Screening for *Chlamydia trachomatis:* whom and how?

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Screening for *Chlamydia trachomatis:* whom and how?

Chlamydia trachomatis screening: wie en hoe?

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Abbreviations

AAD	area address density
AUC	area under the receiver-operating characteristic curve
CI	confidence interval
Ct	Chlamydia trachomatis
PILOT- Ct	Prevalentie en Interventie Landelijk Onderzoek Testen op Chlamydia trachomatis
ELISA	enzyme-linked immunosorbent assay
FP	family planning
GP	general practitioner
HL-test	Hosmer-Lemeshow-test
LCR	ligase chain reaction
LPS	linear predictor for score
MHS	municipal public health service
NAAT	nucleic acid amplification test
OR	odds ratio
LR	likelyhood ratio
PCR	polymerase chain reaction
PID	pelvic inflammatory disease
PPV	positive predictive value
R_o	reproductive rate
SD	standard deviation
SE	standard error
STD	sexually transmitted disease
STI	sexually transmitted infection

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Introduction

Introduction

Chlamydia trachomatis (Ct) is the most common bacterial sexually transmitted infection (STI) worldwide.[1] In the Netherlands the estimated number of new infections is 60 000 per year, of which 35 000 in women. This leads approximately to 3500-7000 women with pelvic inflammatory disease, 1000 women with infertility and 200 ectopic pregnancies per year.[2] Only a small number of those infected are diagnosed and receive treatment. The number of diagnosed infections in the Netherlands has increased in recent years.[3,4]

Control of chlamydia trachomatis infections is an important public health issue in European/Western countries. Vaccination is not possible, and primary prevention in the form of health education and secondary prevention through early diagnosis (screening) and treatment are important chlamydia control strategies. This thesis concentrates on surveillance, active testing by screening and alternative methods to target high-risk groups.

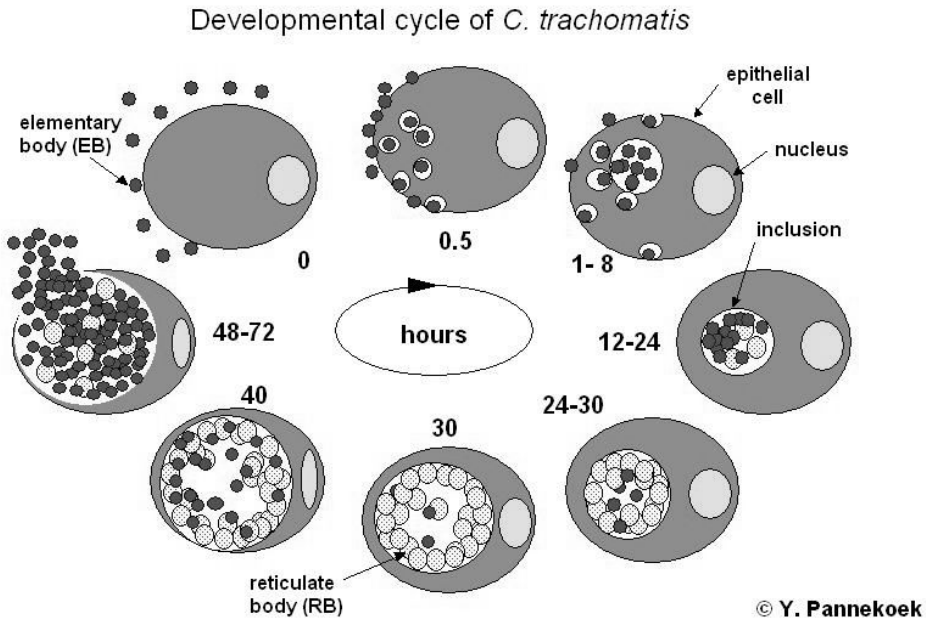
Transmission of STIs

Models of STI epidemiology draw on the concept of 'core groups' of individuals who can maintain the spread of an STI within a larger population. The reproductive rate (R_0) is the number of secondary STI cases arising from one new case. At $R_0 > 1$, the STI spreads; at $R_0 < 1$, it dies out. The three direct determinants of the rate of spread of a sexually transmitted infection are sexual behaviour (average rate of sexual partner change within a population; [c]), the mean duration of infectiousness [D], and the mean efficiency of sexual transmission (average risk of transmission per partner sexual contact)[ß]. Thus $R_0 = c * D * ß$. [5,6] Efficiency of transmission is influenced by host susceptibility and virulence of the pathogen. Condoms can interrupt transmission for many STIs. When average duration of infectiousness is long (like in Ct infection), a low rate of partner change will be sufficient to sustain transmission. With early diagnosis and treatment, D decreases, and the rate of partner change required to sustain transmission increases. Anderson demonstrated that those with highest rates of partner change (the core group) contribute disproportionately to STI transmission.[7] Clustering of STIs within populations means STI prevalence and incidence are high in some subpopulations and low in others. Mixing between members of high and low prevalence subpopulations may constitute risk factors for acquisition and transmission of STIs at the individual level and may facilitate spread at the population level.[8]

Chlamydia trachomatis

Chlamydiales are nonmotile, obligate endosymbiotic bacteria with a characteristic biphasic developmental cycle.[9] The general features of the *C.trachomatis* cycle are shown in Figure 1.1. The elementary body is the extracellular, infectious, metabolically inactive form. Following uptake into the host, elementary bodies remain in vacuolar inclusions where they transform into the intracellular form called a reticulate body. Reticulate bodies are non-infectious, metabolically active, and replicate by binary fission. The reticulate bodies differentiate back to elementary bodies that are released by exocytosis or host cell lysis.

Figure 1.1: Developmental cycle of *C. trachomatis* [10]



A recent classification scheme defines *Chlamydia trachomatis* as an exclusive collection of the human biovars described in Table 1.1.

Table 1.1: *Chlamydia trachomatis* serovar classification and tissue tropism

Biovar	Serovar	Sites of infection
Trachoma	A, B, Ba, C	Conjunctivae, urogenital tract (rare)
Oculogenital	D, Da, E, F, G, Ga, H, I, Ia, J, K	Urogenital tract; conjunctivae; respiratory tract (rare)
LGV	L1, L2, L2a, L3	Inguinal lymph nodes, urogenital tract, rectum

When the term chlamydia is used in this thesis it indicates *Chlamydia trachomatis*. This thesis deals with urogenital Ct infections caused by serovars D to K. Clinical manifestations are described in a paragraph, but in general this thesis deals with the occurence of Ct infections, which are often asymtomatic, in contrast tot chlamydial disease.

Pathogenesis:
Disease process and clinical manifestations probably represent the combined effects of tissue damage from chlamydial replication and inflammatory responses to chlamydiae and the necrotic material from destroyed host cells. There is an abundant immune response to chlamydial infection and there is now evidence that chlamydial diseases result in part from hypersensitivity or are diseases of immunopathology. There must be some sort of protective immune response to the organism, as Ct infections tend to follow a self-limited course, resolving into a low-grade persistent infectio*n*, which may last for years. [9]

Clinical manifestations:
Chlamydia trachomatis is transmitted sexually. It causes urethritis, and in women, cervicitis, with a usually mild symptomatology. Infected women can complain of abnormal vaginal discharge, painful or frequent urination, lower abdominal pain, (post)-coital bleeding and intermenstrual bleeding. However 70% of the infections in women are asymptomatic.[11] The infection may ascend to the upper genital tract, causing endometritis, salpingitis, and pelvic inflammatory disease (PID). PID can appear as an acute abdominal infection but can also develop silently. Tubal scarring can result in ectopic pregnancy[12-14] and tubal infertility.[15] Another complication of chlamydia infection is perihepatitis (Fitz-Hugh-Curtis Syndrome), with right upper quadrant abdominal pain, fever, nausea or vomiting.[7]

Ct infection has been associated with complications during pregnancy and the post-partum period: spontaneous abortion, preterm premature rupture of membranes, chorioamnionitis, and post-partum endometritis.[16-18] During delivery Ct is transmitted to the neonate, and causes neonatal conjunctivitis in 15-37%.[19] The overall risk of neonatal Ct pneumonia has been reported to be 1-22%.[20]

In men, Ct causes urethritis, with abnormal urethral discharge, and painful or frequent urination, in approximately 50% of the patients. Epididymitis, prostatitis and proctitis may occur as well.[21] The role of Ct infection in male infertility is unclear and prevalence estimates of fertility problems vary widely.[22-25] Ct infection is associated with Reiter's syndrome, a disorder more common in men than in women, and consisting of arthritis, urethritis and conjunctivitis.[21]

Transmission, duration of infection and immunity:
The incubation period is probably 7-14 days. The risk of transmission between partners is reported to be lower for chlamydia than for gonorrhoea; from male to female it is reported to be 45%, while from female to male 28%.[26] Quinn *et al.* however, estimated the transmission probability per partnership - when testing by more sensitive nucleic acid amplification tests (NAATs) - to be 68%, both for transmission from man to women and vice versa.[27] Untreated, Ct infection can persist for a long time.[28] Although about 25% of infections in women are cleared within 1-3 months,[29,30] it is found that 50% of 14 women with untreated Ct infections were infected when retested after 16-17 months.[31] Recently it was reported that 46% of 82 untreated Ct infections were persistent at one year, and 18% at two years.[32] Chlamydial antibodies do not indicate protection against infection. Partial immunity is described. Individuals who are infected and get cured or those who recover spontaneously become susceptible again. People can contract several infections, and there

are indications that a second or third infections leads to higher risk for PID[14] and more severe PID.[13]

Diagnosis:
Laboratory testing methods for *C.trachomatis* infections have evolved rapidly since the 1980's. Isolation of the organism in cell culture was the gold standard for the diagnosis of C.trachomatis infection for many years. Methods as immuno-fluorescence and enzyme-linked immunosorbent assay (ELISA) were easier to perform but less sensitive than culture. In the mid 1990s NAATs became available, which include three unique characteristics: 1) improved sensitivity compared to isolation in cell culture and antigen detection; 2) the ability to utilise novel specimen types such as first-void urine, patient collected tampons, or vaginal swabs; and 3) the ability tot test for multiple pathogens simultaneously.[33]

The first NAATs available were the ligase chain reaction (LCX; Abbott Laboratories, Abbot Park, Illinois, USA) assay, and the polymerase chain reaction (PCR; Amplicor; Roche Molecular Diagnostics, Indianapolis, Indiana, USA). Ligase chain reaction assays have recently been taken off the market. The sensitivity of these assays is 85-98%, with a specificity of 95-99.9%, depending on the sample used and the defined gold standard.[34] In a clinical trial for the automated method of PCR (COBAS; Roche Molecular Diagnostics, Indianapolis, Indiana, USA) the sensitivity was, with the infected patient as reference standard, 89.7% for endocervical samples; 89.2% for female urine specimens, 88.6% for male urethral swabs, and 90.3% for male urine; specificities for the respective sites were 99.4% (endocervix), 99.0% (female urine), 98.7% (male urethra) and 98.4% for male urine.[35,36] Other NAATs which have become available quite recently include transcription mediated amplification (Aptima Combo2; Genprobe, San Diego, California, USA); and strand displacement amplification (ProbTec; Becton Dickinson, Sparks, Maryland, USA).[36] Good results were described with vaginal/vulval swabs and tampons with a sensitivity of 80-90%. [37-43] The ability to transport swabs in a dry state to the laboratory extends the utility of the vaginal swab to be easily mailed in a pre-addressed mailing packet, making it a promising option for screening programmes.

There are multiple considerations for selecting screening tests: Test sensitivity is emphasised to minimise occurrence of false-negative tests, which can result in complications of untreated infection and ongoing transmission. The goal of maximising test sensitivity to avoid missing the opportunity of treating infected persons might warrant tolerating false-positive diagnoses. Specificity of a screening test and the infection prevalence influence strongly the proportion of positive tests that reflect infection, the positive predictive value (PPV). In populations with lower prevalence the PPV is lower. A false positive test result for Ct can have adverse medical, social and psychological impacts for a patient. Reducing the rate and consequences of false positives test is important, and specificity can be increased by performing an additional test, which should be positive to diagnose Ct infection.[44]

Costs of NAATs are high, which is problematic for public health programmes. Pooling is a method developed to reduce costs per sample tested and is a technique highly sensitive and specific for chlamydia detection.[45-50] When pooling, a number of urine samples (e.g.

5) are combined and tested together. An added advantage of pooling urine is the confirmation of positive samples when re-testing individual samples after finding a Ct positive pool.

Treatment and resistance:
Treatment of *C.trachomatis* infection is simple and effective in the eradication of infection and prevention of complications. Single-dose treatment of azithromycin (1g) is recommended, with alternative doxycycline (100 mg twice daily for 7 days).[51,52] A meta-analysis showed that azithromycin and doxycycline are equally efficacious in achieving microbial cure and have similar tolerability. The cure rate for azithromycin was 97%, and 98% for doxycycline.[53] During pregnancy erythromycin or amoxycillin are preferred. In case of pelvic inflammatory disease, a fourteen days course of ofloxacin (400 mg twice daily) plus metronidazol (500 mg twice daily) is recommended.[54]

Systematic chlamydia screening may increase the use of azithromycin and possibly influence macrolide resistance, which is reported for other pathogens. The major selection pressure driving changes in the frequency of antibiotic resistance is the volume of drug use.[55] Recently the first report was published of clinically significant multidrug-resistant *C.trachomatis* causing relapsing or persistent infection, this may predict an emerging problem to clinicians and public health officials.[56] The role played by antimicrobial resistance in *C.trachomatis* treatment failures or persistent infection is unclear. Evaluating *C.trachomatis* clinical treatment failures, interpreting laboratory findings, and correlating the two clearly remains extremely difficult, and should be put on the research agenda.[57]

Complication rates:
Pathogenesis of *pelvic inflammatory disease* is a complex interaction of genetic, immunological and bacterial virulence factors.[58] The current understanding of the immunopathological pathways from infection to PID and tubal scarring is incomplete. Chronic sequelae of genital chlamydial infection such as ectopic pregnancy and tubal infertility are thought to be caused by a delayed hypersensitivity reaction to chlamydial 60 kDa chlamydial heat shock protein (HSP-60).[59] Failure to seek treatment within 3 days of the onset of lower abdominal pain can result in a threefold increase in the risk of PID and infertility.[60]

Classification of PID is challenging, as 30% of clinically diagnosed PID's cannot be confirmed laparoscopically.[61,62] Problems associated with PID surveillance are the absence of a simple accurate diagnostic test, various pathogens causing PID, and the clinical case definition in the absence of pathognomonic signs and symptoms of the disease.[63] Unrecognised infection of the upper genital tract occurs frequently with Ct infections.[64,65]

A wide variety of bacteria including enteric organisms, *Mycoplasma hominis* and *Ureaplasma urealyticum* and sexually transmitted infections such as *Neisseria gonorrhoea* and *C.trachomatis*, are associated with PID and the severe upper genital tract pathology associated with repeated episodes of PID. The contributory role of *C.trachomatis* in this progressive process is considered to be well established.[63] A direct correlation between severity of PID and the incidence and level of antibody response against chlamydial antigen has been

reported [66,67] and the risk for hospitalisation for ectopic pregnancy and PID increased with increasing numbers of symptomatic Ct. infections.[14] In cross-sectional studies Ct has been isolated in 29% (range 5-51%) of 1528 PID patients. [68] The rate of PID following Ct infection is generally accepted to be between 8 and 20%. A review of prospective studies of PID rates after Ct infection [69] describes that asymptomatic women who were diagnosed with Ct infection in screening projects had the lowest rate of PID, namely 0-4%,[70] [29] while PID occurred in 12-30% of symptomatic women or women with a higher risk of having a STI (e.g. visitor of an STD clinic, co-infection with gonorrhoea, high risk assessed by questionnaire, having a partner with symptomatic Ct infection).[71-76] The reviewers conclude that the PID rate in women with *C. trachomatis* infection varies considerably. Risk depends on whether the infection was symptomatic and the prior probability of having an STI. In high risk groups for STI the prevalence of other sexually transmitted pathogens also causing PID may be high.[69]

Ectopic pregnancy: The estimated risk of a subclinical and clinical PID leading to ectopic pregnancy and infertility varies between 5-25% [13,64,77,78] and 10-20% [79,80] of PID cases respectively. These assumptions of risk rates are based on data from high-risk populations and symptomatic infections. Westrőm showed that multiple episodes of PID were linked to a significantly increased risk of ectopic pregnancy or infertility.[13]

Chlamydial infection is thought to be responsible for 12 –65% of cases of PID, a third of tubal infertility and the majority of ectopic pregnancies.[59] However, a recent study argues that overestimation of the current complication rates is likely, due to for example misclassification and incorrect diagnoses and the unjustified attribution of complications to Ct infections in studies.[81] Morré found that in 45% of the untreated women the infection resolved spontaneously during the year after diagnosis.[70] Although none of the latter women developed signs of PID, complications with potential sequelae cannot be excluded.

It is apparent that the frequency of complications in chlamydial infection is insufficiently known, which is problematic when considering the need and cost-effectiveness of screening. Since it is unethical to study the natural history of untreated asymptomatic genital chlamydial infection, epidemiological linkage studies may give an indication about complication rates. In a retrospective record-linkage cohort, which included Uppsala resident women aged 15-24 years between January 1985 and December 1989, results of laboratory tests for Ct, hospital diagnoses, and socio-demographic data were linked. The cumulative incidence of PID by age 35 was: 5.6% (95% CI 4.7-6.7%) in women who ever tested positive for chlamydia, 4.0% (3.7-4.4%) in those with negative tests, and 2.9% (2.7-3.2%) in those who were never screened. The corresponding figures were: for ectopic pregnancy, 2.7% (2.1-3.5%), 2.0% (1.8-2.3%), and 1.9% (1.7-2.1%; and for infertility, 6.7% (5.7-7.9%), 4.7% (4.4-5.1%), and 3.1% (2.8-2.3%).[82] This study suggests that the incidence of complications of chlamydia is substantially lower than believed.

Is C.trachomatis infection a good candidate for screening?

If a screening programme is considered on a national scale, knowledge of the burden of infection and disease is required. High prevalences up to 18% are reported throughout Europe, but most studies have been conducted in STI-clinics, youth clinics, sexual health clinics, or in selected general practices.[4,83-85] Clinic based data give an indication of the occurrence of Ct infections in persons seeking health care actively. However, information about the population in general cannot be derived from such data. Surveillance systems based on reports from clinics may show a high or increasing prevalence of infection, but the question is whether such an increase is due to more active testing (e.g. not only diagnostic testing in symptomatic patients but testing of all patients), the use of tests with higher sensitivity, or indeed indicates a real increase of prevalent infections. Is the true prevalence in a population reflected in the current surveillance systems and is universal screening indicated? Difficulties encountered in the monitoring of Ct prevalence at population level are one of the questions this thesis attempts to address.

Wilson and Jungner described criteria to determine whether screening is an appropriate strategy for disease prevention.[86] The disease should be an important health problem for which acceptable and effective treatment is available. The natural course of the disease should be known. The disease has to be found in an asymptomatic phase with an adequate diagnostic test, and facilities for diagnosis and treatment should be available. There should be no ambiguity about the question which people found Ct positive in screening should be treated. The screening has to be acceptable for the target population. Costs for finding cases and treatment should relate reasonably to costs of health care. Finally, case finding has to be a continuous process and not a single action.

Most criteria are met in the case of *C.trachomatis*. Ct infections can be diagnosed in asymptomatic infections with an adequate and acceptable diagnostic test with high sensitivity and specificity, and effective antibiotic treatment is available with few side effects. Several questions however remain to be answered: These include the natural history of Ct infection, the frequency of complications, true Ct prevalence, the acceptability by target populations, cost-effectiveness and feasibility of different screening methods.

This thesis does not investigate the natural history of Ct infection and the frequency of complications. The assessment of Ct prevalence in the Dutch population is one of the main research questions of this thesis. We also study the feasibility of home-based screening. Although participation rates in urine-based screening studies indicate acceptance of the test method,[75,87-89] the acceptability of large-scale population based chlamydia screening and psychosocial consequences are not well known. The possible effects of screening for a sexually transmitted infection, which may lead to stigmatisation, were addressed recently.[90] This issue had not been investigated thoroughly at the start of our research project in 2002 and led to our research question regarding acceptability of Ct screening.

The screening criteria of Wilson and Jungner have been developed for chronic diseases, where screening detects prevalent disease but without any effect on incidence; the number of new cases will not depend on screening. Thus the benefit of screening is felt

primarily by the individual concerned. Contrary to chronic disease screening, infectious disease screening also reduces the incidence of infection. Thus others will benefit, too. An essential condition to obtain advantage from chlamydia screening at population level is that those found infected are treated, preferably together with their partners.

Empirical evidence for effects of screening

There is evidence that screening reduces the prevalence of Ct infections and the incidence of complications and sequelae of chlamydial infection. An effect on the prevalence of Ct has been demonstrated in population subgroups.[91,92] Two randomised controlled trials report effectiveness in the prevention of PID. In the US, women aged 18-34 years, who were enrolled in a health maintenance organisation and who had been selected as high-risk – based on race, nulligravidity, vaginal douching and having two or more sexual partners in a period of one year - were assigned to screening or to usual care. A reduction in PID rate of 56% was seen in the screened group compared to the control group. PID diagnosis was confirmed by checking clinical notes, yet PID cases were compared at group level and not linked to individual Ct cases.[71] In Denmark young students were assigned on home based testing or usual care. Also in this study a reduction of PID was found in the intervention group. However, PID rate was defined by medication prescribed for PID, which is prone to misclassification.[75] Two observational studies in Sweden show a decline in the incidence of PID and ectopic pregnancy after introducing widespread testing for Ct.[93,94] In a case-control study in pregnant women with Ct infection, a lower frequency of pregnancy complications was observed in successfully treated women, compared to women in whom treatment failed.[95] In men it has not yet been shown that screening would reduce the rate of complications.[96]

Material and nonmaterial costs of screening

Adverse effects of screening may include inconvenience of testing, stigma of STI diagnosis and potential partner discord. This had not yet been investigated extensively and will be addressed in this thesis. Other adverse effects of screening may be side effects of antibiotic treatment and development of resistance, both of which are important to consider, but outside the scope of this thesis.

