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# Impact of intensified testing for urogenital *Chlamydia trachomatis* infections: a randomised study with 9-year follow-up

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## ABSTRACT

**Background** DNA amplification assays are increasingly being used to facilitate the 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, 15 459 women and 14 980 men aged 21–23 years were living in Aarhus County, Denmark. A random sample of 4000 women and 5000 men was 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 9980 men received usual care and constituted the control population. All men and women were subsequently followed for 9 years by the use of Danish health registers. Data were collected on pelvic inflammatory disease (PID), ectopic pregnancy (EP), infertility diagnoses, in-vitro fertilisation (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, no differences were found between the intervention group and the control group: HR (95% CI) for PID 1.12 (0.70 to 1.79); EP 0.97 (0.63 to 1.51); infertility 0.87 (0.71 to 1.07); IVF treatment 0.88 (0.62 to 1.26) and births 1.02 (0.95 to 1.10). In men, the HR for epididymitis was 1.25 (0.70 to 2.24).

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

**Trial registration number in www.clinicaltrials.gov** NCT 00827970.

*Chlamydia trachomatis* can cause urogenital infections, and might cause pelvic inflammatory disease (PID), ectopic pregnancy (EP) and infertility in women.<sup>1–3</sup> The organism is frequently asymptomatic, and the US Centres for Disease Control and Prevention,<sup>4</sup> Australia,<sup>5</sup> The Netherlands<sup>6</sup> and England<sup>7</sup> 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 complications.<sup>8</sup>

Two randomised trials reported fewer PID cases after 1 year of follow-up in high-risk women and high-school women tested once for *C trachomatis*.<sup>9 10</sup> 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 *C trachomatis*, ie, EP or infertility, may be noted only several years later when the woman wants to conceive. This obstacle can be overcome by performing randomised studies in communities with unique personal identification numbers and high-validity registers of discharge diagnoses. The Danish healthcare system provides this scenario.<sup>11</sup>

In 1997 we performed a population-based intervention trial in which young men and women were randomly assigned to either an offer to be tested for *C trachomatis* by the use of a home obtained and mailed sample or usual care.<sup>12</sup> In the present paper we report the effect of this intervention after 9 years of follow-up in terms of PID, EP or infertility in women and epididymitis in men.

## METHODS

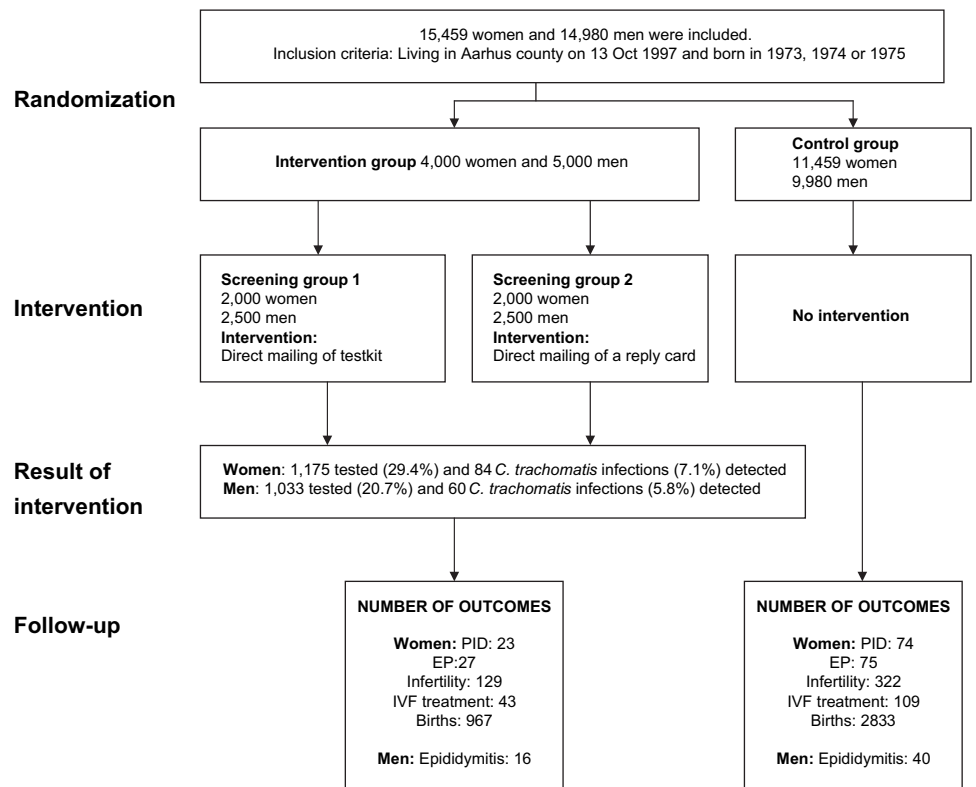
### Study population

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 the 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 21–24 years 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 publication and is only briefly described here (figure 1).<sup>12</sup> In October 1997, a group of 4000 women and 5000 men were randomly selected from the study population. The 9000 individuals were all offered a test for *C trachomatis* by the use of samples

