and ectopic pregnancy in Alexandria, Egypt. *Sex Transm Dis*. 1995;22(5):317-321.
24. Reniers J, Collet M, Frost et al. Chlamydial antibodies and tubal infertility. *Int J Epidemiol*. 1989;18(1):261-263.
25. Thejls H, Gnarpe J, Lundkvist O et al. Diagnosis and prevalence of persistent chlamydia infection in infertile women: tissue culture, direct antigen detection, and serology. *Fertil Steril*. 1991;55(2):304-310.
26. Brunham RC, Peeling R, Maclean I et al. *Chlamydia trachomatis*-associated ectopic pregnancy: serologic and histologic correlates. *J Infect Dis*. 1992;165(6):1076-1081.
27. Coste J, Laumon B, Bremond A et al. Sexually transmitted diseases as major causes of ectopic pregnancy: results from a large case-control study in France. *Fertil Steril*. 1994;62:289-295.
28. Johnsen S, Andersen PL, Stanek G et al. Chlamydia antibody response in healthy volunteers immunized with nonchlamydial antigens: a randomized, double-blind, placebo-controlled study. *Clin Infect Dis*. 2003;36:586-591.
29. Morre SA, van den Brule AJ, Rozendaal L et al. The natural course of asymptomatic *Chlamydia trachomatis* infections: 45% clearance and no development of clinical PID after one-year follow-up. *Int J STD AIDS*. 2002;13 Suppl 2:12-8.:12-18.

30. Oakeshott P, Kerry S, Aghaizu A et al. Randomised controlled trial of screening for *Chlamydia trachomatis* to prevent pelvic inflammatory disease: the POPI (prevention of pelvic infection) trial. *BMJ*. 2010;340:c1642.

Randomization

15,459 women and 14,980 men were included.
Inclusion criteria: Living in Aarhus county on 13 Oct 1997 and born in 1973, 1974 or 1975

Intervention group 4,000 women and 5,000 men

Control group
11,459 women
9,980 men

Intervention

Screening group 1
2,000 women
2,500 men
Intervention:
Direct mailing of testkit

Screening group 2
2,000 women
2,500 men
Intervention:
Direct mailing of a reply card

No intervention

Result of intervention

Women: 1,175 tested (29.4%) and 84 *C. trachomatis* infections (7.1%) detected
Men: 1,033 tested (20.7%) and 60 *C. trachomatis* infections (5.8%) detected

Follow-up

NUMBER OF OUTCOMES

Women: PID: 23
EP: 27
Infertility: 129
IVF treatment: 43
Births: 967

Men: Epididymitis: 16

NUMBER OF OUTCOMES

Women: PID: 74
EP: 75
Infertility: 322
IVF treatment: 109
Births: 2833

Men: Epididymitis: 40

Figure: Flow-chart for individuals in the study