When considering implementing a screening programme, cost-effectiveness is an important factor to take into account. The infectious character of Ct makes a complex dynamic approach necessary to determine the cost-effectiveness of any Ct screening programme.[97] Until recently, only static decision analytical models, without transmission, have been used.[12,98-108] The results of these mathematical models were very sensitive to PID risk. A review of cost-effectiveness of Ct screening concluded that screening is cost-effective at prevalences of 3.1-10.0%, but this was based on static models.[109] Only a dynamic approach accounts adequately for the Ct transmission dynamics and the impact of chlamydia prevention measures on Ct incidence at the population level during longer intervals.[97] Furthermore the risk of becoming re-infected by Ct-infected members of the population, especially through failed partner referral or a new Ct positive partner, requires a dynamic approach. A number of studies have used dynamic modelling of Ct screening.[97,110-112] In dynamic modelling sexual activity (high or low), type of partnership

(steady or casual) and Ct infection (asymptomatic or symptomatic) in both sexes and different age groups can be taken into account. Also concurrent partnerships in persons with high sexual activity (core group) can be included.[113]

With modelling, the effects of the decreasing Ct incidence on the incidence of Ct related complications can be estimated. Medical resources and loss of productivity have to be linked to the averted complications and valued monetarily in order to calculate averted costs. Investment costs of the screening programme – consisting of screening and subsequent treatment costs - have to be computed, and the net costs can be determined and expressed per major outcome averted. Symptomatic PID, chronic pelvic pain, ectopic pregnancy, infertility, and neonatal pneumonia are considered major outcomes.[97]

How to screen? Selective versus universal screening

Screening can be categorised according to the method of recruitment (opportunistic or systematic), and the population targeted (universal or selective). Table 1.2 provides an overview of the various forms of screening.

Opportunistic screening programmes offer screening tests to health service users even if attendance is unrelated to the disease being screened for. This is the most practised form of Ct screening as it is connected to regular curative services. All people in the Netherlands are registered with general practitioners (GP) [A]. But with opportunistic screening only those in the target population are reached who consult their GP. In countries without mandatory registration with a GP, only part of the population can be reached through GP's [B]. This is also the case in health care facilities targeted at specific groups such as family planning (FP) or youth clinics [B]. Therefore opportunistic screening implies selection by reaching only the part of the population which seeks health care. Opportunistic screening can also be carried out outside clinics, for example at youth centres or at school health centres. In opportunistic screening, additionally selective screening criteria can be applied, for example recent partner change. Among those who consult a health care worker and are offered screening, participation rates are usually higher than in systematic screening.

Systematic screening means that people are actively identified in a systematic way and invited for screening (e.g. an invitation letter including a urine test kit is sent to the target population). Systematic universal screening of the general population – within a certain age-range – can be organised by invitation of the whole target population by health care organisations, either public health agencies or GPs [C]. Within systematic screening a high-risk selection of the target group can be made on basis of risk factors or prediction rules [D]. Selective screening aims at screening only those with a high risk, and consequently is associated with lower costs. It requires sensitive and specific screening criteria.

Table 1.2: Categories of screening methods

Population involved Recruitment		Universal within certain age-range		Selective
Opportunistic	A	General practitioner	B	Health care based FP-, STI-, youth-clinic, GP, Schools, youth centres
Systematic	C	Population based screening Public health agency GP in case of mandatory registration	D	Population based screening with self selection

Who should be screened?

Contrary to gonorrhoea and syphilis, which are predominantly found in risk-groups, chlamydial infection is spread among young people in general. The highest prevalence is seen in young adults aged <25 years, and this age-range is used in many selective screening studies, and also in national screening policies.[114-117]

In the Netherlands, population–based data were only available for the capital city of Amsterdam. In a systematic screening study organised by GPs in Amsterdam a participation rate of 51% in women and 33% in men was reported. The Ct prevalence was 2.7% (115/4289) in 15-40 year olds, 3.1% (68/2159) in the age-group 15-29 and 2.2% (47/2130) in those above 30 years.[87] Opportunistic screening in several general practices in Amsterdam revealed a participation rate of 95% among those who were offered testing, with a Ct prevalence of 4.8% in 15-40 year olds. Prevalence was 6.6% (115/1737) in 15-29 year olds, and 3.1% (53/1733) in 30-40 year olds. Coverage was not reported in this study.[88] Obviously in both studies prevalence was relatively low in the group older than 30 years, and if a prevalence of 3% were taken as threshold for large scale screening, inclusion of those above 30 years would not be justified. As the Ct prevalence in both studies was >3% in 25-29 year olds it was justifiable to include this age group in a population based screening project, thus extending the age-limit which was advised at that time in the US.[114] Since the above mentioned studies were from Amsterdam only, there was a need to investigate Ct prevalence in urban and rural areas, elsewhere in the Netherlands. The nation-wide prevalence of Ct in the Netherlands is addressed in this thesis.

Screening is in many cases offered to women only, which appears reasonable as most and most severe complications occur in women. Young women use health care services more frequently, e.g. for contraceptive advice or PAP smears. Therefore in opportunistic screening screening by GPs they are easier to reach than men of the same age. Modelling chlamydia screening has shown that screening women is most cost saving, because complications are avoided. These models assume that sexual partners of infected women are notified and treated.[116]

Although it seems defendable on these grounds to screen women only, there is an important disadvantage to omit men. Chlamydial infection is transmitted sexually, and

men are transmitters of the infection to women and therefore have responsibility in sexual health issues for themselves and for their partners. Screening makes them part of the problem and may increase men's understanding of their sexuality and sexual behaviour.[90,118] Screening women only further minimises men's responsibility for sexual and reproductive health, and labels women both as transmitters and contractors of this sexually transmitted infection.[119] From the view of infectious disease control, failure to identify asymptomatic infections in men may allow for maintenance of a reservoir of untreated Ct infection, consequently hindering efforts to further decrease the incidence of chlamydial infections. [120] In fact identification and treatment of infections in males would constitute primary prevention for women, and would prevent reinfection and recurrences in women.[33] As Ct prevalence at population level is unknown in the Netherlands for women and men, this formed an argument to offer screening to both sexes in a Ct screening Pilot.

Organisation of screening

The routine implementation of a chlamydia-screening programme is another critical issue. The sexual health strategy in England assigns a central role for the primary care setting for prevention and sexual health services, including chlamydia screening. Introducing a new screening programme into primary curative care in England is considered a challenge.[121] McNulty stated that the Department of Health needs to be aware of the extreme pressures that primary care staff are under, and the potential barrier to any Ct screening implementation.[122]

In the Netherlands GPs play a major role as providers of sexual health care.[123] Workload is large, and it is likely that the same barriers will be met as in England.

GPs have a role in screening programmes in the Netherlands. Invitation for and carrying out vaccination against influenza are performed by GPs in the Netherlands. In case of cervix screening the invitation and evaluation is done by a central organisation, mostly municipal public health services (MHS), while GP's perform the PAP smears. While a pilot programme for cardiovascular disease prevention had positive results, it was not followed by programmatic introduction due to doubts about feasibility and high workload by GPs. [124-126] Breast cancer screening is organised by the Public Health Services. MHSs are used to organise large interventions like mass vaccination campaigns, and are responsible for STI/HIV control in their region. The question therefore is whether it is feasible for Public Health Services to organise chlamydia screening. This is one of the issues to be investigated in this thesis.

Research Questions

Based on the issues concerning chlamydia screening as described before, the following research questions were formulated.

Prevalence

1. What difficulties are encountered in monitoring Ct prevalence?
2. What is the prevalence of Ct infection in the Netherlands?

Risk groups

3. Can a prediction rule for the risk of Ct infection, based on risk factors, be developed?

Screening

4. How should population based chlamydia screening in the Netherlands be organised?
5. Can participation of high-risk groups to Ct screening be improved?

In order to address these research questions, a screening project among 15-29 year old men and women was carried out by STD-AIDS Netherlands and four Municipal Health Services, covering rural and urban areas positive predictive value (PPV). The screening included invitation by the municipal public health service (MHS), home-based urine collection, outcome notification by mail, and referral of Ct positive participants to regular curative health care services. The acceptability of such a population-based screening programme in the Netherlands, the experience of participants with the results and effects of screening, and their motivation for participation in future screening was investigated.

In the Ct Pilot, participation of migrants was relatively low. This led to a outreach based study in Rotterdam, in which chlamydia and gonorrhoea testing was offered during STI prevention activities for high-risk migrant youth. This 'STI prevention PLUS' project aimed to determine whether the intervention strategy of outreach testing is feasible and efficient.

Chapter 2 addresses the first research question concerning problems encountered in the monitoring of Ct prevalence in western countries at population level. This is exemplified by analysing and interpreting national Swedish surveillance data. In **Chapter 3** question 2 is assessed: What is the Ct prevalence in urban and rural 15-29 year olds of the Netherlands? Investigation of response rates and non-response are essential for answering this question. Based on data of the Ct Pilot we investigated risk factors for chlamydial infection. Research question 3, the development of a prediction rule and its potential application is addressed in **Chapter 4,** while performance of this prediction rule in different populations is evaluated in **Chapter 9.** The validation was performed on data from a population based screening project in Amsterdam and the STI prevention PLUS project.

The feasibility of home-based population screening (question 4), as organised by municipal public health services is touched in **Chapter 3,** while the aim of **Chapter 5** is to describe lessons learned from the Ct Pilot regarding process organisation, target

population, screening method and response optimisation. Effects of the screening in the sense of outcome of management of index cases and their partners in the Ct Pilot are deliberated in **Chapter 6. Chapter 7** addresses the relevant issue of the acceptability of such a screening for participants and touches on their willingness to be screened in the future. **Chapter 8** addresses research question 5 regarding alternative approaches and evaluates whether offering urine test kits in combination with STI prevention activities can increase test participation particularly in high risk and hard to reach migrant populations.

Chapter 10 (Discussion) reviews the research questions and the results of the study in the context of past and recent literature and draws conclusions that may contribute to the decisions and policy with regards to chlamydia screening in the Netherlands.

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2

Is the increase in notifications of *Chlamydia trachomatis* infections in Sweden the result of changes in prevalence, sampling frequency or diagnostic methods?

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Abstract

Based on clinical and laboratory surveillance data, trends in the incidence rates of genital Chlamydia trachomatis infections in Sweden from 1991 to 1999 were analysed according to age group and sex. The influence of changes in laboratory methods on the reported infections was assessed. After a decrease in the incidence rate of infection of 36% between 1991 and 1994, followed by a period of stability, a 20% increase was observed between 1997 to 1999 (from 157 to 189/100,000). Between 1991 to 1999 the female:male ratio decreased from 1.7 to 1.4. Incidence rates started to increase in 1994 in the 15 - 19 year age group for both sexes. Crude Chlamydia positivity increased from 4.1% (352,050 people tested) in 1994 to 5.4% (305,946 people tested) in 1999. This increase in Chlamydia positivity was seen both in laboratories that had changed to more sensitive methods and in those that had not. Changes in laboratory methods can therefore only partially explain the increase in notified cases. Increased screening of men may have contributed to the increase, but rising incidence rates in all young age groups of both sexes suggest a true increase in prevalence.

Introduction

Genital *Chlamydia trachomatis* infection is prevalent both in industrialised countries and in the developing world. The World Health Organisation estimated that in 1995 there were 89 million cases of *C.trachomatis* infection world-wide.[1] The prevalence of infections ranged from 3 - 5% for asymptomatic men in general medical settings and to 15 - 20% for men in sexually transmitted disease (STD) settings, whereas the corresponding figures for women were 3 - 5% and 20%, respectively.[2] Prevalence studies of *C.trachomatis* infection in Sweden showed ranges of 2.1 – 8.9% in asymptomatic women [3-8], up to 40% in symptomatic women [9] and 10% in asymptomatic men[10]. The incidence of the disease is not well-defined because in most countries *C.trachomatis* infections are not notifiable, not microbiologically confirmed and often asymptomatic, and thus tend to escape detection.[2] Sweden is one of the few countries where reporting of all *C.trachomatis* cases is mandatory. It is still questionable, however, whether the number of reported cases mirrors the true prevalence of *C.trachomatis* infections in the population.

In Sweden, diagnostic laboratories have reported genital *C.trachomatis* infections numerically on a voluntary basis since 1982. In April 1988, mandatory notification of clinical cases was introduced.[11] National case figures based on clinical and laboratory reports are compiled and analysed by the Swedish Institute for Infectious Disease Control.

Since the change in the Communicable Disease Act in 1988, physicians have been required to examine patients with suspected genital chlamydial infection for the presence of *C.trachomatis* and to trace contacts of infected patients. Examination and treatment is free of charge for the patient.[11] In the 1980s, extra resources to enable the introduction of preventive measures were made available for STD clinics and youth clinics.

Laboratory testing methods for *C.trachomatis* infections have evolved rapidly since the 1980s. Antigen and nucleic acid detection techniques have become widely used, together with the standard approach of isolation of the organism in cell culture. In the 1990s nucleic acid amplification tests became available, offering improvements in sensitivity compared to isolation in cell culture and antigen detection.[12] A switch to a more sensitive test could result in an increase in Chlamydia test positivity without a change in disease prevalence, leading to an overinterpretation of reported disease trends. However, the change from less specific antigen detection methods, such as enzyme-linked immunosorbent assay (ELISA), to the more specific nucleic acid amplification tests would result in fewer false-positive findings.

The objectives of the present study were to analyse trends in notifications of *C.trachomatis* infections in Sweden between 1991 and 1999 and to assess whether these trends could be attributed to a change of laboratory methods and sampling frequency or whether they reflected a true change in prevalence.

Chapter 2

Materials and Methods

Surveillance data: clinical and laboratory notifications

All clinical notifications of *C.trachomatis* infections received from all 21 counties since 1991 were included in the study. Clinical notifications include both symptomatic patients, indicating incidence of *C.trachomatis* infections, and asymptomatic cases found by screening in STD clinics, partner notification and screening of pregnant women, which together comprise the prevalence figures in the population. Notified cases are all confirmed by laboratory tests and are reported using a code that includes the year of birth and the 4 figures of the unique 10-digit national identity number from which the sex and age of the patient can be deduced. Analysis is based on the date of reporting. Incidence rates of reported *C.trachomatis* infections (crude, age-specific and sex-specific) were calculated by dividing the number of reported cases in the calendar year by the end-of-year resident population provided by Statistics Sweden. Age-specific incidence rates were calculated for 5-y age groups, starting with the group aged 15-19 y. Complete data by age group were only available from 1992 onwards.

Reporting of aggregate cases by county laboratories and private laboratories is voluntary and includes the number of persons tested, as well as the number of positive cases by sex. Since 1998, denominator data have also been available by sex. Some of the laboratories report the number of tested persons and the number of positive persons in 5-year age groups.

The number of reporting laboratories has changed since 1991 owing to reorganisation. Since 1997, 28 laboratories have been diagnosing *C.trachomatis* . Regional laboratories mostly receive samples from their own county, but 3 laboratories provide services for several counties. To calculate the degree of under-reporting we compared the numbers of cases reported by the 2 methods. "Chlamydia positivity" was defined as the number of positive cases divided by the total number of persons tested.

Laboratory survey of diagnostic methods and comparison with laboratory surveillance data

To analyse the association between the introduction of more sensitive laboratory methods and Chlamydia positivity, a questionnaire was sent to all laboratories diagnosing *C.trachomatis* infections in 1996, 1998 and 1999. The type of Chlamydia tests used and the proportion of use of each test method were assessed. The aim was to test the hypothesis that laboratories, which had changed to a more sensitive method, would show an increase in Chlamydia positivity whereas laboratories using older, less sensitive, methods would not.

The following definitions of "change of diagnostic method" were used to categorise the laboratories:

No change: use of the same method as in the year of the last survey or a <5% increase in the use of nucleic amplification methods;

Change: switching from ELISA or culture methods only to analysing >90% of samples using nucleic acid amplification methods, either PCR or ligase chain reaction (LCR);

Mixed: all laboratories not included in the above definitions. These laboratories used a mixture of culture and nucleic acid amplification methods and showed an increase in the use of nucleic amplification methods of >5%, although the total use of LCR/PCR was <75%.

Data from the numerical surveillance system for the years 1996, 1998 and 1999 were analysed and the numbers of tested persons and positive persons were extracted from each categorised laboratory. For the periods 1996–98 and 1998–99, the observed percentage change in Chlamydia positivity was calculated using the formula:

$$\% \text{ change} = \left(\frac{\text{observed Chlamydia positivity (\%) in the second year of observation}}{\text{observed Chlamydia positivity (\%) in the first year of observation}} \times 100 \right) - 100$$

The numbers of tested persons and positive persons were summarised for each category of laboratory and Chlamydia positivity, was calculated for these pooled data.

Statistical analysis

Assuming that the variation in the incidence could be modelled using a Poisson distribution and that the number of cases was large enough for the distribution to be approximated by a normal distribution, a *t*-test was used for comparison of the number and incidence rates of cases for testing on a 5% significance level. A X^2-test was performed for comparison of proportions (e.g. Chlamydia positivity) with a significance level of 5%. Changes in the average incidence rate over several years were analysed using Poisson regression techniques. We investigated differences between age groups for males and females separately. The year of diagnosis was fitted as a continuous variable for the analysis of trends between 1994 and 1999, giving the average percentage change per year. Changes were considered significant if 95% confidence intervals (CIs) around the percentage changes did not cross 0%. Calculations were performed using Microsoft Office Access and Excel 97 (Microsoft Company, Seattle, WA). Poisson regression was performed using Stata version 6 (Stata Corporation, College Station, TX).

Results

Surveillance data

Clinical notifications: Overall trends and sex distribution

Between 1991 and 1994, the number of clinical notifications decreased by 35%, from 20,980 cases to 13,600 cases; (p<0,001). After a period of stability during the following 3 y, the number of cases increased by 20% (18% in women and 23% in men) from 13,900 cases in 1997 to 16,700 cases in 1999 (p<0.001). The sex ratio (women : men) declined from 1.7 in 1991 to 1.4 in 1999. The incidence rate of clinically notified Chlamydia cases per 100,000 person years decreased from 244 in 1991 to 155 in 1994 (36% decrease; p<0,001). From 1997 onwards, an increase in the yearly incidence rate was seen, from 157 in 1997 to 189 in 1999 (p<0.001). In 1997, the incidence rate per 100,000 person years was 130 in males and 184 in females, compared to values of 160 and 216, respectively in 1999 (p<0.001 for both sexes).

Age distribution: The largest numbers of diagnosed infections in 1999 were in men aged 20 - 24 years (N=2893) and in women aged 20 - 24 years (N=4098). Cases in the age group 15 - 29 years represented 86 % of all cases, and 94 % of all cases are in the age group 15 - 34 years. These proportions have been stable since 1991, and further age-specific analysis is restricted to these age groups. The proportion of cases in 15 - 19 year-olds was lowest in 1994 (19%) and increased to 23% in 1999 (p<0.001), while the proportion in 20 - 24 year-olds decreased from 45% in 1995 to 42% in 1999 (p<0.001). Throughout the study period the highest incidence rates of *C.trachomatis* notifications were observed in the age group 20 - 24 years. Incidence rates per 100,000 person years in the 15 - 19 year age group started to increase from 1994 onwards (Figure 2.1). Further analysis showed that significant increases in the incidence rates of notified *C.trachomatis* infections were seen between 1994 and 1999 in all age groups for both sexes, except for females aged 30 - 34 years. Incidence rates increased most in the 15 - 19 year age group, with average annual rises of 7.3% in girls (95% CI: 6.3 - 8.3) and of 10.0% in boys (95% CI: 8.1 - 12.0).

Laboratory data were received from all laboratories performing Chlamydia diagnostics. The number of persons with *C.trachomatis* infection reported by the laboratories showed a parallel trend with the number of clinically reported cases. However, clinical under-reporting (laboratory-confirmed cases not being clinically notified) was seen and varied 4.2% to 8.7% per year (mean 5.7%) between 1991 and 1999.

Between 1991 and 1997 the number of tested persons decreased from 431,516 to 305,946, followed by an increase to 328,365 tested persons in 1999. Chlamydia positivity decreased from 5.2% in 1991 to 4.1% in 1994, and then increased to 5.4% in 1999 (Figure 2.2).