**Figure 1** Flow chart for individuals in the study. EP, ectopic pregnancy; IVF, in-vitro fertilisation; PID, pelvic inflammatory disease.



obtained at home. The remaining 11 459 women and 9980 men constituted the control group. In the period between 31 October 1997 and 6 December 1997, all 9000 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 2000 women and 2500 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 as a result of the intervention are described in figure 1. A total of 1175 women (29.4%) and 1033 men (20.7%) was 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 3 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.<sup>12</sup>

### Randomisation

A computer-based randomisation was performed by administration personnel of Aarhus County. To check that the randomisation of individuals was successful, we collected data on important social characteristics by the 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 study<sup>13</sup> 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).<sup>14</sup>

In the present study all *C. trachomatis*-positive individuals also received a second offer to be tested for the infection by the use of a home-obtained and mailed sample 24 weeks after the initial test. A total of 59 women was tested and three were *C. trachomatis* positive for the second time. The corresponding number in men was that 32 submitted a second sample and one was *C. trachomatis* positive for the second time.<sup>15</sup>

### 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 International Classification of Disease, version 10 (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/obstetrics.<sup>11</sup> In our study the codes used for PID were N700, N709, N710, N719, N730, N733, N735, N738, O030, O035, O040, O045 and 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 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 the use of doxycycline (an antibiotic, ie, 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: IVF 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 fertilisation (IVF) procedure.

### Outcomes: EP, female infertility and births

All of the women in the study population were followed up by means of the Danish Hospital Discharge Registry for 9 years after random assignment. The following outcomes were considered: discharge diagnosis of EP, infertility, or childbirth. The codes used were O00 (all subcodes) for EP; N97 (all subcodes) for female infertility; and O80, O81, O82, O83, or O84 (all subcodes) 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%,<sup>16</sup> 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 the inclusion of 3607 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

randomisation (31 October 1997) to the first date of an event. If no event occurred, the follow-up ended on 5 February 1999 for PID and epididymitis (1 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 HR (control group compared with intervention group) and 95% CI were calculated for each event. Second, we performed a sub-analysis within the intervention group by calculating the events per 100 person-years at risk and the corresponding HR for participants and non-participants. 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 HR.

Stata 9 was used for the statistical analysis of data.

## RESULTS

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

Among the entire population of 15 459 women, 97 had a diagnosis of PID within the first year (6.3 cases per 1000 women years at risk). Twenty-three of these women were admitted to hospital and 74 were treated in general practice. During the entire 9-year study period, a total of 102 women was hospitalised with EP (0.73 cases per 1000 women years at risk), 451 had a diagnosis of infertility (3.2 cases per 1000 women years at risk), and 3800 gave birth to at least one child (27.3 births per 1000 women years at risk). During the 7-year follow-up for IVF treatment, 152 received this procedure (1.4 per 1000 women years at risk). During 1 year of follow-up for the 14 980 men, seven were discharged from a hospital with a diagnosis of

**Table 1** Living status, occupation and country of origin for all randomly assigned individuals

	Intervention (n = 9000)		Control (n = 21 439)		All participants (n = 30 439)	
	n	%	n	%	N	%
<b>Living status*</b>						
Living alone	2457	27.3	5718	26.7	8175	26.8
Married	1644	18.3	3759	17.7	5403	17.8
Living with partner †	2218	24.7	5493	25.6	7711	25.3
<b>Occupation*</b>						
Student	1150	12.8	2896	13.5	4046	13.3
Employed	6323	70.3	14 935	69.6	21 258	69.8
Unemployed	354	3.9	831	3.8	1185	3.9
Welfare payment ‡	1104	12.3	2647	12.3	3751	12.3
<b>Origin*</b>						
Danish	8411	93.5	20 067	93.6	28 478	93.5
Immigrant	467	5.1	1122	5.2	1589	5.2
Descendant	53	0.6	120	0.6	173	0.6

Data are extracted from Danish registers.

\*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.

epididymitis and 49 received treatment in general practice (3.9 per 1000 men years at risk) (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 (HR (95% CI)): PID 1.12 (0.70 to 1.79); EP 0.97 (0.63 to 1.51); infertility 0.87 (0.71 to 1.07); IVF treatment 0.88 (0.62 to 1.26) and births 1.02 (0.95 to 1.10). In the analysis of men, we found no significant reduction in epididymitis, with a HR of 1.25 (95% CI 0.70 to 2.24).