Figure 2.1: Age and sex-specific incidence rate of notified C.trachomatis infections, 1991-99, Sweden

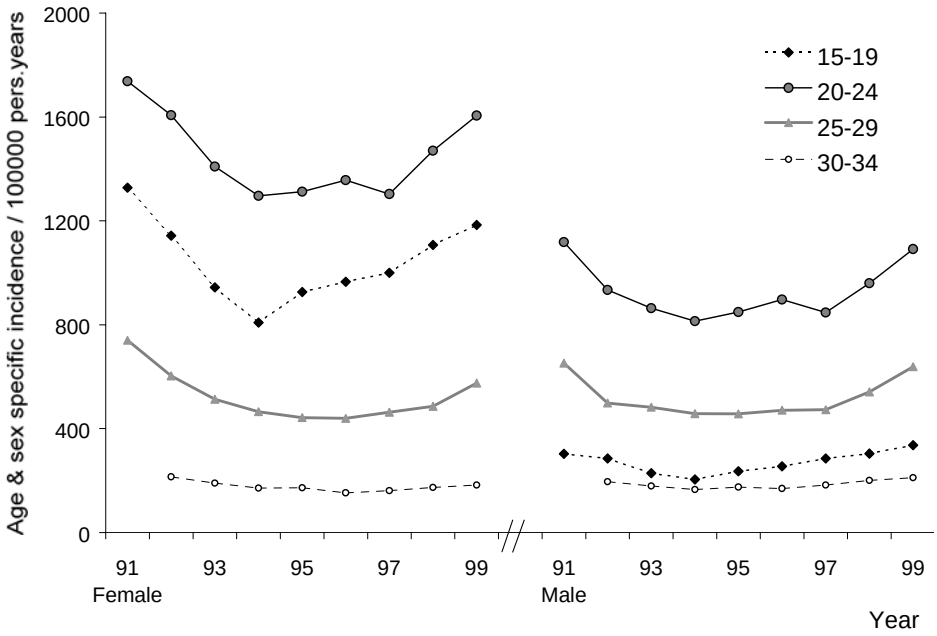
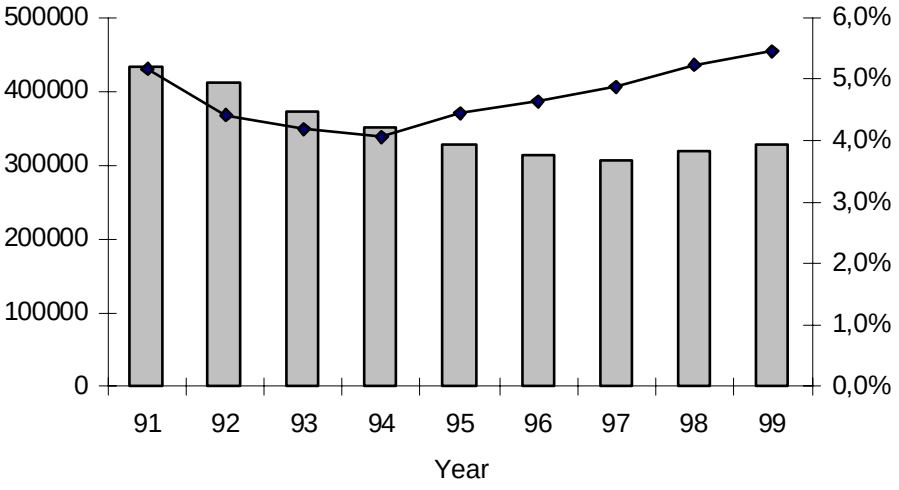


Figure 2.2: Number of persons tested for *C.trachomatis* and Chlamydia positivity in percent in Sweden 1991-99



Left Y-axis : number of persons tested (bars); Right Y-axis: percentage positives (line)

Chlamydia positivity by sex: In 1999, 67,185 men and 259,784 women were tested, representing increases from 1998 of 5.1% and 3.3%, respectively. The sex of 1396 tested persons was not registered. In 1999, the proportion of *C.trachomatis* -positive men was 11.0%, compared to 10.6% in 1998 (p=0.02). For women these proportions were 4.0% and 3.8% respectively (p<0.001).

Chlamydia positivity by age group and sex: In 1999, complete data for age group analysis were available for 10/28 laboratories, representing 37% of all tested persons. Among men, the highest Chlamydia positivity was observed in the 20-24 y age group (13.7%), whereas in women the highest Chlamydia positivity was observed in the 15 - 19 y age group (5.4%; Table 2.1).

Table 2.1: Laboratory notifications of C.trachomatis infections 1999: Chlamydia positivity by age group and sex

	Male				Female			
Age (yrs)	positive	tested	% pos	95% CI	positive	tested	% pos	95% CI
Unknown	13	276	4.7	2.2 - 7.2	9	309	2,9	1.0 - 4.8
10-14	9	60	15.0	6.0 - 24.0	25	608	4,1	2.5 - 5.7
15-19	350	2728	12.8	11.6 - 14.1	1084	20063	5,4	5.1 - 5.7
20-24	1069	7819	13.7	12.9 - 14.4	1446	28305	5,1	4.9 - 5.4
25-29	737	6328	11.6	10.9 - 12.4	626	20438	3,1	2.8 - 3.3
30-34	280	3258	8.6	7.6 - 9.6	231	11962	1,9	1.7 - 2.2
35-39	138	1915	7.2	6.0 - 8.4	78	7133	1,1	0.9 - 1.3
40-44	46	1108	4.2	3.0 - 5.3	26	3666	0,7	0.4 - 1.0
45-49	20	704	2.8	1.6 - 4.1	10	1587	0,6	0.2 - 1.0
>=50	27	1125	2.4	1.5 - 3.3	15	1281	1,2	0.6 - 1.8
Total*	2689	25321	10.6	10.2 - 11.0	3550	95352	3,7	3.6 - 3.8

* Data from 10 laboratories

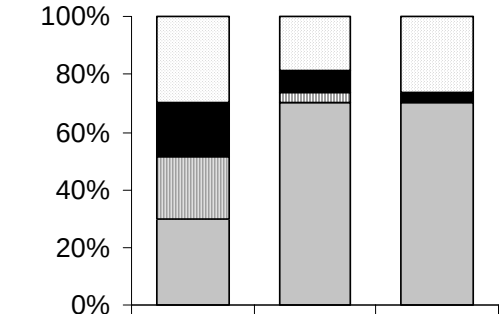
Laboratory survey on diagnostic methods and comparison with laboratory surveillance data

Data from 27 laboratories were available for analysis for 1996, 1998 and 1999, representing 88.3%, 95.7% and 99.7%, respectively of all persons tested. The distribution of the diagnostic methods is shown in Figure 2.3. The results of the comparison of diagnostic methods per category of laboratory are shown in Table 2.2. Between 1996 and

1998, nine of the laboratories had changed laboratory methods, but the change in Chlamydia positivity was only statistically significant in 2 of these laboratories. Fifteen of the laboratories had not changed their methods. Among these were laboratories using only one method (EIA, culture, PCR, or LCR), and some using various methods. In six of the fifteen laboratories, the increase in chlamydia positivity was statistically significant.

Between 1998 and 1999, only one laboratory had changed laboratory methods (from ELISA to PCR), whereas 22 laboratories had not changed their methods. For the latter group, 18 laboratories used nucleic acid amplification methods only, 1 used culture only and 3 used various detection methods. The data from these 22 laboratories showed a total increase in Chlamydia positivity of 6%, 9 showing a decrease in positivity ($p<0.05$ for 3) and 13 showing an increase in positivity ($p<0.05$ for 7).

Figure 2.3: Distribution of use of diagnostic methods among 27 laboratories in 1996, 1998 and 1999



	1996	1998	1999
Mix	8	5	7
Culture	5	2	1
Elisa	6	1	0
PCR/LCR	8	19	19

Table 2.2: Chlamydia positivity (Ct pos) in 1996, 1998 and 1999 by laboratory category

Changes between 1996 and 1998								
		1996			1998			
Laboratory category	n	No. pos	No.tested	Ct pos (%)	No. pos	No.tested	Ct pos (%)	change Ct pos 1996-1998
No change	15	6377	138146	4.6%	7121	138760	5.1%	11% *
Change	9	3673	80868	4.5%	4354	80585	5.4%	19% *
Mixed	3	2864	58038	4.9%	4227	84906	5.0%	1%

Changes between 1998 and 1999								
		1998			1999			
Laboratory category	n	No. pos	No.tested	Ct pos (%)	No. pos	No.tested	Ct pos (%)	change Ct pos 1998-1999
No change	22	11850	237318	5.0%	13711	257191	5.3%	6% *
Change	1	438	7312	6.0%	530	7283	7.3%	21% *
Mixed	4	3379	59621	5.7%	3583	62832	5.7%	1%

* $p<0.005$

Discussion

Before our study period a decline in notifications of Chlamydia infection had already been observed in Sweden. The highest incidence of *C.trachomatis* infections in laboratory reported cases was 450/100,000 persons, in 1986. Following the introduction of mandatory reporting and partner notification, a decreasing trend in the number of reported cases of *C.trachomatis* infections was observed in Sweden after 1989. A stable level seemed to be reached between 1994 and 1997, after which there was an increase in the number of reported cases. This increase was the stimulus for further analysis.

One possible explanation for the observed increase could be that more people were being tested, and thus more cases were found. An increase in prevalence in the tested population (either real or due to more selective testing) would also result in more cases being found. Another explanation for the increase may be the increased use of more sensitive tests for diagnosis of *C.trachomatis* infection, such as nucleic acid amplification methods, which would detect more cases in a stable population. The reporting of a relatively larger proportion of male cases in recent years, indicated by a decreasing female:male ratio among notified C.trachomatis infections, reflects the increased testing

of males, facilitated by the introduction of urine tests. However, this does not necessarily reflect a more rapid increase in incidence in males opposed to females. Improved diagnostic techniques were discussed as a possible reason for the rise in the number of new diagnoses of *C.trachomatis* infections observed in the UK [13] and US [14] in 1998.

The impact of switching laboratory tests on reported trends in *C.trachomatis* infections was investigated by Dicker et al.[15], who found an increase in Chlamydia positivity after switching to more sensitive tests, although this was unlikely to represent an increase in true Chlamydia positivity. They pointed out that nucleic acid amplification methods appeared to detect more infections in asymptomatic women and in women >20 y, which stresses the importance of the nature of the population being tested for Chlamydia positivity.

Our surveillance system of clinical cases of *C.trachomatis* infection and the incidence rate calculated do not take into account the size of the tested population. The voluntary laboratory notifications provided us with denominator data that allow further interpretation of previously obtained data. In Figure 3, three patterns are visible in Fig. 3. Between 1991 and 1994 fewer persons were tested than in subsequent years, and the percentage of positives decreased from 5.2% to 4.1%. During this period there were no major changes in diagnostic methods, and the decline in reported *C.trachomatis* infections most likely mirrored a genuine decrease in the underlying prevalence. During the period 1994–97, although fewer persons were tested, Chlamydia positivity increased slightly to 4.9%. This resulted in a stable number of reported cases, which could be due to better-directed screening, a real increase in prevalence or the introduction of nucleic acid amplification methods, which had begun in 1995. From 1997 onwards, more tests were performed and the Chlamydia positivity increased to 5.4%. Again this could be due to the use of more sensitive test methods, or of testing a population with a higher prevalence because of a true increase in incidence or better-directed screening.

Analysis of aggregated laboratory data from 1998 and 1999 showed that increases in the number of tested persons occurred for both sexes, but relatively more so in men. In both sexes an increase in Chlamydia positivity was seen, which could be due to more selective testing, the use of more sensitive methods or a genuine increase in prevalence in the population. The higher positivity in men suggests that male cases are detected by partner notification or when symptomatic, whereas female cases are mainly found by screening, a finding shared by others.[16] The Chlamydia positivity was highest in the age groups 15-19 y and 20 - 24 y for both sexes, which indicates that either the most effective testing is performed in these age groups or that there is a higher incidence and/or prevalence in these groups.

Our survey, which assessed diagnostic methods used to diagnose Chlamydia in 1996 and 1998, showed that an increase in Chlamydia positivity was not confined to the laboratories that had changed to a more sensitive method of diagnosis. We have pointed out that the changes in Chlamydia positivity were not significant for the majority of the laboratories. Two of the 6 laboratories in the no-change category with a statistically significant increase in Chlamydia positivity tested fewer people in 1998 compared to 1996,

which may reflect a more selective screening process or a true increase in incidence; the other 4 had tested more persons, which may mirror an increase in prevalence.

Between 1998 and 1999 the majority (N=22) of the laboratories did not change their methods. This allowed us to study the effects of other factors on Chlamydia positivity. Among these 22 laboratories we saw 2 different patterns. Three out of 9 reported a significant decrease in Chlamydia positivity, which could be due to less specific screening or to a decrease in prevalence in a stable test population. A decrease in prevalence is less likely when one looks at the incidence rates, while less specific testing of a larger group of persons is more likely in view of the more practicable method of testing patients. Seven of 13 laboratories in the no-change category reported a significant increase in Chlamydia positivity, suggesting either more selective screening or an increase in prevalence in a similar test population.

Our results clearly indicate that the increase in Chlamydia positivity is not confined to those laboratories that used more sensitive tests for diagnosis of *C.trachomatis* infections. The increase in the number of notified cases can therefore only partly be explained by the change in methods. Tracing when and where new testing methods are being used and considering this information when interpreting surveillance data is a methodological approach which would seem essential, as stated by others.[15] Our data do not allow an analysis according to the reason for testing or symptomatology. Thus the influence of changes in testing practices according to sex and age group on the number of notified cases cannot be evaluated. The relatively higher increase in incidence rates in males compared to females may reflect the fact that screening policy has mainly changed for males. However, the fact that the incidence rates increased in both females and males and in all 5-year age groups between 15 and 29 year suggests that the prevalence of *C.trachomatis* infections is increasing (at least in a segment of the population). We could also show that the increase in incidence rates in the youngest age group (15-19 years) had already started in 1994, and a cohort effect is visible when comparing the various age groups. The stable number of cases between 1994 and 1997 was in fact a false stability, which became obvious when the data were related to denominator data. This underlines the importance of denominator data.

Although as a result of Swedish law there is comprehensive notification of cases, we are aware that case finding is not complete, as screening of asymptomatic persons and partner notification is not performed to the same extent everywhere.[17] The degree of under-reporting in the clinical surveillance system compared with the laboratory system indicates that case reporting, although mandatory, is not done exhaustively. Also, we cannot ignore the fact that some persons tested are registered twice in the laboratory system or that there is accidentally faulty reporting of the number of tests. Likewise, clinical cases may be reported twice as the coded system used, which does not involve complete personal identification, does not allow for control of duplicates. However, we do not think that this will affect the analysis of the trends observed. Our crude Chlamydia positivity rate is obviously determined by the type of clinic and by the characteristics of patients attending, varying from asymptomatic pregnant women to patients with symptoms of *C.trachomatis* infection. Unfortunately the Swedish surveillance system does not allow for analysis by clinic type. The 21 Swedish counties have different policies for

C.trachomatis screening, and the analysis of nationwide data allows for only a crude explanation of the observed trends.

In conclusion, we could show that the increase in the number of notified *C.trachomatis* infections could not be explained by a switch to more sensitive laboratory methods or a change in sampling frequency alone, but instead reflected a real increase in prevalence.

This increase is not dramatic when compared to the figures from the end of the 1980s, when the surveillance system was started. However, the decrease in the number of *C.trachomatis* cases was not as extensive as we had hoped, in view of the preventive measures taken. The rise in notified cases is a reason for concern, and the screening of risk groups free of charge and optimal contact tracing remain the cornerstones of *C.trachomatis* prevention.

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3

Prevalence of urogenital *Chlamydia trachomatis* increases significantly with level of urbanisation and suggests targeted screening approaches: results from the first national population based study in the Netherlands

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Abstract

Objectives: *Chlamydia trachomatis* (Chlamydia) is the most prevalent sexually transmitted bacterial infection and can cause considerable reproductive morbidity in women. Chlamydia screening programs have been considered but policy recommendations are hampered by the lack of population-based data. This paper describes the prevalence of Chlamydia in 15–29 year old women and men in rural and urban areas, as determined through systematic population based screening organised by the Municipal Public Health Services (MHS), and discusses the implications of this screening strategy for routine implementation.

Methods: Stratified national probability survey according to "area address density" (AAD). 21 000 randomly selected women and men in four regions, aged 15–29 years received a home sampling kit. Urine samples were returned by mail and tested by polymerase chain reaction (PCR). Treatment was via the general practitioner, STI clinic, or MHS clinic.

Results: 41% (8383) responded by sending in urine and questionnaire. 11% (2227) returned a refusal card. Non-responders included both higher and lower risk categories. Chlamydia prevalence was significantly lower in rural areas (0.6%, 95% CI 0.1 to 1.1) compared with very highly urbanised areas (3.2%, 95% CI 2.4 to 4.0). Overall prevalence was 2.0% (95% CI 1.7 to 2.3): 2.5% (95% CI 2.0 to 3.0%) in women and 1.5% (95% CI 1.1 to 1.8) in men. Of all cases 91% were treated. Infection was associated with degree of urbanisation, ethnicity, number of sex partners, and symptoms.

Conclusion: This large, population based study found very low prevalence in rural populations, suggesting that nationwide systematic screening is not indicated in the Netherlands and that targeted approaches are a better option. Further analysis of risk profiles will contribute to determine how selective screening can be done.

Introduction

Chlamydia (*Chlamydia trachomatis*) is the most prevalent sexually transmitted bacterial infection. WHO estimates that 92 million new infections occur annually, of which five million occur in Western Europe.[1] In women, chlamydial infections are an important cause of pelvic inflammatory disease (PID), ectopic pregnancy, tubal infertility, and chronic abdominal pain. In men infections can cause prostatitis and epididymitis.[2] Vertical transmission from mother to infant can lead to conjunctivitis and pneumonia. Chlamydial infection increases HIV infectiousness and susceptibility.[3] Approximately 70% of the infections in women and 50% in men are asymptomatic or subclinical.

Active case finding and early treatment are strategies to prevent the development of sequelae and to reduce transmission. Screening initiatives undertaken in Sweden showed a steep decrease in prevalence of chlamydial infections followed by decreasing incidence of reported PID and ectopic pregnancy.[4,5] In the United States, annual screening of sexually active young women is recommended and screening programmes reduced prevalence in areas where this intervention has been in place for several years.[6] In two randomised controlled trials, screening women reduced the risk of developing PID by half.[7,8] Economic and human costs attributed to chlamydial infections are considerable. Modellers suggest that screening is cost saving if prevalence exceeds 3%[9] and there is strong advocacy to scale up screening activities.[10-14] However, the strength of the evidence surrounding the range of probabilities of sequelae of untreated asymptomatic infection is still limited, generating wide confidence intervals in cost effectiveness estimates[15,16] and fuelling the discussion of whether Wilson and Jungner screening criteria for chlamydia are fulfilled completely.[17,18]

If a screening programme is considered on a national scale, insight into the burden of disease is required. High prevalence of up to 18% has been reported throughout Europe, but most studies have been conducted in STI clinics, youth clinics, sexual health clinics, or in selected general practices ("opportunistic screening").[19,20] Many studies focus on women, and are carried out in highly urbanised areas. Surprisingly, rural populations have rarely been the subject of study. Yet, unlike gonorrhoea and syphilis, which are usually found in well-defined risk groups, chlamydial infection is more dispersed among young people in general. Novel approaches to the laboratory diagnosis of *C trachomatis*, like nucleic acid amplification tests (NAAT) using first void urine or vaginal swabs, created expanding opportunities for home based postal screening, targeting both women and men ("systematic" or home based screening).[8,17,21]However in the Netherlands, population based data are not available except for the capital city of Amsterdam.

The routine implementation of a chlamydia screening programme is another critical issue. General practitioners (GPs) play a major role as providers of sexual healthcare in the Netherlands.[22] Mainstreaming a new and large scale screening programme via GPs, who practise mainly curative care, is considered a major challenge.[14] We investigated the feasibility of a screening programme organised not through general practice, but also by the Municipal Public Health Service (MHS), with referral of positive cases to the regular care providers. This paper describes the prevalence of chlamydial infection among 15–29

year old men and women in rural and urban areas and discusses the implications of this screening strategy for routine implementation.

Material and Methods

Population size and sampling method

The study population consisted of 21 000 men and women from the general population aged 15–29 years, stratified into three five year age groups. Sample size calculation was based on an expected prevalence in the general population of 3%, with a confidence interval of 1% around the expected prevalence for each age group separately, and a response rate of 50% for females and 33% for males.[23]Because complications of chlamydial infection are found primarily in females, taking a larger sample of females increased statistical power.

The sample was stratified according to "area address density" (AAD). Statistics Netherlands divides every municipality in the Netherlands into one of the following five AAD categories: (1) very highly urbanised (>2500 addresses/km^2); (2) highly urbanised (1500–2500 addresses/km^2); (3) moderate urbanised (1000–1500 addresses/km^2); (4) low urbanisation (500–1000 addresses/km^2) and (5) rural (<500 addresses/km^2). The total sample of 21 000 was divided over these five strata according to the distribution of these areas in the Netherlands. AAD categories 1 and 5 were oversampled because of an expected lower response rate in very highly urbanised areas and an expected lower prevalence in rural areas. The study took place in four non-randomly selected Public Health regions in different parts in the Netherlands. Study areas were selected purposively from MHS that were willing to participate in the study in a major city outside Amsterdam, and areas covering the north, south, and central part of the country. For each region it was decided which AAD categories would be included, taking into account the AAD profiles of the municipalities in each region, and an equal distribution of the total sample over the four regions. In every AAD category, a random sample was taken from the civil registration of the municipalities involved, with respect to the required number of females and males in each age group. In effect, the sampling procedure reflects a national probability sampling, including four regions of the country, which together are considered to reflect the general population of the Netherlands.

Population size and sampling method

Between September 2002 and March 2003 the selected people received a package by mail containing an introductory letter, an information leaflet on chlamydia, a urine sampling kit with instructions, a 18 item questionnaire concerning demographic characteristics (age, sex, education, ethnic group), sexual behaviour, symptoms of STI, and history of STI. The urine sample and questionnaire could be returned by mail in a postage paid plastic envelope to the central laboratory. All subjects, whether sexually active or not, were invited to participate; any person not wishing to participate could indicate this on a refusal card. Non-respondents received a reminder after six weeks. All participants received their test result by mail within three weeks. For people who tested positive, treatment of both the participant and partner(s) was provided through the regular services (GP or STI/MHS

clinic). The study was approved by the medical ethics committee of the Free University Amsterdam, the Netherlands. Fifteen year old participants needed to add an informed consent form signed by their parent or guardian.

Diagnostics

Nucleic acid amplification tests, such as polymerase chain reaction (PCR), are currently advised for *C trachomatis* testing.[24] As a pooling strategy was estimated to reduce the laboratory costs by half,[25] urine samples were pooled by five (based on an expected prevalence of 3%) and tested for the presence of chlamydial DNA by means of polymerase chain reaction (PCR Roche Diagnostic Corp, Indianapolis, IN, USA). From positive pools (OD >0.8), all individual samples were tested to identify the *C trachomatis* positive person. Samples of pools in the grey zone (OD 0.2–0.8) and "inhibited" pools were retested individually by PCR. If an inhibited sample or a result in the grey zone could not be confirmed by dilution/specimen preparation and/or discrepant analysis, a new urine sample was asked from the participant. A positive result of both pool and individual specimen was labelled as a positive test. Results were communicated to the MHS, who in turn informed the participants by mail.

Treatment of cases

In case of a positive result, people were advised to be treated by a regular care provider, being GP or STI/MHS clinic. A letter was included to give to their care provider, containing information on the findings, current standard of care for treatment of index and partner(s), and a return slip for the MHS to monitor treatment. Upon arrival of the return slip with information on (partner) treatment, the GP received Euro 22, the price of a standard consultation.

Non-response

Possible selection bias between participants and non-participants were studied in three different ways: (1) by comparing basic demographic variables from the civil registration available for all invited people (age, sex, residence, country of birth, and AAD) between participants (who returned urine and questionnaire) and non-participants (those who returned a refusal card and non-respondents); (2) by studying reasons for non-participation, as indicated on the refusal cards; and (3) by telephone interview with a structured questionnaire of a random sample of 700 non-respondents 12 weeks after the initial invitation. Contacted non-respondents were asked to answer questions about most important reason for non-response, demographic characteristics, sexual behaviour, symptoms of STI, and history of STI. People could stop this interview at each step. General and specific characteristics of this group were compared with those of the participants.

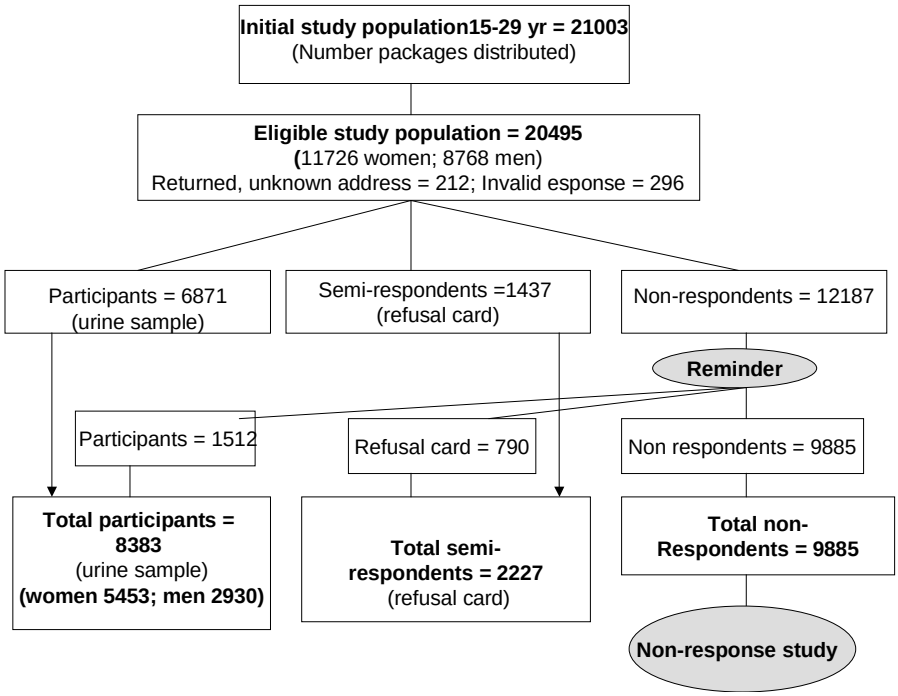
Statistical analysis

Analysis was performed with the SPSS package version 10.0 (SPSS Inc, Chicago, IL, USA). Prevalence rates were calculated with 95% confidence intervals. Adjusted prevalence rates were computed by using specific weights according to sex, age group, and AAD, calculated by inverse probability weighting[26] based on national figures for 2002

as provided by Statistics Netherlands. Unless otherwise specified, weighted prevalence data are given.

Differences in characteristics between participants and non-responders were analysed using the *X*-squared or Fischer's exact test. Associations between prevalence and several characteristics were assessed by univariate logistic regression analyses.

Figure 1: Flowchart PILOT CT study



Results

Response rates

Of all 21 003 packages distributed, 212 (1%) were returned by post because of unknown address. These people were excluded from analysis. A further 296 participants (1.4%) were excluded because of invalid responses, mainly due to inconsistencies in age and sex as reported on the questionnaire and as documented in the civil registry. Of the 20 495 remaining people, 8383 sent in urine (41% participants), 2227 sent in a refusal card (11% refusals), and 9885 did not respond (48%) (fig 1). Participation was lowest in very highly urbanised areas (AAD 1, 37%; AAD range 1–5, 37%–46%; $p<0.001$). Reminders contributed 1512 of 8383 participants (18%). Women participated more often than men (47% v 33%; $p<0.001$). Participation was 38% in 15–19 year olds and 43% in 20–24 and 25–29 year olds ($p<0.001$). People born in the Netherlands participated more often than those born abroad (42% v 31%; $p<0.001$). Response rate among people born in Surinam was 32.5%, Antilles 30.1%, Turkey 25.8%, Morocco 22.9%, other countries 30.4%.

The reasons for non-participation mentioned on the refusal cards are given in table 3.1; 32% reported that the main reason was "never had sex". Of the random sample of 700 non-responders, 410 could not be reached due to missing telephone numbers or no contact after five different attempts in three consecutive days in daytime and evening hours. Of the 290 remaining non-responders, 40% gave as main reason for non-participation no interest or no time. Two hundred and thirty eight were willing to answer the structured questionnaire in more detail.

Table 3.1: Main reason for non-participation among men and women as reported on refusal cards

Reason non participation	Men	%	Women	%	Total	%
No interest	357	42	331	32	688	36
Never had sex	239	28	357	34	596	32
Do not want to tell	119	14	112	11	231	12
Other	58	7	101	10	159	8
Doubts about privacy	30	4	42	4	72	4
Tested during last year	12	1	53	5	65	3
No time	24	3	27	3	51	3
Too much burden	16	2	16	2	32	2
TOTAL*	855	100	1039	100	1894	100

* No information provided on 15% of the 2227 returned refusal cards

Compared with the participants, non-responders more often had an intermediate level of education. Non-responders reported fewer STI related symptoms (p<0.001) and reported "never had sex" more often (p = 0.002). Among sexually experienced non-responders, the number of lifetime partners was quite similar to the participants, but they reported less STI in the past and more condom use during their last act (table 3.2)

Table 3.2: Specific characteristics of participants and a subset of non-responders (non-response study)

	Participants			Non-responders			
	n	N	%	n	N	%	p-value
Ethnicity							0.11
Dutch	7516	8181	92%	218	230	95%	
Non Dutch	665	8181	8%	12	230	5%	
Education							<0.001
Low	2093	8073	26%	51	232	22%	
Intermediate	3394	8073	42%	131	232	56%	
High	2586	8073	32%	50	232	22%	
Symptoms&							
Yes (men)	218	2918	8%	3	117	3%	0.05
Yes (women)	1978	5421	37%	17	121	14%	<0.001
Yes (total)	2196	8339	26%	20	238	8%	<0.001
Ever had sex							
Yes (men)	2317	2842	82%	78	103	76%	0.14
Yes (women)	4688	5342	88%	79	99	80%	0.02
Yes (total)	7005	8184	86%	157	202	78%	0.002
Number lifetime partners*							0.45
1	2545	6945	37%	56	155	36%	
2-5	3257	6945	47%	72	155	46%	
6 or more	1143	6945	16%	27	155	17%	
Sex in the past 6 months*							
Yes (men)	1999	2308	87%	62	74	84%	0.48
Yes (women)	4304	4677	92%	61	70	87%	0.14
Yes (total)	6303	6985	91%	123	144	85%	0.06
New partner last 2 months#	765	6280	12%	13	115	11%	0.78
Condom used last contact#							
Yes (men)	565	1993	28%	19	61	31%	0.63
Yes (women)	765	4291	18%	17	60	28%	0.04
Yes (total)	1330	6284	21%	36	121	30%	0.02
Ever diagnosed with STI*							
Yes	388	6970	6%	3	154	2%	0.05

Missing values reduce the denominator in several categories.
P = p-value of Chi-square or Fischer's exact test.
* Only if sexually active (ever)
# Only in sexually active in the past 6 months
& Symptoms in men: pain in passing urine, more frequent urination and/or penile discharge. Symptoms in women: intermenstrual or postcoital bleeding, abnormal vaginal discharge, pain in passing urine, frequent urination and/or lower abdominal pain

Table 3.3: Adjusted* chlamydia prevalence (%) according to age-group, sex and urbanisation (Area Address Density)

		Prevalence (95% CI)										n/N	N
		AAD 1 Very high urban		AAD 2 High urban		AAD 3 Moderate urban		AAD 4 Low urban		AAD 5 Rural		Total		UW	WT
15-19	M	2.9	(0.6-5.1)	0.6	(0.0-1.3)	1.0	(0.0-2.2)	0.7	(0.0-1.6)	0.0	(0.0-1.9)	1.0	(0.4-1.5)	9/ 916	1350
	F	4.3	(1.5-7.0)	2.6	(0.9-4.3)	1.9	(0.2-3.5)	3.5	(1.4-5.7)	0.0	(0.0-2.0)	2.6	(1.7-3.4)	42/1657	1284
20-24	M	1.4	(0.0-2.7)	0.5	(0.0-1.2)	1.1	(0.0-2.4)	3.0	(1.0-5.1)	0.6	(0.0-1.8)	1.3	(0.7-1.9)	14/1023	1370
	F	3.4	(1.4-5.4)	1.8	(0.5-3.1)	0.8	(0.0-1.9)	2.1	(0.3-4.0)	0.7	(0.0-2.1)	1.9	(1.2-2.7)	32/1869	1342
25-29	M	4.1	(2.1-6.2)	0.9	(0.0-1.9)	3.2	(1.1-5.3)	0.7	(0.0-1.8)	1.2	(0.0-2.8)	2.1	(1.4-2.8)	20/979	1509
	F	3.3	(1.4-5.1)	3.6	(1.8-5.3)	2.9	(0.9-4.8)	2.3	(0.5-4.1)	1.3	(0.0-3.0)	2.9	(2.0-3.7)	48/1895	1485
Total	M	2.9	(1.8-4.0)	0.7	(0.2-1.2)	1.8	(0.9-2.7)	1.4	(0.6-2.2)	0.6	(0.0-1.2)	1.5	(1.1-1.8)	43/2918	4228
Total	F	3.5	(2.3-4.8)	2.7	(1.8-3.6)	1.9	(0.9-2.8)	2.7	(1.6-3.8)	0.6	(0.0-1.3)	2.5	(2.0-3.0)	122/5421	4111
Total	T	3.2	(2.4-4.0)	1.7	(1.2-2.2)	1.8	(1.2-2.5)	2.0	(1.3-2.7)	0.6	(0.1-1.1)	2.0	(1.7-2.3)	165/8339	8339
n/N	UW	60/1769		31/1547		29/1565		33/1505		12/1953					
N	WT	1767		2325		1626		1621		1000					

* Adjusted prevalence: inverse probability weighted for age/sex/AAD (see Methods)
Area Address Density: AAD1, very high urban (>2500 addresses/km^2); AAD2, high urban (1500-2500 addresses/km^2); AAD3, moderate urban (1000-1500 addresses/km^2); AAD4, low urban (500-1000 addresses/km^2); and AAD5, rural (<500 addresses/km^2);
n/N, number positives among total participants; UW, unweighted; WT, weighted.

Table 3.4: Adjusted* chlamydia prevalence (%) among participants according to selected variables

	MEN			n/N	N		WOMEN			n/N	N		TOTAL			n/N	N	
	Prev	95% CI		UW	WT	P ¶	Prev	95% CI		UW	WT	P	Prev	95% CI		UW	WT	P
Overall	1.5	(1.1-	1.8)	43/2918	4228		2.5	(2.0-	3.0)	122/5421	4111		2.0	(1.7-	2.3)	165/8339	8339	<0.001
Ethnicity						0.052						<0.001						<0.001
Dutch	1.4	(1.0-	1.8)	36/2608	3759		2.2	(1.7-	2.7)	98/4908	3688		1.8	(1.5-	2.1)	134/7516	7446	
Suriname/Antilleans	4.4	(0.0-	9.3)	2/43	68		12.1	(5.4-	18.8)	13/104	91		8.2	(3.9-	12.5)	15/147	158	
Turkish/Moroccan	6.3	(1.0-	11.7)	3/50	79		1.2	(0.0-	3.6)	1/97	82		3.1	(0.4-	5.8)	4/147	160	
Other	1.4	(0.0-	3.0)	2/142	213		3.3	(0.7-	5.8)	7/229	184		2.3	(0.8-	3.7)	9/371	397	
Education						0.001						0.004						<0.001
Low	2.5	(1.6-	3.3)	21/859	1257		3.6	(2.4-	4.7)	40/1234	956		2.9	(2.2-	3.6)	61/2093	2214	
Intermediate	1.5	(0.9-	2.1)	16/1124	1579		2.6	(1.8-	3.3)	53/2270	1670		2.1	(1.6-	2.6)	69/3394	3250	
High	0.6	(0.2-	1.1)	6/832	1243		1.5	(0.8-	2.1)	24/1754	1359		1.1	(0.7-	1.5)	30/2586	2602	
Symptoms §						<0.001						<0.001						<0.001
Yes	5.2	(2.8-	7.7)	10/218	325		3.8	(2.8-	4.8)	67/1978	1527		4.0	(3.1-	4.9)	77/2196	1851	
No	1.2	(0.8-	1.5)	33/2700	3904		1.7	(1.2-	2.2)	55/3443	2584		1.4	(1.1-	1.7)	88/6143	6488	
Sexually active						0.001						<0.001						<0.001
Yes	1.8	(1.3-	2.2)	41/2317	3354		2.8	(2.3-	3.4)	119/4688	3550		2.3	(2.0-	2.7)	160/7005	6904	
No	0.4	(0.0-	0.8)	2/525	760		0.2	(0.0-	0.6)	1/654	499		0.3	(0.0-	0.6)	3/1179	1259	
No. lifetime partners#						<0.001						<0.001						<0.001
1	0.5	(0.1-	0.9)	5/716	1007		0.6	(0.2-	1.0)	10/1829	1345		0.6	(0.3-	0.9)	15/2545	2353	
2-5	1.3	(0.7-	1.9)	13/1057	1518		2.9	(2.1-	3.8)	58/2200	1667		2.1	(1.6-	2.6)	71/3257	3184	
6 or more	4.1	(2.7-	5.5)	21/518	784		8.0	(5.6-	10.3)	49/625	514		5.6	(4.4-	6.9)	70/1143	1298	

Adjusted prevalence: inverse probability weighted for age/sex/AAD (see Methods); ¶ P-value of Likelihood ratio test in univariate logistic regression; §Symptoms in men: pain in passing urine, more frequent urination and/or penile discharge; Symptoms in women: intermenstrual or postcoital bleeding, abnormal vaginal discharge, pain in passing urine, frequent urination and/or lower abdominal pain; # only if sexually active (ever); Missing values reduce the denominator in several categories; n/N, number of positives among total participants with information on this variable; UW, unweighted; WT, weighted.

Prevalence

Urine samples were available from 8383 respondents. Inhibition occurred in less than 0.5% of the samples. For 44 participants (0.5%), urine test results were not available (missing second urine sample in case of inhibition in the first sample or missing parental informed consent). Thus, prevalence was based on urine test results of 8339 participants. 165 tested positive. Adjusted prevalence did not differ much from the unweighted prevalence in our national probability sample. Overall (inverse probability weighted) prevalence was 2.0% (95% CI 1.7 to 2.3); higher in women (2.5% (2.0–3.0)) compared with men (1.5% (1.1–1.8)). Age group specific prevalence was 1.7% (1.2–2.2) in 15–19 year olds, 1.6% (1.1–2.1) in 20–24 years, and 2.5% (1.9–3.1) in 25–29 year olds. Prevalence was significantly lower in rural areas: (0.6% (0.1–1.1)) compared with very highly urbanised areas (3.2% (2.4–4.0)) (table 3.3). The highest prevalence was found in very highly urbanised areas in 15–19 year old women (4.3%) and in 25–29 year old men (4.1%). In all age groups, prevalence was higher among women compared with men.

In univariable logistic regression analysis prevalence was dependent of (high) urbanisation, (low) education, non-Dutch ethnicity (especially belonging to Surinamese or Antillean population), STI symptoms, and sexual behaviour (table 3.4). For sexually active participants we developed a risk factor model by multivariable logistic regression analysis. Degree of urbanisation, age group, ethnicity, education, symptoms (for women, postcoital bleeding; for men, frequent urination), no condom use at last sexual contact, number of sex partners, and recent partner change were independent risk factors. Prediction rules for selective screening could be developed (see Chapter 4).[27]

Treatment

For 150/165 (91%) positive index cases, information that they were treated was available. Eighty two per cent of the 150 cases visited the GP; the others were treated by STI/MHS clinic. For all these cases, on the return slip was indicated that partner treatment was discussed.

Discussion

This study is the first nationwide study in the Netherlands and internationally one of the largest population based studies, covering both women and men, and focussing not only on urban but also on rural populations. Fifty two per cent of those invited responded: 41% participated by returning urine and a questionnaire, and 11% returned a refusal card. The overall prevalence was 2%. A striking finding was the remarkably low chlamydia prevalence in rural areas (0.6%). In very highly urbanised areas the prevalence rate was 3.2% and participation 37%, compared with 44% in rural areas. We demonstrated that organising a home based screening through the MHS, referring screen positives to regular care providers, was feasible, and that 91% of screen positives were treated.

Remarkably, we found that the prevalence of chlamydia did not decline in those aged 25–29 years. This is consistent with the results of recent studies from Belgium and Finland.[28,29] Chlamydia screening is considered for women aged 15–25 years because high

prevalence is reported in this young age group. Although our finding might reflect persistent infections detected in a first screening round, epidemiological patterns may differ between and within countries and algorithms for age selective screening need local validation. The highest prevalence was found in very highly urbanised areas in 15–19 year old women (4.3%) and in 25–29 year old men (4.1%). Although women suffer the major burden of disease, evidence is growing that men need to be targeted as well, making them rather part of the solution instead of the problem.[18,30]

Even though our study was population and not clinic based, 26% of the participants reported possible STI related symptoms and chlamydia prevalence was significantly higher among them (4.0% *v* 1.4%; $p<0.001$). This warrants more attention to health care seeking behaviour and for diagnostic testing in primary care.

Prevalence was found to be dependent on sexual risk behaviour, but was also independently associated with other risk factors such as degree of urbanisation and ethnicity. Prevalence among Surinamese/Antillean women was as high as 12%—a finding in line with previous studies[23,31] and reflecting sexual risk behaviour, mixing patterns, and background prevalence within sexual networks. We describe a prediction rule for selective screening in a separate paper.[27] Further research on risk factors is warranted to determine prediction rules for selective screening that perform well in ongoing screening programmes based on prevalence.[32]

Limitations

One limitation of our study was the relatively low response rate. We did, however, collect demographic information on all non-respondents and details of sexual behaviour in a subset. We found evidence of participation bias that might influence our prevalence estimates in both directions. On one hand there was lower participation in people from minority ethnic groups and in highly urbanised areas, where prevalence was higher. On the other hand non-respondents reported fewer STI related symptoms, more frequent condom use, and were less likely to have a history of STI. This reflects the conflicting evidence about participation in screening programmes that high-risk groups tend to decline screening, but on the other hand people make "informed" choices for non-participation if (they consider themselves) at lower risk. For instance, one third of the reasons mentioned on the refusal cards for not participating were "not being sexually active" or "having been tested recently".

A second limitation is the fact that our study - like so many other published "screening" studies - was in fact a cross sectional prevalence study, at only one point in time. Response, participation of professionals, and prevalence is likely to change once screening becomes a routine programme. We reported that acceptability of future screening offered with regular intervals is significantly lower among screen negatives than in screen positives,[33] suggesting that participation (of lower risk groups) would decrease in an ongoing programme. However, this limitation might be turned into a positive strategy, as has been proposed recently in screening for cardiovascular risk.[34] Because many screening programmes harbour (negative) side effects, harms, and uncertainties,[35,36] well informed choices can motivate those people to participate who are most likely to benefit. Thus, instead of perpetuating the public health imperative of maximising response, selective

non-response in systematic screening based on informed choices may yield higher prevalence and offer client centred and more cost effective screening opportunities.

A third issue to be considered in screening studies is the use and possible abuse of screening tests. This issue was recently explored in depth.[37] In low prevalence settings, even excellent tests have poor positive predictive value (PPV). The example was given of a "new" and excellent chlamydia test in a 3% prevalence setting, ending up with a PPV of 0.5, incorrectly labelling 50% of the positives. In our study we had chosen for a pooling strategy, a positive test result being based on two positive tests (a positive pool and a second positive sample). Further analysis of positive samples using another chlamydial genomic target (MOMP gene) showed that only two of 165 positive samples could not be confirmed with this different test. Thus, our testing strategy yielded a PPV of 0.99.

Pooling reduces cost substantially,[25] but there is some concern that pooling might affect sensitivity and lead to a lower prevalence rate and untreated positives in the community. However, in contrast with pooling by 10, pooling by 5 (as we did in our study) appears to be as sensitive in identifying positive people compared with individual testing using the Roche PCR.[38,39]

Context and comparison

Internationally, our participation rates (women 47%, men 33%) compare favourably with the Danish in-home sampling (women 39%, men 27%)[21] and the UK CLASS population based studies (women 34%, and men 25%),[40] although higher prevalence rates are reported in these studies.

Our participation and prevalence rates in the very highly urbanised areas (AAD 1: response 42% in women and 30% in men, and a prevalence of 3.5% and 2.9% respectively) are similar to a previous systematic home based screening in the capital Amsterdam (AAD 1).[23] In that survey, where the invitation letter and home sampling kit was sent by the GP, participation among 15–30 year olds was 47% in women and 30% in men, and prevalence 3.3% and 2.9% respectively.