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.

## Discussion

In this randomised study we included more than 30 000 individuals and offered 9000 of these the opportunity to be tested for *C trachomatis* by the 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 randomised 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 registers.<sup>11</sup> Population-based randomised studies with long follow-up at the level of the individual are 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 of 3% was not reached in the study as we expected from the power calculation, which may wrongly result in the rejection of the hypothesis that widespread testing prevents PID. However, as this was a randomised 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 with the control group, but this was not significant and would not have been significant if the expected incidence had actually been reached in the same

**Table 2** Comparison of long-term effects of *C trachomatis* testing in the intervention group versus the control group (intention-to-screen analysis)

	Control group (n = 21 439)		Intervention group (n = 9000)		HR	95% CI
	IR	n	IR	n		
Women		11 459		4000		
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		9980		5000		
Epididymitis	0.32	40	0.25	16	1.25	0.70 to 2.24

For the pelvic inflammatory disease (PID) and epididymitis diagnoses, the follow-up time was 1 year. For in-vitro fertilisation (IVF) treatment, the follow-up time was 7 years, and for all other outcomes, the follow-up time was 9 years. Cox regression analyses were performed. IR, incidence rate per 100 person-years at risk. EP, ectopic pregnancy.

**Table 3** Comparison of long-term effects of *C trachomatis* testing for participating and non-participating individuals in the intervention group

	Non-participants (n = 6792)		Participants (n = 2208)		HR	95% CI
	IR	n	IR	N		
Women		2825		1175		
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		3967		1033		
Epididymitis	0.20	10	0.46	6	0.44	0.14 to 1.20

For the pelvic inflammatory disease (PID) and epididymitis diagnoses, the follow-up time was 1 year. For in-vitro fertilisation (IVF) treatment, the follow-up time was 7 years, and for all other outcomes, the follow-up time was 9 years. Cox regression analyses were performed. IR, incidence rate per 100 person-years at risk. EP, ectopic pregnancy.

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 an underestimation of the effect of the intervention.

Partner notification is important in sexually transmitted infection control and lack of partner notification can possibly eliminate the effect of testing for *C trachomatis* because index patients can very quickly be re-infected. In our study partner notification was not measured, but only few infected individuals were *C trachomatis* positive 6 months later. This indicates that lack of partner notification 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 1 year after the intervention,<sup>9 10 13</sup> and both studies reported a reduction in PID incidence in contrast to our study. The study by Scholes *et al*<sup>9</sup> was performed in a high-risk population, which therefore does not permit its direct comparison with the present study. The study by Ostergaard *et al*<sup>10</sup> was in high schools, which is also a low low-risk population, but that 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<sup>9 10</sup> (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 a quarter of the invited individuals in our study participated in the intervention and, as in cancer screening studies, non-participants could be at a higher risk of 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 place.<sup>17</sup> Also in our analysis of non-participants,<sup>12</sup> we found that those who declined the invitation to be tested probably had a lower infection risk than those who accepted the invitation. The testing of asymptomatic

individuals may give rise to psychosocial problems for the tested individuals,<sup>18 19</sup> 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 strong.<sup>20</sup> Our knowledge of the association between *C trachomatis* infections and PID, EP and infertility stems from important landmark studies by Weström and colleagues.<sup>1 21</sup> Those 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 studies<sup>22–27</sup> have supported the idea that asymptomatic infections facilitate fertility complications. However, those studies have a retrospective design and are based on serology, which may have invited erroneous conclusions.<sup>28</sup> On the contrary, in a small study by Morre *et al*,<sup>29</sup> 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 al*,<sup>30</sup> 2529 women were randomly assigned either to test immediately and treatment or no intervention. Within 1 year 9.5% of control women compared with 1.6% of women in the intervention group developed PID. This difference seemed apparent but was not statistically significant and the authors concluded 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 detect 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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**Competing interests** None.

**Ethics approval** The study was approved by the local ethical committee in the County of Aarhus and by the Danish Data Protection Agency.

**Contributors** 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.

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## Key messages

- ▶ A widespread offer in a Danish population aged 21–24 years to be tested for *C trachomatis* infection by the use of a home-obtained and mailed sample was successful in terms of the number of tested individuals and detected infections.
- ▶ After 1–9 years of follow-up the intervention could not be shown to have any impact on PID, EP or infertility in women or epididymitis in men.
- ▶ The long-term effect of widespread testing for *C trachomatis* is still unknown.

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