In general, opportunistic screening has a higher yield than systematic screening. In an opportunistic screening pilot of women aged 16–24 years in the UK at venues such as family planning clinics, STI clinics, and general practices, prevalence ranged from 3.4%–17.6%, being approximately 9% in general practice.[20] Opportunistic screening in several general practices in Amsterdam revealed a prevalence of 6.6% (15–29 year olds).[31] Among sexually active women in Belgium, visiting their GP for routine gynaecological care, prevalence was 5%.[28] If an opportunistic screening design is chosen, incorporating general practice is crucial, as impact on population prevalence will depend on reaching a substantial proportion of the at-risk population. Given financial constraints in health care, professional attitude and manpower deficiency in general practice, this is a major bottleneck. Organising prevalence based, selective chlamydia screening via the MHS, whose focus is on public health, is an alternative if cost effectiveness analysis proves to be favourable.

Conclusions

Population prevalence, also outside the big cities, is important to determine the burden of disease and to guide policy recommendations, especially if a new national programme is envisaged. We found very low prevalence rates in rural populations, suggesting targeted approaches and prioritising high-risk areas in the enrolment of screening in the Netherlands. Our pilot study indicates that home based urine testing, organised by the MHS and in close cooperation with regular primary care providers for treatment of screen positives, is feasible, although participation problems clearly exist. There are still gaps in our knowledge regarding the issue of chlamydia screening and expanding the body of evidence is needed before a new nationwide screening programme is widely implemented in the Netherlands. Analysis of risk profiles and cost effectiveness will contribute to determining how selective screening can be used. Meanwhile more active case finding of chlamydial infections is warranted in high-risk areas, in high-risk groups, in cases of high-risk sexual behaviour, and in cases of clinical suspicion (diagnostic testing).

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4

A prediction rule for selective screening of *Chlamydia trachomatis* infection

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Abstract

Background

Screening for *Chlamydia trachomatis* infections is aimed at the reduction of these infections and subsequent complications. Selective screening may increase the cost-effectiveness of a screening programme. Few population-based systematic screening programmes have been carried out and attempts to validate selective screening criteria have shown poor performance. This study describes the development of a prediction rule for estimating the risk of chlamydial infection as a basis for selective screening.

Methods

A population-based chlamydia screening study was performed in the Netherlands by inviting 21.000 15-29 year old women and men in urban and rural areas for home-based urine testing. Multivariable logistic regression was used to identify risk factors for chlamydial infection among 6303 sexually active participants, and the discriminative ability was measured by the area under the receiving operating characteristic curve (AUC). Internal validity was assessed with bootstrap resampling techniques.

Results

The prevalence of *C.trachomatis* infection was 2.6% (95% CI 2.2-3.2) in women and 2.0 % (95% CI 1.4-2.7) in men. Chlamydial infection was associated with high level of urbanisation, young age, Surinam/Antillean ethnicity, low/intermediate education, multiple lifetime partners, a new contact in the previous two months, no condom use at last sexual contact, and complaints of (post)coital bleeding in women and frequent urination in men. A prediction model with these risk factors showed adequate discriminative ability at internal validation (AUC 0.78).

Conclusion

The prediction rule has the potential to guide individuals in their choice of participation when offered chlamydia screening and is a promising tool for selective Ct-screening at population level.

Introduction

Chlamydia trachomatis infection is the most prevalent sexually transmitted bacterial infection. It is usually asymptomatic and persistent of nature, and distributed widely in the population, particularly in young people.[1] The prevalence of chlamydial infection has increased recently in many countries, including the Netherlands.[2-5] In women, chlamydial infections are a major cause of pelvic inflammatory disease (PID), ectopic pregnancy, tubal infertility and chronic abdominal pain.[1] Active case-finding and early treatment are crucial strategies to reduce transmission. Systematic screening of women has been shown to reduce the incidence of PID and ectopic pregnancy.[6,7] Simple screening strategies (e.g. home-based) to detect people with an asymptomatic infection has become feasible by improved detection methods of *C.trachomatis* in urine[8-11] and by the availability of effective single-dose treatment. Universal screening is not likely to be cost-effective in a population with relatively low chlamydia prevalence. Selective screening, incorporating risk assessment may increase the cost-effectiveness and confronts fewer individuals with an unnecessary test. However, it could lead to an unacceptably high proportion of missed infections. Selective screening criteria for women have been applied in various clinic-based, opportunistic chlamydia screening programmes, but their effectiveness has not been evaluated sufficiently.[12,13] Selection criteria for both sexes have been studied recently in population-based screening programmes, but these have not led to practical guidelines for selection.[14,15]

The objective of our study was firstly to describe risk factors for chlamydial infection among sexually active responders in a large population-based chlamydia screening pilot study, including men and women aged 15 to 29 years from both urban and rural areas in the Netherlands.[16] Secondly, we wanted to identify a combination of risk factors that discriminated adequately between those who are infected and those who are not.

Methods

Study population

The data of this study were collected in a national probability survey in the Netherlands, which was implemented in four Municipal Public Health Service (MHS) areas and stratified according to area address density (AAD). From September 2002 through March 2003, 12.000 women and 9000 men aged 15-29 years received a package by post with a urine sampling kit and a questionnaire concerning demographic data (sex, age, self assigned ethnicity, education), symptoms, history of STI and sexual behaviour. Urine analysis was done by nucleic acid amplification test (PCR, Roche, Basel, Switzerland). The method of sampling and screening as well as response rates, non-response and weighted prevalence among all participants are described elsewhere.[16] The present analysis is restricted to those participants who reported sexual activity in the last six months, because risk factors were only available for this group. The Medical Ethics Committee of the Free University Amsterdam approved the study.

Statistical analysis

Univariate logistic regression analyses were performed, with self reported characteristics as independent variables and diagnosis of *C.trachomatis* as the dependent variable. For the odds ratios, 95% confidence intervals (CI) were calculated. Variables showing an association of $p < 0.2$ were included in the multivariable analysis. Backward stepwise selection was performed with a p-value for the likelihood ratio-test > 0.10 as the criterion for elimination of variables from the model. Interactions between predictors and sex were assessed to study whether effects of predictors were different for men and women. The goodness of fit (reliability) of the model was tested by the Hosmer-Lemeshow statistic. The model's ability to discriminate between participants with or without a chlamydial infection was quantified by using the area under the receiver-operating characteristic curve (AUC). AUC values 0.7-0.8 are considered acceptable, 0.8-0.9 excellent, and >0.9 outstanding.[17] Calibration was assessed graphically by plotting observed frequencies of chlamydial infection against predicted probabilities.

The performance of screening criteria in a study population, from which the model is developed, is known to often be too optimistic. The internal validity of the regression model was therefore assessed to estimate the performance of the model in new participants, similar to the population used to develop the model. We used bootstrapping techniques: random samples, with replacement, were taken one hundred times from the study population. At each step predictive models were developed, including variable selection.[18-20] Bootstrapping may help to reduce the bias in the estimated regression coefficients, and give an impression of the discriminative ability in similar participants of screening. The outcome is a correction factor for the AUC, and a shrinkage factor to correct for statistical over-optimism in the regression coefficients and to improve calibration of the model in future participants.[18,21,22] External validity was assessed by leaving out the four MHS in the sample one by one, and fitting regression models, including variable selection, on the remaining data. The discriminative ability of this model was assessed externally on the MHS data not included in the fitting procedure. This procedure replicates the situation in which the prediction model is applied in another MHS region with a population that may to some extent be different.

For the presence or level of each characteristic in the regression model, a score was calculated, based on the regression coefficients with rounding to simplify the calculation in practice. These scores are an immediate reflection of the logarithm of the odds ratios.[23] For each individual these scores were added into a sum score, on the basis of which a regression formula was calculated, taking into account the shrinkage factor derived from the bootstrap procedure. An estimate of the probability for chlamydial infection can be calculated through the regression formula $p(Ct) = 1/1+\exp^{(-LPS)}$, where LPS is linear predictor for score. All possible sum scores and their corresponding predicted probabilities of chlamydial infection were combined in a graph with 95% CIs of the predicted probabilities. The confidence interval was calculated, based on a covariance matrix. The average Standard Error (SE) of the rounded linear predictor values was used to calculate the 95% CIs of the predicted probabilities $(1/1+ e^{-(LPS +/- 1.96xSE)})$.[24]

For consecutive cut-offs of the sum scores, sensitivity, specificity, fraction positive and positive predictive values were calculated. Statistical analysis was done with SPSS statistical software version 10.0 (SPSS, Inc., Chicago, IL, USA) and with the Design Library for S-plus 2000 (Insightful Inc, Seattle, WA, USA).

Results

Prevalence among sexually active participants

The participation rate was 41% and the prevalence of chlamydial infection among sexually active responders was 2.3% (160/7005).[16] Among the 6303 participants who reported being sexually active in the previous 6 months, 153 tested positive (2.4% [95% CI 2.1-2.8]). The prevalence was 2.6% (95% CI 2.2 to 3.2) in women and 2.0 % (95% CI 1.4 to 2.7) in men.

Performance of predictive model and development of prediction score

Multivariable logistic regression analysis showed that chlamydial infection was associated with high urbanisation, young age, ethnicity (Surinamese/Antillean), low/intermediate education, multiple lifetime partners, a new contact in the previous two months, no condom use at last sexual contact, and complaints of (post)-coital bleeding in women and frequent urination in men (Table 4.1). The only statistically significant interaction term in the model was sex and the number of lifetime partners.

The Hosmer-Lemeshow goodness of fit test had a p-value of 0.12, indicating adequate goodness of fit. The model discriminated well between participants who were and were not infected by *C.trachomatis*, with an AUC of 0.81 [95% CI 0.77 to 0.84). Internal validation showed optimism in the AUC of 0.03, resulting in a correction of the AUC from 0.81 to 0.78. In the external validation similar sets of predictors were selected. When tested in each separate MHS, the AUC varied from 0.74 to 0.80. When leaving out the MHS representing mainly AAD 1 and 2, ethnicity did not remain in the model developed from the three other MHS areas. This is related to the finding that the majority of non-Dutch participants in our study population were from this particular MHS area.

Table 4.2 shows the scores of the prediction rule. The sum score for a 16 year old Surinam woman living in an moderate urbanised area, with intermediate education, 3 lifetime partners and a new contact in the previous two months, no postcoital bleeding and condom use during last intercourse, is 11 (1 + 2 + 2 + 2 + 3 + 1 + 0 + 0). The predicted probability of chlamydial infection for this participant is 11% (95% CI, 6 to 20%) (Figure 4.1). The discrimination on the basis of the sum score was as good as the discrimination of the original model (AUC 0.80 [0.76 to 0.84]).

Plots of observed frequency of infection against predicted probabilities showed that calibration of both the model and the score were good for the predicted probabilities up to 10% (Fig 4.2).

Table 4.1 Prevalence of C.trachomatis infection and risk factors among participants sexually active in the previous 6 months in a screening programme

				Univariable			Multivariable		
	n	N	%	OR	95% CI	p LR	OR	95% CI	p LR
Sex									
Men	39	1999	2.0%	1.0					
Women	114	4304	2.6%	1.4	0.9-2.0	0.088			
Age group						0.030			0.084
15-19 yrs	45	1440	3.1%	1.2	0.8-1.8		1.4	0.9-2.1	
20-24 yrs	43	2359	1.8%	0.7	0.5-1.0		0.8	0.5-1.2	
25-29yrs	65	2504	2.6%	1.0			1.0		
AAD #						<0.001			<0.001
AAD1	57	1344	4.2%	5.8	3.0-11.1		3.9	1.9-7.7	
AAD 2-4	85	3507	2.4%	3.3	1.7-6.1		2.6	1.4-4.9	
AAD5	11	1452	0.8%	1.0			1.0		
Ethnicity						<0.001			0.005
Dutch	125	5802	2.2%	1.0			1.0		
Surinamese/Antillean	15	116	12.9%	6.7	3.8-11.9		3.2	1.7-6.2	
Other	12	370	3.2%	1.5	0.8-2.8		1.0	0.5-1.9	
Education †						<0.001			<0.001
Low	55	1508	3.6%	2.8	1.8-4.4		3.0	1.8-4.9	
Intermediate	66	2567	2.6%	1.9	1.2-3.0		2.2	1.4-3.6	
High	29	2151	1.3%	1.0			1.0		
Women: complaints previous 4 weeks									
(Post) coital bleeding						0.004			0.053
Yes	12	184	6.5%	2.7	1.5-5.1		2.0	1.0-4.0	
No	102	4120	2.5%	1.0			1.0		
Intermenstrual bleeding						0.002			
Yes	18	321	5.6%	2.4	1.4-4.0				
No	96	3983	2.4%	1.0					
Abnormal vaginal discharge						0.025			
Yes	29	741	3.9%	1.7	1.1-2.6				
No	85	3563	2.4%	1.0					
Painful urination						0.228			
Yes	14	385	3.6%	1.4	0.8-2.5				
No	100	3919	2.6%	1.0					
Frequent urination						0.014			
Yes	21	465	4.5%	1.9	1.2-3.1				
No	93	3839	2.4%	1.0					
Lower abdominal pain						0.025			
Yes	29	741	3.9%	1.7	1.1-2.6				
No	85	3563	2.4%	1.0					

				Univariable			Multivariable		
	n	N	%	OR	95% CI	p LR	OR	95% CI	p LR
Men: complaints previous 4 weeks									
Frequent urination						0.016			0.051
Yes	6	102	5.9%	3.5	1.4-8.6		2.8	1.1-7.2	
No	33	1897	1.7%	1.0			1.0		
Painful urination						0.060			
Yes	4	71	5.6%	3.2	1.1-9.3				
No	35	1928	1.8%	1.0					
Urethral discharge						0.103			
Yes	2	26	7.7%	4.4	1.0-19.1				
No	37	1973	1.9%	1.0					
Age at first sex						<0.001			
<=15	61	1413	4.3%	3.0	2.0-4.6				
16-17	57	2433	2.3%	1.6	1.0-2.5				
>=18	32	2315	1.4%	1.0					
No. Lifetime partners (women)						<0.001			<0.001
1	8	1633	0.5%	1.0			1.0		
2-5	55	2045	2.7%	5.6	2.7-11.8		4.6	2.4-8.9	
6 or more	49	597	8.2%	18.2	8.5-38.6		13.5	6.8-27.1	
No. Lifetime partners (men)						<0.001			<0.001
1	4	567	0.7%	1.0			1.0		
2-5	13	919	1.4%	2.0	0.7-6.2		2.6	1.1-5.9	
6 or more	20	491	4.1%	6.0	2.0-17.6		5.3	2.4-11.7	
No. partners previous 6 months						<0.001			
1	103	5509	1.9%	1.0					
2-5	43	717	6.0%	3.3	2.3-4.8				
6 or more	7	77	9.1%	5.2	2.4-11.7				
Sexual preference						0.194			
Heterosexual	148	6179	2.4%	1.0					
Homo/bi-sexual	5	110	4.5%	1.9	0.8-4.8				
New contact previous 2 months						<0.001			0.004
Yes	47	765	6.1%	3.3	2.3-4.8		1.9	1.2-2.8	
No	106	5515	1.9%	1.0			1.0		
Condom use al last sexual contact						0.204			0.029
Yes	26	1330	2.0%	1.0			1.0		
No	126	4954	2.5%	1.3	0.9-2.0		1.6	1.0-2.6	
Contraception at last sexual contact						0.169			
Yes	124	5312	2.3%	1.0					
No	28	895	3.1%	1.4	0.9-2.0				
History of self reported STI						0.005			
Yes	18	371	4.9%	2.2	1.3-3.7				
No	132	5894	2.2%	1.0					

* AAD1 - very high urban (>2,500 addresses/km2); AAD2 - high urban (1,500-2,500 addresses/km2); AAD3 - moderate urban (1,000-1,500 addresses/km2); AAD4 - low urban (500-1,000 addresses/km2); AAD5 - rural (<500 addresses/km2). † Low – primary school, lower vocational or lower general secondary education; Intermediate – intermediate vocational education, intermediate or higher general secondary education; High – higher vocational education or university education

Table 4.2: Prediction rule for quantifying the probability of Ct infection

Predictor	Women	Men
Age group (years)		
15-19 years	1	1
20-24 years	0	0
25-29 years	0	0
AAD		
Rural (AAD5)	0	0
Low-moderate-high urban (AAD 2-4)	2	2
Very high urban (AAD1)	3	3
Ethnicity		
Dutch or other	0	0
Surinam or Antillean	2	2
Education		
Low or intermediate	2	2
High	0	0
*Urogenital symptoms **	1	2
Lifetime sexual partners		
1	0	0
2-5	3	2
6 or more	5	3
New partner previous 2 months	1	1
No condom last sexual contact	1	1

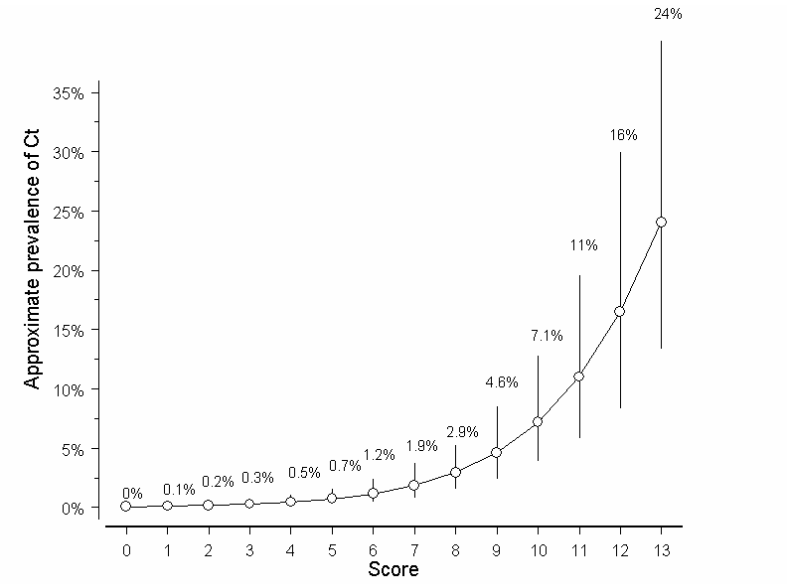
*Women: (Post)coital bleeding previous 4 weeks; Men frequent urination previous 4 weeks
An estimate of the probability of C.trachomatis infection can be calculated using the formula p(Ct)= 1/1+exp (-LPS), where LPS = -7.26+0.47x score

Table 4.3: Implications of using the prediction rule for screening for chlamydia

Cut-off Sum score*	Sensitivity†	Specificity‡	Fraction positive §	PPV ||
≥0	100.0%	0.0%	100.0%	2.3%
≥1	100.0%	0.5%	99.5%	2.4%
≥2	100.0%	2.4%	97.7%	2.4%
≥3	100.0%	4.6%	95.5%	2.5%
≥4	99.3%	14.4%	85.9%	2.7%
≥5	94.4%	23.0%	77.4%	2.9%
≥6	93.1%	38.3%	62.4%	3.5%
≥7	86.8%	56.0%	45.0%	4.5%
≥8	79.2%	68.4%	32.7%	5.7%
≥9	59.0%	83.2%	17.8%	7.8%
≥10	41.7%	92.2%	8.6%	11.4%
≥11	27.8%	96.8%	3.7%	17.5%
≥12	11.8%	98.9%	1.4%	20.5%
≥13	4.2%	99.8%	0.3%	31.6%
≥14	1.4%	99.9%	0.1%	25.0%

* Selection criterion for screening; † Percentage of detected chlamydial infections among our study participants when screening under the given selection; ‡ Percentage of chlamydia negative participants who would not be screened justly ; § Percentage of the total population that is eligible for screening under the given selection; || PPV: Prevalence in the screened population (predictive value of selection criterion)

Figure 4.1. Predicted probability of *C.trachomatis* infection as a function of the sum score



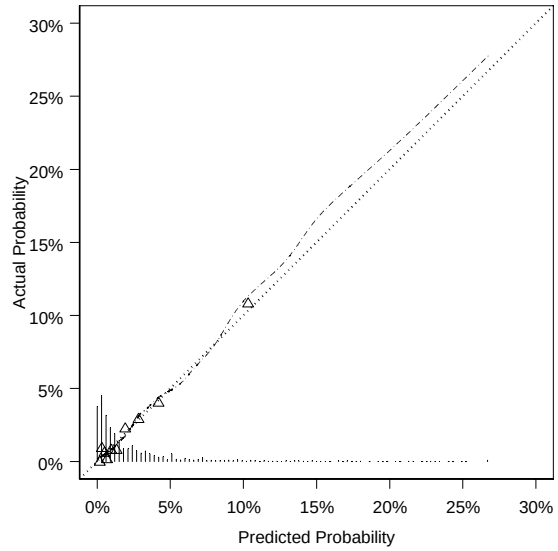
The sum score (horizontal axis) was derived from the prediction rule (table 4.2). On the vertical axis the predicted prevalence of C.trachomatis is depicted. Vertical lines represent 95% CIs. Since only eight participants had a sum score of 14 (predicted prevalence 33% [18-55%], this score is no shown.

Application of the prediction rule

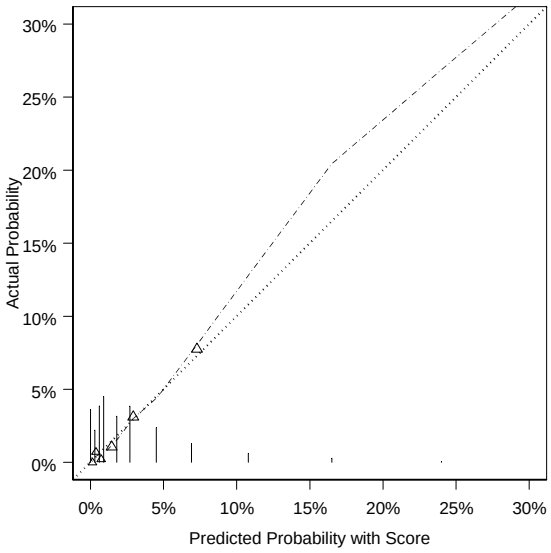
The probability of chlamydial infection according to the prediction rule can be used for selection in chlamydia screening. Table 4.3 shows the results for different cut-off levels of sum scores. The first row gives the scenario for performing screening in our whole study population and therefore identifying all patients with a *C.trachomatis* infection (sensitivity 100%). When screening is performed in all sexually active participants with a sum score ≥ 8, the number to be screened in our study population would be reduced to 33%. However, 21% of the cases would then be missed (sensitivity 79%). The expected prevalence in the screened group would be 5.7%, in contrast to 2.3% on average. By lowering the cut-off from a sum-score ≥ 8 to ≥ 6, one would have to screen an additional 30% of the population to find 93% of the cases. By doing this, the percentage of unnecessary screened people in the study population would increase from 32% to 62%.

Figure 4.2: Observed frequencies of *C.trachomatis* infection against predicted probabilities

Calibration plot of original model



Calibration plot of score (including shrinkage)



Triangles indicate observed frequencies by group of patients with similar predicted probabilities

Discussion

In this large, population-based study demographic, behavioural, clinical, and geographic risk factors in 15-29 year old women and men were identified from which a prediction rule for *C.trachomatis* infection could be developed. This study has led to a promising tool for selective chlamydia screening at population level.

Risk factors identified

Young age predicted chlamydial infection independently, as has been reported by others.[25] Surinamese/Antillean ethnicity proved to be a strong predictive factor, confirming previous findings in Amsterdam.[15,26] Contrary to other population based studies, we observed low and intermediate education to be predictive for chlamydial infection in both sexes.[15,25,27] Ethnicity and level of education as a risk factor may merely reflect risky sexual behaviour. Nevertheless, we assume the independent character of these variables to reflect risks involved in sexual partner choice: in case of unsafe sex, acquisition of a chlamydial infection is related to chlamydia prevalence background rates within particular sexual networks. Area address density (AAD), a geographic factor, remained an independent risk factor for chlamydial infection. As expected, people living in very highly urbanised areas (AAD1) have the highest risk. However, living in less urbanised areas (AAD2-4) was also associated independently with chlamydia infection. This finding may be important for decision making regarding future screening programmes. Incorporating AAD score points in selective screening decisions takes care of variations in prevalence within and between regions.[28]Although symptoms of frequent urination and (post)-coital bleeding in the previous four weeks symptoms were relatively infrequent and have probably not led to health care seeking behaviour, they predicted chlamydial infection. The number of lifetime partners was a strong independent predictor for chlamydial infection, but with a difference in the strength of association for men and women. Other indicators of sexual behaviour that proved predictive were a new contact in the previous two months, and unsafe sex at last contact. This finding is in line with systematic and opportunistic screening programmes in women.[15,25,27,29] Young age at first sex and multiple partners in the previous six months were significant univariable risk factors but did not remain in the model, which can be explained by correlation with lifetime partners.

Methodological considerations

An important objective of this study was to develop a prediction model, based on risk factors that discriminate adequately between those who are infected with *C.trachomatis* and those who are not. Logistic regression is the most appropriate statistical technique to achieve this goal. Decisions about selection in screening could also be based on a decision tree type model, but in comparative studies the performance of classification and regression trees was not better than classical regression methods.[30-32] We therefore preferred logistic regression as for our statistical analysis.

In first instance we had constructed separate models for females and males, but due to low numbers the separate male model was not very robust. Also, most risk factors had very similar effects in both sexes (Appendix table 4.4 and 4.5). To enhance power, we

combined males and females in one model. Interactions between sex and all other determinants for chlamydial infection were tested extensively and the only interaction present was between sex and the number of lifetime partners. This effect was included in the combined model, resulting in different scores for this factor for females and males. The strength of the combined model is illustrated for the variable ethnicity. This variable disappeared in the male model because of a lack of power, causing a separate male model to be awkward to work with in practice. In a combined model, effects in males can be influenced by effects in females, but as the ratio of females to males is approximately 2:1, we consider the balance between the sexes in the combined model to be acceptable.

Performance of screening criteria in a study population is often too optimistic, and is seldom evaluated in another population. This is illustrated by disappointing performance of selective screening criteria for asymptomatic chlamydial infection in an inner-city population[33] and in different clinics.[12,13,15] While those studies used one part of their data as development sample and another part to validate their screening criteria, we used bootstrap re-sampling, which is statistically more efficient.[20] Bootstrapping may help to improve calibration of predictions, and give an impression of the discriminative ability in similar populations. In our test for generalizability (external validation), the model showed acceptable performance for the various MHS regions when using the three other MHS regions for developing the model. The lower AUCs at external validation can be explained to some extent by the sampling method, which was designed to obtain a representative sample for the Netherlands. Not all AAD categories were present in the respective MHS samples. Although our internal and external validation procedures showed satisfactory results in general, further validation is necessary before the prediction rule can be applied reliably in practice. Validation could be done on existing data sets that used similar definition of the predictor variables and for presence of chlamydial infection.

A limitation of our data is that we asked for details of sexual behaviour only in persons who had been sexually active in the previous six months – as this had consequences for partner tracing. Therefore, multivariable analysis could only be done for 90% (6303) of all sexually active participants and the derived score can be applied only to those who have been sexually active in the previous six months. The prevalence among those ever sexually active, but not in the previous six months, was 1% (7/681). Assuming no recent partner change and condom use at last contact (both score zero), allowed us to estimate the sum score with the available data. We then predicted chlamydial infection among the persons ever sexually active (through the formula in table 4.2). The AUC of the prediction in all ever sexually active participants was 0.80 (0.76-0.83) compared with the AUC of 0.81 (0.77-0.84) in the participants who were sexually active recently. This result provides an argument that in practice the prediction rule can be applied to all sexually active people. Another possible limitation of our study is the fact that the relatively low response rate, especially among men, non-Dutch and those with intermediate education, might affect our results due to selection bias.[16]

Application of the prediction rule for screening

Our sum score allows for prediction of chlamydial infection in individuals as well as applications for cut-off values for decisions in screening programmes at population level.

Usually a fixed choice of risk factors is used as selection criterion for screening. Instead, our sum score consists of varying combinations of risk factors, mirroring the probability of infection. Not every person has to fulfil a fixed combination of criteria for screening. The sum score can (potentially) guide individuals in their decision to accept the screening test. As we have shown, the predictive value of the screening criterion based on a selection of a score ≥ 8 would be 5.7%. Hence 94.3% of the eligible population screened would not have chlamydia. However, the absolute number of persons screened unnecessarily is lower than when screening without selection. The issue of the most efficient cut-off level depends on both costs and priorities – either finding most cases or minimising unnecessary screened people. In population-based screening – whether in a specified age group in the whole population or in a restricted geographic area - a prediction rule can be applied to motivate people with a score above a certain level to participate. For instance, an invitation letter for screening could include a simple questionnaire for calculating a personal score, together with a request form for a test kit, or a referral to a website on the Internet. In opportunistic screening, the clinician can inquire about the predictive criteria.

In conclusion this study found demographic, geographic, and behavioural characteristics as well as urogenital symptoms as indicators for chlamydial infections in 15 – 29 year old women and men in a population-based study. Our study indicates that one could consider screening all young women and/or men universally, whether systematic or opportunistic, in regions or settings with high prevalence, or apply the predictive score in regions or settings with lower prevalence. The prediction rule for chlamydial infection opens new avenues for risk assessment in population-based screening and possibly in opportunistic screening as well. Applicability of our prediction rule and performance when implemented require further study.

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Appendix

Table 4.4: Prevalence of *Ct* infection and risk factors among female participants

				Univariable			Multivariable		
	n	N	%	OR	95% CI	p LR	OR	95% CI	p LR
Women	114	4304	2.6%						
Age group						0.021			0.022
15-19 yrs	38	1041	3.7%	2.0	1.2 - 3.2		2.1	1.2 - 3.6	
20-24 yrs	30	1594	1.9%	1.0			1.2		
25-29yrs	46	1669	2.8%	1.5	0.9 - 2.4		1.2	0.7 - 2.0	
AAD *						<0.0001			0.002
AAD *	41	896	4.6%	6.2	2.9 - 13.2		3.5	1.6 - 7.9	
AAD 1	65	2369	2.7%	3.6	1.7 - 7.6		2.8	1.3 - 6.0	
AAD 2-4	8	1039	0.8%	1.0			1.0		
Ethnicity						<0.0001			0.0009
Dutch	93	3981	2.3%	1.0			1.0		
Surinamese	7	49	14.3%	7.0	3.0 - 15.9		3.9	1.5 - 10.2	
Antillean	6	32	18.8%	9.6	3.9 - 24.0		7.4	2.7 - 20.7	
Other	7	232	3.0%	1.3	0.6 - 2.8		1.0	0.4 - 2.3	
Education						0.001			0.005
Low	37	950	3.9%	2.6	1.5 - 4.4		2.4	1.3 - 4.2	
Intermediate	51	1814	2.8%	1.8	1.1 - 3.0		2.0	1.2 - 3.4	
High	23	1481	1.6%	1.0			1.0		
Intermenstrual bleeding						0.002			
Yes	18	321	5.6%	2.4	1.4 - 4.0				
No	96	3983	2.4%	1.0					
(Post) coital bleeding previous 4 wks						0.004			0.043
Yes	12	184	6.5%	2.7	1.5 - 5.1		2.1	1.1 - 4.2	
No	102	4120	2.5%	1.0			1.0		
Vaginal discharge						0.025			
Yes	29	741	3.9%	1.7	1.1 - 2.6				
No	85	3563	2.4%	1.0					
Painful urination						0.228			
Yes	14	385	3.6%	1.4	0.8 - 2.5				
No	100	3919	2.6%	1.0					
Frequent urination						0.014			
Yes	21	465	4.5%	1.9	1.2 - 3.1				
No	93	3839	2.4%	1.0					
Lower abdominal pain						0.025			
Yes	29	741	3.9%	1.7	1.1 - 2.6				
No	85	3563	2.4%	1.0					
Age at first sex						0.0002			
<=15	45	1020	4.4%	2.7	1.7 - 4.5				
16-17	44	1749	2.5%	1.5	0.9 - 2.5				
>=18	24	1454	1.7%	1.0					
No. lifetime partners						<0.0001			<0.0001
1	8	1633	0.5%	1.0			1.0		
2-5	55	2045	2.7%	5.6	2.7 - 11.8		5.4	2.4 - 12.1	
6 or more	49	597	8.2%	18.2	8.5 - 38.6		17.2	7.4 - 39.8	
No .partners previous 6 months						<0.0001			
1	81	3856	2.1%	1.0					
2-5	30	415	7.2%	3.6	2.4 - 5.6				
6 or more	3	33	9.1%	4.7	1.4 - 15.6				
Sexual preference						0.038			
heterosexual	110	4246	2.6%	1.0					
homo/bi-sexual	4	45	8.9%	3.7	1.3 - 10.4				

New contact previous 2 months						<0.0001				0.015
Yes	33	443	7.4%	3.7	2.5 - 5.7		1.9	1.1 - 3.0		
No	81	3849	2.1%	1.0			1.0			
Condom use at last sexual contact						0.110				0.012
Yes	14	765	1.8%	1.0			1.0			
No	99	3526	2.8%	1.5	0.9 - 2.7		2.1	1.1 - 3.9		
Contraception at last sexual contact						0.229				
Yes	92	3634	2.5%	1.0						
No	21	617	3.4%	1.4	0.8 - 2.2					
History of self reported STI						0.022				
Yes	14	283	4.9%	2.1	1.2 - 3.7					
No	98	3993	2.5%	1.0						

* AAD1 very high urban (>2,500 addresses/km^2); AAD2 high urban (1,500-2,500 addresses/km^2); AAD3 moderate urban (1,000-1,500 addresses/km^2); AAD4 low urban (500-1,000 addresses/km^2); AAD5 rural (<500 addresses/km^2).

Table 4.5: Prevalence of *Ct* infection and risk factors among male participants

				Univariable				Multivariable			
	n	N	%	OR	95% CI		p LR	OR	95% CI		p LR
Men	39	1999	2.0%								
Age group							0.676				
15-19 yrs	7	399	1.8%	1.0	0.4	2.6					
20-24 yrs	13	765	1.7%	1.0							
25-29yrs	19	835	2.3%	1.3	0.7	2.7					
AAD *							0.009				0.011
AAD 1	16	448	3.6%	5.1	1.5	17.5		5.0	1.4	- 17.9	
AAD 2-4	20	1138	1.8%	2.4	0.7	- 8.3		2.2	0.7	- 7.6	
AAD 5	3	413	0.7%	1.0				1.0			
Ethnicity							0.079				
Dutch	32	1821	1.8%	1.0							
Surinamese/Antillean	2	35	5.7%	3.4	0.8	- 14.7					
Turkish /Moroccan	3	33	9.1%	5.6	1.6	- 19.3					
Other	2	105	1.9%	1.0	0.2	- 4.4					
Education							0.012				0.006
Low	18	558	3.2%	3.7	1.5	- 9.4		4.3	1.6	- 11.2	
Intermediate	15	753	2.0%	2.2	0.9	- 5.8		2.6	1.0	- 6.8	
High	6	670	0.9%	1.0				1.0			
Painful urination							0.060				
Yes	4	71	5.6%	3.2	1.1	- 9.3					
No	35	1928	1.8%	1.0							
Frequent urination							0.016				0.052
Ja	6	102	5.9%	3.5	1.4	- 8.6		2.8	1.1	- 7.0	
nee	33	1897	1.7%	1.0				1.0			
Urethral discharge							0.103				
Yes	2	26	7.7%	4.4	1.0	- 19.1					
No	37	1973	1.9%	1.0							
Age at first sex							0.006				
<=15	16	393	4.1%	5.3	1.8	- 16.0					
16	8	343	2.3%	3.0	0.9	- 10.0					
17-18	11	697	1.6%	2.0	0.6	- 6.3					
>=19	4	505	0.8%	1.0							
No. lifetime partners							0.0001				
1	4	567	0.7%	1.0							
2-5	13	919	1.4%	2.0	0.7	- 6.2					
6-10	6	259	2.3%	3.3	0.9	- 11.9					
10 or more	14	232	6.0%	9.0	2.9	27.7					
No. partners previous 6 months							0.0003				0.003
1	22	1653	1.3%	1.0				1.0			
2-5	13	302	4.3%	3.3	1.7	- 6.7		2.7	1.3	- 5.4	
6 or more	4	44	9.1%	7.4	2.4	- 22.5		5.8	1.8	- 18.4	
Sexual preference							0.799				
heterosexual	38	1933	2.0%	1.0							
homo/bi-sexual	1	65	1.5%	0.8	0.1	- 5.8					
New contact previous 2 months							0.003				
Yes	14	322	4.3%	3.0	1.5	- 5.8					
No	25	1666	1.5%	1.0							
Condom use al last sexual contact							0.737				
Yes	12	565	2.1%	1.0							
No	27	1428	1.9%	0.9	0.4	- 1.8					
Contraception at last sexual contact							0.514				
Yes	32	1678	1.9%	1.0							
No	7	278	2.5%	1.3	0.6	- 3.0					
History of self reported STI							0.113				
Yes	4	88	4.5%	2.6	0.9	- 7.5					

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Lessons learned from a population based chlamydia screening pilot

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Abstract

Objectives

Large-scale *Chlamydia trachomatis* (Ct) screening programmes face challenges such as process organisation, choice of target population, screening method and response optimisation. These issues were evaluated in a systematic home-based Ct screening project in the Netherlands among 15-29 year old women and men, organised by the Municipal Public Health Services (MHS).

Methods

Computer-supported data flow from population sampling to informing participants of the result. A reminder – either a new test kit or a letter – was sent to non-respondents after 6 weeks. Fifteen year olds were invited for screening, requiring parental consent.

Results

The median periods between invitation and urine sampling, urine arrival at laboratory, sending out results and consultation of physician in case of infection were 7, 10, 17 and 24 days respectively. Urine arrived at the laboratory 4 (1-11) days after collection, indicating good specimen quality. A reminder contributed to 18% of the total response of 41%, with test kits having a higher response than letters (15% versus 10%). Sexual activity corresponds with an increase in response of 15-19 year olds. A Ct positivity of 2% warrants the extra efforts of including parental consent to invite 15 year olds.

Conclusion

Purpose made computer software is essential for an efficient screening programme. Home based Ct screening by sending urine by mail does not impair urine diagnostics. Reminders are necessary and effective after 4 weeks. Necessary parental consent for under 16 year olds should not be a deterrent to offer Ct screening to this age group.

Introduction

Chlamydia trachomatis (Ct) screening aims at reducing the prevalence of Ct infections and subsequent complications. Nucleic amplification tests (NAAT) using first void urine or vaginal swabs, created novel opportunities for home based postal screening, targeting both women and men.[1] Several countries advise screening of sexually active young women.[2,3] Recently screening pilots have been carried out, both opportunistic [4-9] and population based.[10,11] In England a National Chlamydia Screening programme has been established among both sexes.[12] In the Netherlands there is not yet a Ct screening policy. Once it is resolved whether a national chlamydia screening programme should take place, decisions with regard to choice of target population (age group and sex), screening method, co-ordination and implementation, and response optimisation have to be made.

In the Netherlands Ct screening could be organised by either GP's or Municipal Public Health Services (MHS). We carried out a Ct-pilot screening programme among 15-29 year old men and women in rural and urban areas in four MHS regions in the Netherlands. The primary aims of the Ct Pilot were to assess urban and rural chlamydia prevalence and to study the feasibility of the method used. The sampling methods and main results of the Ct pilot are described earlier.[13,14]

This paper reports on specific issues regarding process organisation, target population, screening method and response optimisation. We consider the lessons learned in this regard of general interest and importance.

Methods

Screening procedure and specimen collection

From September 2002 through March 2003, 21000 randomly selected 15 to 29 year old men and women received a package by mail containing an introductory letter, a information leaflet on chlamydia, a urine sampling kit with instructions, a 18-item questionnaire concerning demographic characteristics (age, sex, education, ethnic group), sexual behaviour, symptoms and history of STI. Sexual activity was defined as contact of penis with vagina or anus. The urine sample and questionnaire could be returned by mail in a postage-free plastic envelope to the laboratory. All persons, whether sexually active or not, were invited to participate. Any person not wishing to participate could indicate this on a refusal card. Next to information campaigns, a response increasing activity was a reminder to non-respondents after 6 weeks, either a letter or a new test-kit. All participants received their test-result by mail. Persons with a Ct positive test-result were referred to the regular services (GP, STD- or MHS-clinic). A medical ethics committee approved the study. 15 year old participants needed to add an informed consent form signed by their parent or guardian. The study methodology and results are described in detail elsewhere.[13]

Logistics and data processing

Actions of all screening partners were co-ordinated centrally. There were four MHS, a central laboratory and a central office for data analysis (EPI). A set of integrated, purpose made and user-friendly databases was developed in Microsoft Access. Questionnaires were scanned and delivered as SPSS database for EPI. The Ct Pilot *MHS database* was prepared by importing basic data of sampled persons (name, address, postcode, community, sex, birth date, and country of birth) from the municipal population registers. A 6-digit ID-number was assigned to each participant. Only the MHS database included personal data. The *EPI database* consisted of the combined data from four regions, including ID-numbers, sex, birth date, country of birth and 4-digit postcode. The *Laboratory database* included ID numbers. The following data were entered during the process: Response, date, presence of urine and/or questionnaire, consent form and Ct results (positive, negative, indeterminate). These data were transferred as secured database twice weekly to the four MHS by email.

Implementation phase

For the invitation for screening the database created address labels with ID number. The date of first mailing was registered automatically. After input of laboratory data into the MHS database, the programme generated letters with results to the participants. In case of indeterminate result the participant received a request for a repeat test with a new test kit. Non-infected participants received a result letter with safe-sex information. An explanatory letter and return slip for their physician was included additionally for infected participants. Data on treatment and partner notification from the return slip were entered manually into the database. At the end of week six the programme calculated the non-responders and created the reminder mailing. Non-responders with even ID-numbers received a reminder letter and those with odd ID-numbers received a new test kit.

Planning workload MHS and laboratory

We intended to carry out the study within 6 months. As all specimens were processed by a single laboratory the workload in the laboratory had to be regular, not exceeding 1000 specimens a week. For prediction of workload we assumed a response rate of 40% after the first mailing and 20% after the reminder. The 5250 test kits per region were divided into two bulks of 3000 and 2250 each, the regions starting with a two-week interval. Reminders started in week 7 for each region. The process was repeated from week 8-13 for the second bulk. Response evaluation was done in week 14.

Parental consent for 15 year olds

We included 15 year olds in our population sample. According to Dutch law, informed consent of parents or guardians was necessary. For 15 year olds an information letter including a consent form was sent together with the test kit. The consent form had to accompany the urine specimen and a 15 year old participant without a signed consent form did not receive a test result.

Statistical methods

Analysis was performed with the SPSS package version 10.0 (SPSS, Inc., Chicago, Illinois). Prevalence rates were calculated with 95% confidence intervals (95%CI). The χ^2-test was used to compare proportions. For differences in means, a t-test and variance analysis was performed. P values < 0.05 were considered statistically significant. Due to missing values denominators are different.

For calculation of the process intervals only data from the first screening round were used. The periods between sending test kit and urine collection, arrival of urine at laboratory, and sending the result to the participant was calculated. For 116 Ct-positive participants the time of consultation in relation to receipt of test kit could be calculated. Determinants for response were analysed, stratified by first mailing versus reminder.

Results

Response

The total urine response was 41% (8383/20495). The mean number of urine samples arriving at the laboratory per week was 289 (median 210; range 2-847). Valid test results were available for 8339 participants (44 inhibition /missing parental consent).

Screening process intervals

Electronic data-handling was felt by the executing organisations as immense time-saving and error preventing. The median period between invitation and urine sampling, arrival at the laboratory, result letter and consultation of the physician by infected participants was 7, 10, 17 and 24 days respectively (Figure 5.1). Within the first round, 95% of the urine samples had arrived at the laboratory within 29 days.

At individual level the median period between collecting urine and arrival of the specimen at the laboratory was 4 days (1-11), independent of Ct result. Eighty-eight percent of the specimens had arrived at the laboratory within 6 days, 98% within 8 days. The median interval between individual's specimen arrival at the laboratory and mailing the result letter to the participant was 5 days (1-18). Eighty percent of the result letters were sent within one week.

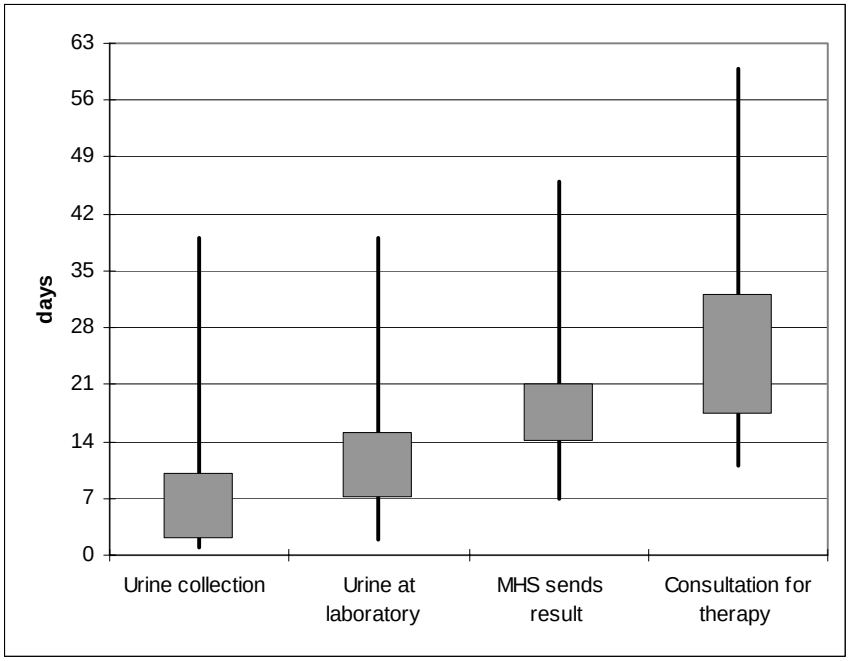
Determinants for response after first invitation and reminder

The urine response was 34% (6877/20495) after the first mailing and 12% (1462/12185) after the reminder. 18% (1462/8339) of the response was due to the reminder. Chlamydia positivity was not different in response to first mailing (2.0%) and reminder (2.1%).

Women were more likely to respond than men were (46% versus 33%; RR 1.39 [95%CI 1.34-1.44]), both after first and reminder mailing. Among the total response in men, 20% was due to the reminder compared to 16% in women (p <0.001). Persons born in the Netherlands were more likely to respond than persons born abroad were (42% versus 31%; RR 1.39 [95%CI 1.30-1.48]), a difference seen after the first mailing (35% versus

22%; RR 1.58 [95%CI 1.46-1.71]) in contrast to the reminder (13% versus 12%; RR 1.09 [95%CI 0.95-1.26]; p=0.21). Among the total response among persons not born in the Netherlands, 27% was due to the reminder compared to 17% in participants born in the Netherlands (p<0.001).

Figure 5.1: Periods between invitation for screening and various screening processes during first screening round



Response by method of reminder

Fifteen percent (908/6037) of the participants who received another test kit as reminder returned urine, compared to 9.8% (604/6148) who received a reminder letter (P <0.001). Men responded more often to the test kit than to the letter (12.9% [372/2892] versus 8.1% [236/2906]; p<0.001). No significant difference was found among persons not born in the Netherlands between response to test kit and letter (12.6% [104/824] versus 10.4% [94/901], p=0.15). Of the 604 participants who responded to the reminder letter, 6.3% (38) requested new test kit.

Sexual activity and response in 15-19 year olds

The response in the lowest 5 year age group (38%) was slightly lower than in the 20-24 and 25-29 year groups (both 43%).[13] Analysis per year of age revealed a response of 33% in 15 year olds, with a gradual increase to 41% (p < 0.001), a percentage corresponding

with the crude response rate in the Ct Pilot (41%). The required parental consent was missing in 5.6% (25/445) of the 15 year olds. Non response analysis for all ages showed a higher sexual activity in participants compared to non-responders.[13] This holds also for adolescents aged 15-19 years, the percentage of sexual activity was 64% for 2509 participants (increasing from 24% - 86%) and 51% (12% - 81%) among 69 non-responders ($p = 0.02$).

Age-group specific prevalence among all 15-19 year old participants was 2.0% (95% CI 1.5% - 2.6%). Among sexually active participants in this age group this was 3.0% (95% CI 2.3%-3.9%) compared to 1.8% (95%CI 1.4%-2.4%) in those aged 20-24 years and 2.6% (95%CI 2.0%-3.3%) among 25-29 year olds.[14] Chlamydia prevalence in adolescents per one year age group is shown in Table 5.1.

Table 5.1: Participation rate and chlamydia prevalence among 15-19 year old sexually active participants of the Ct Pilot.

Age	Invited persons	Participation rate (%)	Participant not sexually active	Participant sexually active	% sexual active participants	Ct-pos sex. active	% Ct pos sex.active (95% CI)
15	1340	33	316	97	23	2	2.1 (0.5-7.2)
16	1368	35	223	235	51	11	4.7 (2.6-8.2)
17	1351	39	167	331	66	11	3.3 (1.9-5.8)
18	1399	41	117	446	79	10	2.2 (1.2-4.0)
19	1442	41	81	493	86	14	2.8 (1.7-4.7)
15-19	6900	38	904	1602	64	48	3.0 (2.3-3.9)

Discussion

Process organisation

Large scale population screening requires an efficient and accurate process starting from invitation to notifying participants of their results and register treatment outcomes. We achieved a short period between inviting participants, their specimen collection and sending out of results by a purpose made integrated database. A short interval between specimen collection and result reduces stress in participants, and enables timely treatment [15], which contributes to the reduction of duration of infectiousness of screened participants.

In order not to loose quality of urine during the transport, one needs to register time intervals between specimen collection and arrival at a laboratory. Our median period between collection of urine and arrival at the laboratory was 4 days and 88% of the samples were at the laboratory within 6 days (in the Netherlands freepost may take 2-3

days). The longer observed periods could be due to test kits not posted immediately after urine collection. Urine samples were stored at 4°C in the laboratory and tested at day of arrival or the day after. It has been demonstrated that urine specimens remain stable up to one week at room temperature in the laboratory after a transport time of 4 days, without loss of sensitivity.[16] By registering duration of transport we could proof that our urine specimens were of good quality at arrival at the laboratory.

Response optimisation – are reminders needed, when and how?

The efficiency of a Ct screening program is determined by the response rate, particularly of high risk groups. The question how to optimise response is crucial. Our first question was whether a reminder was necessary at all. As the reminder contributed to 18% of the total response, the answer is yes. This is also supported by the fact that chlamydia positivity was not lower among respondents after the reminder. Our total response was comparable to a postal screening project by GP's in Amsterdam (42%); whether that response was affected by a reminder was not reported.[10]

Timing of the reminder requires a balance between too early (ineffective as participants were anyway planning to participate) and too late (test kits might be lost). The reminder was sent rather arbitrary after 6 weeks. From our process analysis we could show that 95% of the urine samples had arrived at the laboratory at day 29. Of the participants who responded to a reminder letter after 6 weeks, only 6.3% requested a new test kit, in other words 94% of them still had the test kit at home six weeks after the first mailing. Therefore we advise to send reminders after 4 weeks.

There is a dilemma of the importance of increasing of uptake, and budgetary constraints in screening programmes. Sending a test kit to everybody and a second test kit as reminder is the most expensive method. Our comparative study of sending test kits or letters as reminder showed clearly the higher yield of test kits. The reverse was the case in the ClaSS study, in which a postal reminder increased the uptake by 5%.[11,17] Should participants then be reminded by a new test kit? We calculated that obtaining one additional urine sample in our study cost Euro 24 with test kits as reminder, in contrast to Euro 5.32 for postal reminders. These extra costs exemplify the above mentioned dilemma. Taking only costs into consideration, a postal reminder appears more feasible in large scale screening projects.

In fact, by sending only letters on the first invitation to participate and those interested can then request a test kit, may reduce costs even more. In a comparative study in Denmark the response among participants who had to order a test kit was only slightly (6%) lower than among those receiving a test kit by direct mail.[8] Motivation of participants by using risk evaluation in the invitational letter, to be followed by request of a test kit by various means of communication (postal card or Internet) might increase response under potentially Ct infected persons in the future.[15,18]

Response of men compared to women was lower after both the first mailing and reminder indicating that specific attention should be given to men when a screening programme includes them.[17,19] Among participants not born in the Netherlands the reminder had obviously an additional motivating effect. With a low response this group

remains challenging.[10,20] Innovative approaches are needed to motivate specific ethnic groups with a high risk for Ct infection to get tested. A personal approach by tailored community outreach testing may increase test rates among those high risk groups.[21]

The 15-19 year olds

Legislation in the Netherlands is such that 12 to 16 year olds visiting a GP can request STD testing or the contraception pill without consent of parents. Inviting youngsters of 15 year old to a screening programme however needs parental consent. Apart from the cumbersome efforts to obtain consent we feared that the response would be impaired in this youngest group. We assumed that youngsters of this age who engage in sexual behaviour are also confident in asking parental consent. Our results indicate that 15 year olds did obtain consent, but not all. The response is probably affected by the need for consent, creating participation bias. Ct screening projects often do not include 15-year olds. [5,6,8,11] In the opportunistic National Chlamydia Screening Programme in England people under 16 years of age are offered screening if they are regarded by the test initiator to understand their choices and the potential outcomes (known as "Frazer/Gillick competency").[12] In case of large scale screening programmes information about legal aspects and motivation for inviting sexually active young persons should be included. Legislation should be reviewed in view of chlamydia screening of adolescents.

Apart from possible consent problems, the apparent low response among the age group 15-19 years can be explained partially by a lower rate of sexual activity. Both sexual activity and response increase in 15-19 year olds, indicating a well-informed self-selection. Chlamydia prevalence in sexually active participants is highest in the age-group 15-19 years, and above 2% in 15- year olds (possibly due to self-selection effects). This indicates the need to consider inclusion 15 year olds (depending on local epidemiology even younger adolescents) in active Ct testing.

In conclusion, purpose made computer support is essential for large-scale chlamydia screening programmes. Home based Ct screening by sending urine by mail does not impair urine diagnostics because transportation time is kept within acceptable limits. Reminders elevate participation rates substantially and are effective after 4 weeks. A active test offer to sexually active 15 year olds should be considered.

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6

Management of chlamydia cases and their partners – results from a home based screening programme organised by Municipal Public Health Services with referral to regular health care

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Abstract

Background:

Screening for *Chlamydia trachomatis* (Ct) infections aims at the reduction of Ct infections and complications. We evaluated the management of Ct cases and partners found in a systematic home-based Ct screening project in the Netherlands among 15-29 year old women and men, organised by the Municipal Public Health Services (MHS).

Methods

Infected participants (N=165) were advised by mail by the MHS to seek therapy with regular curative services. Information on recommended treatment of index and partner notification was provided in a separate letter to the patient's physician.

Results

Including the effect of a reminder, the treatment rate of all index cases was 91% (150/165), lower among persons with non-Dutch ethnicity (81%). Treatment was adequate in 99% of cases. The majority of cases (82%) consulted the general practitioner (GP) for treatment as opposed to STD/MHS clinics (18%). 85% of cases were treated within two weeks. The confirmed treatment rate of partners in the last six months was 49% (86/176), and of current partners 57% (81/141). Patient referral was advised in an additional 18% (25/141) of current partners (potentially treated). Partner notification rate of reported ex-partners was 14%.

Conclusion

This large scale home-based Ct screening program achieved 91% index case treatment rate. The necessity of a reminder and the lower treatment rate in non-Dutch high-risk groups deserve attention. Low confirmed treatment rate of current partners carries the potential of re-infection. Home-based Ct screening and treatment through regular treatment facilities has proven to be effective in the Netherlands.

Introduction

Chlamydia trachomatis (Ct) is the most prevalent and usually asymptomatic bacterial sexually transmitted infection (STI). The mean duration of Ct infection is about 12 months.[1] In women, Ct-infections are a major cause of pelvic inflammatory disease (PID), ectopic pregnancy, infertility, and chronic abdominal pain.[2]Active case finding and early treatment are the major strategies to reduce transmission. Simple home based screening strategies to detect people with an asymptomatic infection have become feasible by improved detection methods of Ct in urine [3-5] and by the availability of effective single dose treatment.[6]

Adequate treatment of participants found Ct positive in a screening program as well as successful partner notification and treatment determines the effectiveness of any screening programme.[7] Reports on management of cases are usually findings with regard to chlamydia screening programs where invitation for screening and management of cases is carried out be regular health care services, e.g. general practices (GP),[8,9] STD or family planning clinics.[10-13] Treatment of index cases is not always successful or reported at all. It has been shown that partner tracing and treatment contribute substantially to the reduction of prevalence. Even low percentages of treated partners may have a noticeable impact on the success of a screening programme.[14]

In this paper we report on the evaluation of the management of Ct infected participants and their partners in a large population based Ct-screening study (CT PILOT), organised by Municipal Public Health Services (MHS) in the Netherlands, with referral of cases to regular health care.

Methods

The present study is based on data from the CT PILOT project, which was designed to investigate prevalence of Ct infections in rural and urban areas in the Netherlands, and the feasibility of home based screening organised by MHS with referral of cases to regular health care. Local GP's and STD clinics were informed about the Ct screening program and their expected role. The study was implemented from September 2002 through March 2003 in four MHS areas, representing various degrees of urbanisation.[15] A total of 21,000 women and men aged 15-29 years received a package by mail with a urine sampling kit and a questionnaire concerning socio-demographic data (age, sex, education, self assigned ethnicity, symptoms and history of STI, and sexual behaviour). Participants could return the coded urine sample and questionnaire by mail to a central laboratory. Urine analysis was done by a nucleic acid amplification test (PCR Roche Diagnostic Corp., Indianapolis, IN, US) in a central laboratory. Urine was pooled by 5 and a chlamydia positive result was based on a positive pool and a positive individual urine sample.

Laboratory results were transferred to the MHS concerned, where the results were linked to personal data and the participants informed by mail. Chlamydia positive participants received information per mail about the infection and the need of treatment and partner notification, and were asked to consult the regular medical services.

Participants could choose either their GP or another STD service available in their region. As their choice was not known beforehand, an explanatory letter for the health care provider was included about the screening program and management of chlamydia infection (antibiotic choice, confirmed testing in case of doubts about the diagnosis, and further STD examination if indicated).

Besides index treatment, notification of partners of the previous 6 months was asked for, with emphasis on the preference of direct treatment of the current partner by the GP/STD-clinic. If the index-patient's physician did not provide a prescription for the current partner, the index was to be encouraged to notify the current and preferably also possible ex-partners during the previous six months. Assistance by the MHS nurses was offered. These instructions are in line with current practice guidelines in the Netherlands. Testing of partners before treatment was not obligatory, but a partner test kit was offered by the project. Alternatively, testing could be performed at a local laboratory. A return slip for the treating physician was included to obtain feedback on the management of cases, discussion of partner notification, and number of eligible and treated partners. On this evaluation form GP´s could request payment of a private consultation fee (21 Euro). When no feedback was received after four weeks, index cases received a reminder telephone call or a letter in order to obtain missing information. Outcome evaluation was performed within two months after sending the result. Index and partner management information was linked anonymously to the Ct Pilot database.

The index treatment rate was defined as the percentage of chlamydia cases with confirmation of treatment (prescription of antibiotics) as reported by the health care provider or the index patient. Determinants of confirmed treatment were investigated. Adequacy of antibiotic choice was assessed. Distribution of choices of health care was determined, as well as the period between mailing the result and consultation date (delay period), where consultation date was assumed to be treatment date.

Successful partner management rate was defined as the percentage of partners out of all partners elicited during counselling with confirmed treatment (prescription), or adequate management after testing. Potential treatment was defined as advice given to patients to refer their partners to their GP.

A test of cure is currently not advised in the Netherlands.[16] To distinguish between treatments of various partners, the treatment rate was calculated for all partners of the previous 6 months, with stratification of the first partner and other partners. The number of partners during the previous 6 months as reported in the questionnaire and thus

eligible for partner notification, was compared with the number of elicited partners during counselling.

Statistical analysis

Data were analysed using the SPSS package version 10.0 (SPSS, Inc., Chicago, Illinois). The Chi square statistic was used to compare proportions. Statistical significance was considered to be $p < 0.05$.

Results

Management of Ct-positive participants (index cases)

Of the 8339 participants in the CT PILOT whose urine was examined, 165 (2.0%) were chlamydia positive (43 men and 122 women).[15,17] Treatment was confirmed in 150 cases (91%). No follow-up information was available for 13 Ct positive cases. In the remaining two cases, follow-up information revealed that one was still planning to consult a GP, while the other was not yet treated. The rate of confirmed treatment was lower among persons with non-Dutch compared to Dutch ethnicity (81% [25/31] versus 93% [125/134]; $p = 0.03$). No difference was found between Ct positives with confirmed treatment and the group with unknown treatment according to urbanisation, age, sex, education, reporting symptoms, reported history of STI, recent partner change, and number of lifetime sexual partners.

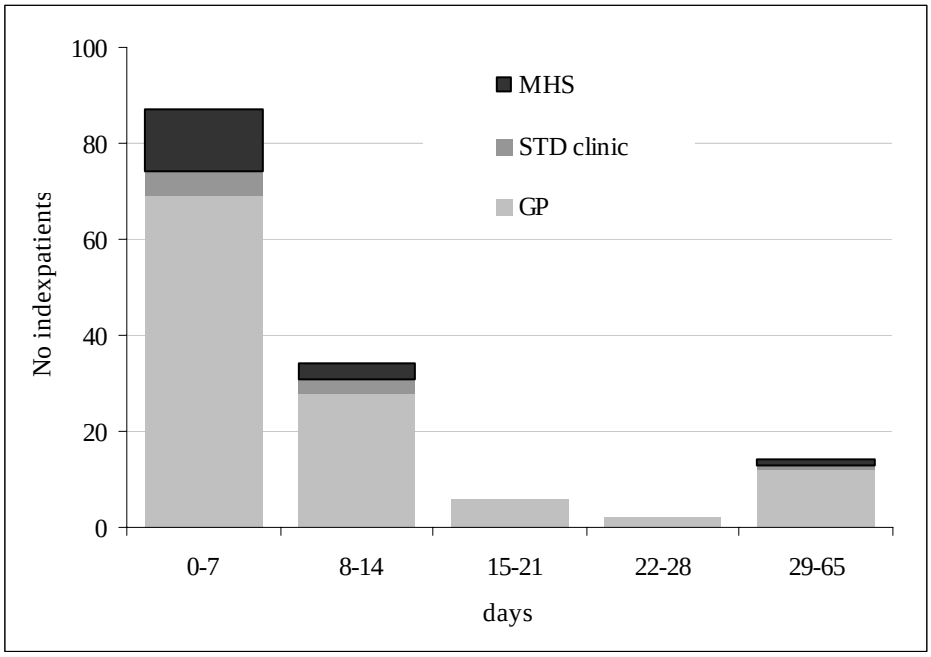
Choice of health care: In one of the four regions in the study participants could choose between consulting their GP or a STD clinic. In the other three regions the choice was between GP and MHS. A vast majority of 82% (123 cases) consulted their GP, varying by region from 74% to 90% ($p = 0.49$). No significant differences in preference of treatment location were found by age, sex, ethnicity or urbanisation.

Treatment delay: Among 143 infected participants with known consultation date, the median delay period was 7 days (range 1-65 days). There was no difference in delay between GP's and alternative treatment facilities. 87 cases (61%) sought treatment within one week, 34 cases (24%) in the second week, and 8 cases (5%) within 3 to 4 weeks. Finally, 14 cases (10%) had the consultation more than one month after the result (Figure 6.1). In seven of these 14 cases additional information was available: One person visited the GP after 41 days without having received a reminder; two initially had not received the result due to change of address and consulted a GP after being reminded; four only consulted a physician after having received a reminder.

Prescription: Of all 150 confirmed treated cases, 128 (85%) received treatment of first choice (azithromycin or ampicillin/erythromycin on indication); 20 (13.3%) treatment of second choice (doxycyclin); and in 2 cases (1.3%) the antibiotic prescribed was unknown. It was concluded that at least 148 (99%) of the treated cases received adequate

prescription. A total of 107 out of 123 consulted GP's (87%) sent a return slip to the MHS. In the remaining cases feedback was actively sought for from the index case.

Figure 6.1: Period between sending result to participant and consultation with health care provider (delay period)



Management of partners

For 147 of the 150 treated index cases (98%) information was available with regard to partner management. All health care workers reported to have discussed partner notification. A total of 113 index cases (77%) reported one partner in the previous six months, 25 (17%) reported two or more partners, and in three cases the number of partners was unknown (Table 6.1). With six index cases reporting no partners in the previous six months, 141 index cases remained where partner notification was indicated, with 176 partners eligible for partner notification and treatment (Table 6.1). Per index case the mean number of partners in the previous 6 months was 1.25 (women 1.21; men 1.35).

Table 6.1: Number of index patients and corresponding partners eligible for partner notification (PN)

No. of elicited Partners*	No. of index patients	No.of partners eligible for PN
0	6 (4.1%)	
1	113 (76.9%)	113
2	18 (12.2%)	36
3	4 (2.7%)	12
4	3 (2.0%)	12
Unknown ¶	3 (2.0%)	3
	147 (100%)	176

Number of partners during the previous 6 months as elicited during counselling.
In cases of unknown partners we assumed for analysis at least one partner; this was confirmed by the original questionnaire.

Partner treatment: A total of 86 partners were treated successfully, with a mean number of partners per index case of 0.6 (86/141). Successful partner management rate was 49%. In addition, 16% may potentially have been treated in the sense that advice was given to index cases to refer their partners to their GP for treatment (Table 6.2). At least the first (current) partner was treated successfully in 57% of cases, with 61% of female index cases and 47% of male index cases (p=0.16). The treatment rate of partners other than the first partners was 14%. Successful partner management rate was statistically significant lower (p = 0.08) in index patients with recent partner change compared to those without recent partner change.

In most cases treatment for the partners was provided during the first consultation, before or without Ct-testing. The physician waited for laboratory results in 10 out of 176 eligible partners (6%) before providing treatment. Only 15 diagnostic kits that were provided by the MHS were used, of which 6 (40%) were Ct positive. Direct treatment of at least one partner was done by GP's in 52% (60) of the index cases, while MHS/STD clinics treated current partners in 81% (21) of the index cases (p=0.02) (Table 6.3). The offer of assistance by MHS nurses was not taken up by any of the GP's.

Partner reporting: Partner notification starts with the process of eliciting partners during counselling. In 139 cases where the necessary information was available, we could compare the number of partners reported in the return slip with the number reported in the original questionnaire. Nine index patients (6.4%) mentioned more partners in the previous 6 months during counselling than in the questionnaire. Those participants might have a new recent partner. In 27 index patients (20%) less partners were elicited during counselling than they had reported in the anonymous questionnaire. Twenty-two of these (81%) reported one partner during counselling, contrary to the 2-5 partners mentioned in the questionnaire.

Table 6.2: Partner management according to current versus other partners by sex and recent partner change

		First partner (Current)			Other partners			All partners		
	Category management *	Nr.	%	p	Nr.	%	p	Nr.	%	p
All index patients	A	81	57%		5	14%		86	49%	
N=141	B	25	18%		3	9%		28	16%	
	C	35	25%		27	77%		62	35%	
	No. partners eligible	141	100%		35	100%		176	100%	
Men	A	16	47%		4	33%		20	43%	
N=34	B	6	18%		0	0%		6	13%	
	C	12	35%		8	67%		20	43%	
	No. partners eligible	34	100%		12	100%		46	100%	
Women	A	65	61%	0.16	1	4%	0.02	66	51%	0.76
N=107	B	19	18%		3	13%		22	17%	
	C	23	21%		19	83%		42	32%	
	No. partners eligible	107	100%		23	100%		130	100%	
Recent partner change	A	21	53%		4	17%		25	40%	
N=40	B	8	20%		0	0%		8	13%	
	C	11	28%		19	83%		30	48%	
	No. partners eligible	40	100%		23	100%		63	100%	
No recent partner change	A	54	59%	0.57	1	10%	0.59	55	54%	0.08
N=92	B	16	17%		2	20%		18	18%	
	C	22	24%		7	70%		29	28%	
	No. partners eligible	92	100%		10	100%		102	100%	

* A: successful treatment (confirmed direct treatment or adequate management after testing); B: potential treatment; C: unknown.
No. partners eligible: Number of partners in the previous 6 months as elicited during counselling.
Differences in denominators are due to missing values.

Table 6.3: Treatment rates for current partners according to STD care

Categories partner management	GP		MHS/ STD clinic		All	
No. index cases	115	82%	26	18%	141	100%
confirmed successful	60	53%	21	81%	81	57%
probably successful	23	20%	2	8%	25	18%
unknown	32	28%	3	11%	35	25%

Discussion

Index case management

Our rate of confirmed index treatment was 91%, which is comparable to earlier findings from opportunistic [18,19] and systematic[20] screening programmers. The treatment rate of non-Dutch participants was less (81%). This finding is in line with a population based study in Amsterdam,[20] where participants of Surinam and Antilles origin were also less often treated. This deserves special attention in view of the high prevalence and a lower acceptance of screening in these groups.[21] We may have underestimated our treatment rate of 91% because some of the 15 cases without confirmed treatment actually may have been treated. We assume that positive cases that participated in the study are willing to take medication.

The majority of cases with confirmed treatment (85%) were treated within two weeks. However, 10% were treated only after one month. Reports from follow-up of Ct positive clinic attendees are comparable.[22] Our results indicate that for 10% of the cases a reminder was necessary and that only 82% (136 cases) would have been treated without one. This suggests that active reminders are necessary to achieve optimal treatment results.

The MHS had facilitated management of cases by providing information for physicians. The quality of choice of treatment was very good, 99% of the treated patients, received adequate treatment. Focus on the medication of first choice is important, as compliance in asymptomatic patients is expected to be better with the short treatment course.

We received feedback from 87% of the GP´s. This result was probably influenced positively by introducing an incentive (payment of consultation). The vast majority (83%) of our index cases sought treatment with their own GP, reflecting the important role of GPs as providers of sexual health care. In a study on the acceptance of home based screening we found that 82% of participants preferred to be invited by MHS's for regular testing.[23] But once a diagnosis was made, there was a preference to be treated by their own GP. On the other hand, in the case of sexually transmitted diseases some people prefer anonymous treatment or at least another health care worker than their own GP.

Partner management

Treatment of current partners in order to avoid re-infections is crucial in STI control. For this reason it was stressed in this project that physicians should give treatment directly to index and current partner. Although all treating physicians indicated that partner notification was discussed, we wanted to evaluate whether partner notification and treatment was confirmed or not. The overall successful partner management rate was 49%. Direct treatment for at least one partner was given in 57% of all cases. Although this could mean that 43% of current partners were not treated, we know that 18% of first

partners were referred to their own GP through patient referral resulting in a potential treatment rate of at least one partner of 75%.

A limitation of this study is that we do not have data about current versus ex-partners. We assume that if one partner was treated, this will most likely be the current partner. As reported partners in the previous six months may be ex-partners as well, reflecting less current partners, the actual treatment rate of current partners could be slightly higher. The results of our partner treatment are comparable to earlier screening studies in the Netherlands. In the opportunistic screening program in Amsterdam, where GP's screened and treated their own patients, at least one partner was managed adequately in 61% of the index patients.[18] In a systematic screening program performed by GP's in Amsterdam, 62% of index cases informed successfully at least one partner.[24] In a British opportunistic screening project, 41-52% of partners of the last 3 months had been managed adequately.[19]

At STD/MHS clinics, relatively more partners were treated directly. GP's might restrict direct partner treatment to those who are actually within their practice. Encouraging direct partner treatment of current partners during GP consultation deserves more attention. Treating partners by patient delivered therapy has been feasible and beneficial.[25-28] Our data illustrate the challenge of notification of ex- and non-regular partners, as treatment was confirmed in only 14% of elicited partners (other than first partner). As reported earlier, partners of people with recent partner change and multiple ex-partners are less likely to be treated than partners of those with one steady partner.[11,24,29-31] Partner notification could be supported by MHS nurses and potentially by GP practice nurses.

Partner testing was not required, as we did not want to change regular practice. Partner testing by patient delivered test-kit could be potentially helpful in finding new index cases among multiple partners.[32] Eliciting partners however, is time consuming. This is illustrated by the discrepancies found in our study between partners reported in an anonymous questionnaire and reporting fewer partners to the GP. This might partially be due to the patients' resistance to report a casual partner next to the steady partner to for instance a GP. On the other hand eliciting partners is part of the art of STI counselling. In the daily practice GP's probably restrict themselves to inquiring about the current partner.[33] Although we did not find significant differences, our data suggest that partners of female index patients are more likely to be treated than first partners of male index patients. This sex difference was noticed before.[30,34] Furthermore patient referral is described as less effective than provider referral.[35 36]

Conclusion

In this systematic Ct screening program we could confirm the treatment of 91% infected participants. Without a reminder the treatment rate would have been lower, particularly in non-Dutch risk groups. We showed the need for both GP practices and alternative STD treatment facilities. Information given to GP's and STD clinics led to adequate case management. In case of a large-scale screening program, training for GPs concerning counselling of unexpected STI results and partner notification appears necessary. Given our treatment rate of current partners it is to be expected that re-infections will occur. We recommend expansion of the practice of patient delivered treatment for the current partner.

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7

Acceptability and consequences of screening for *Chlamydia trachomatis* by home based urine testing

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Abstract

Objectives

The objective of this study was to study the acceptability and consequences of home-based chlamydia (Ct) screening by Municipal Public Health Services (MHS) among 15- to 29-year- old participants.

Study design

This study consisted of a cross-section 156 Ct-positives and 600 random sampled Ct-negatives after receiving the result of their Ct-test.

Results

Thirty-eight percent of the men and 59% of the women responded. The screening method was well-accepted. Seventy percent (52) of the Ct positives were surprised about their result. Infected women more often than men reported a feeling of being dirty and of anxiety about infertility. Curiosity for the Ct result was decisive for participation in 68% and perception of personal risk was poor. The willingness to be tested regularly was determined by present chlamydial infection, young age, multiple lifetime partners, short relationship, and earlier test for chlamydia.

Conclusions

Chlamydia screening organised by MHS is acceptable for future screening. Participants with an elevated risk are interested in screening as long as testkits are easily available. Counselling with focus on effects of Ct, especially on women, is essential. Alternative approaches are needed to motivate men and non-Dutch high-risk groups.

Introduction

Chlamydia trachomatis (Ct) infection is a leading cause of reproductive morbidity in women.[1] Screening has been shown to reduce the prevalence of chlamydial infection in women and the incidence of pelvic inflammatory disease.[2,3] Population-based screening is being debated in several countries, including the Netherlands. An important condition for large-scale screening programs is that the criteria of Wilson and Jungner are met.[4] One of these criteria is acceptability of the program for the population screened.[5] Besides technical aspects of the method used, this includes complex reactions to an often unexpected sexually transmitted infection (STI) diagnosis. In qualitative studies of the psychosocial impact of a Ct diagnosis in women, three main themes were found: 1) a diagnosis of chlamydia was perceived as a stigma (feelings of guilt, unexpected results leading to stress); 2) the awareness of possible infertility despite early treatment; and 3) fear for the reaction of a partner.[6]

In this study, we firstly investigated the acceptability of screening in a population-based screening program in The Netherlands (Ct Pilot), which included invitation by the Municipal Health Service (MHS), home-based urine collection, outcome notification by mail, and referral of positive cases to regular healthcare services. Second, we assessed the experience of participants with the results and effects of screening. Third, the motivation for participation in future screening was studied.

Materials and methods

In the Ct Pilot study on screening of Chlamydia by home-based urine testing, four MHSs in the Netherlands invited 21,000 women and men aged 15 to 29 years. The participants received a package by mail containing an introductory letter, an information leaflet about chlamydia, a urine sampling kit with instructions, and a questionnaire. The coded (ID number) urine sample and questionnaire could be returned to the laboratory by mail and the MHS informed all participants of the result by mail. Chlamydia-positive participants received information about the infection, treatment, and partner notification, and were asked to consult the regular services. The participation rate was 41% (8,383); overall Ct prevalence was 2%, as was described elsewhere.[7,8]

Study Population and Questionnaire

To study the acceptability of the screening method, a comparative cross-sectional study was carried out among 156 Ct-positives and a random sample of 600 Ct-negatives (75 men and 75 women per MHS region). Information on sociodemographic characteristics (age, sex, education, self-chosen ethnicity, sexual behaviour, symptoms and history of STI) was collected through the questionnaire accompanying the initial screening offer.

Six to 12 weeks after receiving the result of their Ct-test, participants were invited to fill out a questionnaire with open questions, multiple-choice questions or five-point scale. The participants' opinion about the method of screening and their experiences with the procedure of urine collection and receipt of the result by mail were explored; for items, see Table 7.1. The motivation for participation and perceived consequences for partnerships was assessed in an open question asking for the reason for participation. The

participants' feelings when receiving the result and their perception of disclosure of the result was assessed with items as described in Table 7.2. The experiences of infected persons with their healthcare workers were assessed. Participants were asked if they had discussed participation in the screening and the result with partner, family, friends or colleagues. Infected participants were asked about the probable source. Actual experiences with disclosure of the result were scored. Awareness of possible infertility and fear of personal impaired fertility was asked for. The perceived importance of safe sex and intention of condom use with the current partner or with a new partner were assessed. Knowledge about chlamydia was evaluated. Perceptions of personal chlamydia screening, the wish for regular testing, and the preferred method were inquired.

Statistical Methods

Open questions were coded, and for validation reasons, 10% of the questionnaires were coded by a second person. The chi-squared test was used to compare proportions. For differences in means, a t-test and variance analysis was performed. P values < 0.05 were considered statistically significant. As a result of missing values, denominators are different. All items measured on a five-point scale were recoded, e.g., a negative feeling/disagreement would have a score of 1, and a positive feeling/agreement score of 5. Analysis of reliability of the score was performed on items measuring the same concept and a sum score was computed when Cronbach's α was > 0.70.[9]

The sum scores were divided by the number of items, resulting in scores from negative/disagree (1) – positive/agree (5). Multiple logistic regression analysis was performed, with self-reported characteristics as independent variables and willingness to be tested in the future (vs. not wanting or not knowing) as the dependent variable. Only respondents who had been sexually active in the past were included in the regression analysis, because behavioural variables were available for this group only. The final model's ability to discriminate between participants according to their willingness to be tested in the future was quantified using the area under the receiver-operating characteristic curve.[10] Statistical analysis was done with SPSS statistical software version 10.0 (SPSS, Inc., Chicago, Ill).

Results

Response

The study population included 156 Ct-positives and 600 Ct-negatives. Eleven of these 756 persons were excluded from analysis because of sex/age differences with the original participant, or returned mail because of unknown addressee. Overall response was 50% (374/745). As a result of missing ID numbers in 23 respondents, analysis could be done for 351 responders (including 14 male and 62 female infected persons), and 105 male and 170 female non-infected persons. Nonresponse analysis revealed only a significant difference by sex (male 38% versus female 59%; $P < 0.001$).

Acceptability Screening Method

The invitation for the chlamydia test was well received by 84% (288) responders, 9% (32) felt neutral, 4% (12) experienced uncertainty and 3% (10) felt annoyed about the screening offer. The majority of the participants highly appreciated the screening method and valued the possibility of collecting urine at home (Table 7.1). Internal reliability between these questions was good (Cronbach's α 0.71), resulting in an opinion score. The mean opinion score among infected participants was 4.05 (standard deviation [SD] 0.66) in men and 4.33 (SD 0.47) in women; among noninfected 3.88 (SD 0.47) in men and 4.00 (SD 0.44) in women, a significant difference according to both sex (P <0.01) and result (P <0.001). A majority of 87% (266) thought it fine to receive the result by mail, 35% of these mentioned that access to additional information was satisfactory. Thirteen percent (44) thought the mailed result was difficult or too anonymous.

Table 7.1. Participants' Opinion About the Screening Method

	All participants (N = 351)					
	(Very Much) agree		Neutral		(Very Much) Disagree	
Screening method	No.	Percent	No.	Percent	No.	Percent
Fine by mail	266	76	73	21	11	3
Fine approach by Municipal Health Services	260	74	82	23	9	3
Information material was inviting	212	61	123	35	13	4
Prefer general practitioner	29	8	116	33	204	58
Clear explanation	324	93	17	5	9	3
Difficult	12	3	27	8	311	89
Privacy warranted	272	78	67	19	8	2
Urine collection/test procedure						
Fine to do at home	340	97	10	3	1	0
Clear explanation	328	93	17	5	6	2
Collection urine easy	228	65	52	15	70	20
Sending urine by mail acceptable	288	83	47	13	14	4

Differences in denominator are the result of missing values

Experiences With Test Results of Chlamydia Screening

Surprise, stress and anxiousness about health are reported mainly by chlamydia-positives and relief by -negatives. Remarkably, relief about the result was felt also by 15% positives (11, among whom 10 were women). Infected women more often than men reported a feeling of being dirty (30% [18] vs. 23% [3]; P = 0.04). Among Ct-positives 20% (14) were reassured, five of these took part because of own risk behaviour. Of Ct-negatives, 17% (44) were not reassured (Table 7.2). The feeling score (Cronbach's α 0.89) differed between Ct-positives (mean 2.61; SD 0.66) and Ct-negatives (mean 4.16; SD 0.40); (P <0.001). This indicates neutral feelings about the result in infected participants compared

with positive feelings among noninfected participants. Among infected persons, 27% had no idea about the source of infection.

Sixty-three Ct patients reported about their consultation with the healthcare worker. Most of them (67%) experienced the consultation as pleasant, 18% as neutral and 16% as bothersome. During the consultation, 20% felt uneasy, 13% did not get their questions answered, 15% felt the healthcare worker was in a hurry, and 15% did not trust the healthcare worker. Compared with noninfected participants, Ct-positives expressed their need to share the result more often, found talking about it difficult, and felt relieved after talking (Table 7.2).

Seventy percent of the participants thought their social environment would approve their testing for chlamydia. Sixty percent disclosed the result to family and friends, 92% to the current and 72% to the exporter, independently of the test result. The experience with sharing the result was predominantly positive (75%) or neutral (22%). Fifty-one percent (81 of 162) of the noninfected reported that their partner was relieved. Forty percent of infected persons (19 of 48; all but one were women) expected a negative influence of the test result on their partnership. They reported feelings of guilt, anxiousness for the reaction of the partner, loss of trust, betrayal and unfaithfulness. Six partners of infected participants (16%) were shocked about the result. However, the majority (92%) reported partners showing sympathy. Three women mentioned the end of the relationship, noting that it had been bad anyway.

Effects of Screening

Sixty percent of the infected persons self-reported an increase in knowledge after the screening compared with 40% of the noninfected (P <0.001). Questions regarding infecting others without having symptoms were answered correctly by 93% (326) and regarding infertility by 83% (286) participants. Approximately 50% of all men and noninfected women reported more awareness of possible infertility as a complication of chlamydial infection compared with 89% of infected women. Personal fears about own and/or partners' impaired fertility were reported more often by infected women than infected men (62% vs. 36%; P = 0.08). Infected participants expressed more often that safe sex was important for them than noninfected participants (84% of 76 vs. 39% of 267; P <0.001). There was only a minor difference in the reported intention to use a condom with a new partner between infected and noninfected (93% of 75 vs. 82% of 264; P 0.06).

Motivation for Participation and Willingness to be Tested in the Future

A majority of 68% (224) took part in the screening program out of curiosity for their Ct-result; 25 of these 224 (12%) considered themselves at risk of having contracted Ct. Actual infection was found in 17 out of these 25 (68%). For 62 of the curious participants (28%), certainty about being not infected was decisive; eight of these were Ct-positive, of which seven doubted the result.

Fifty percent (166) of the participants wanted to be tested regularly in the future, whereas 30% (103) did not want this and 21% (71) did not know. After adjustment in logistic regression analysis, current Ct infection, younger age groups, multiple lifetime partners, short duration of or no partnership, and previous testing for chlamydia remained

independent predictors for willingness to be tested in the future (Table 7.3). Interaction terms were not included, because they did not improve the model significantly. The Hosmer-Lemeshow goodness-of-fit test had a P-value of 0.60, indicating adequate goodness of fit. The model discriminated well between participants willing to be tested and those who did not want to be tested or were not sure (area under the curve 0.82 [95% confidence interval 0.77-0.87]). Of those who wanted to be tested regularly, 82% (134) would like to be invited by the MHS for screening, 12% (19) would take care of their testing themselves, 6% (13) wanted to visit or be invited by their general practitioner (GP). Participants especially mentioned the importance of the low threshold for getting test materials.

Table 7.2. Feelings About Result and Perception of Disclosure of Chlamydia trachomatis-Infected Compared with Noninfected

	Infected (N = 74)						Non-infected (N = 266)						
	(Very Much) Agree		Neutral		(Very Much) Disagree		(Very Much) Agree		Neutral		(Very Much) Disagree		p
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	
Feelings about result													
Surprised	52	70.3	19	25.7	3	4.1	16	6.1	44	16.7	203	77.2	*
Doubts	15	20.5	12	16.4	46	63.0	3	1.1	13	4.9	247	93.9	*
Stressed	38	52.1	15	20.5	20	27.4	5	1.9	12	4.5	247	93.6	*
Relief	11	15.3	15	20.8	46	63.9	111	41.7	78	29.3	77	28.9	*
Did not worry	8	11.1	10	13.9	54	75.0	174	65.9	58	22.0	32	12.1	*
Shame	26	35.1	12	16.2	36	48.6	2	0.8	14	5.3	247	93.9	*
Dirty	21	28.8	15	20.5	37	50.7	4	1.5	8	3.0	251	95.4	*
Despaired	26	36.6	25	35.2	20	28.2	9	3.4	20	7.7	232	88.9	*
As expected	7	9.7	18	25.0	47	65.3	217	81.6	38	14.3	11	4.1	*
Reassured	14	19.7	15	21.1	42	59.2	156	58.9	65	24.5	44	16.6	*
Anxious about health	46	64.8	13	18.3	12	16.9	14	5.4	32	12.3	214	82.3	*
Perceptions about disclosure result													
Private business	3	1.1	13	4.9	247	93.9	3	1.1	13	4.9	247	93.9	*
Not important	4	1.5	14	5.3	248	93.2	92	34.3	70	26.1	106	39.6	0.6
Need tot talk	37	50.0	13	17.6	24	32.4	49	18.2	80	29.7	140	52.0	*
Difficult to talk	35	49.3	19	26.8	17	23.9	17	6.5	51	19.6	192	73.8	*
Expect good reaction	53	73.6	19	26.4	0	0.0	184	68.9	69	25.8	14	5.2	0.3
Relief	26	35.6	31	42.5	16	21.9	26	9.7	143	53.6	98	36.7	*

* P <0,001; differences in denominator are the result of missing values

Table 7.3. Willingness to be tested in the future for *Ct* infection

Legend Table 7.3 (See next page).
* Only sexually active participants included in model
# AAD1 very high urban (>2,500 addresses/km^2); AAD2 high urban (1,500-2,500 addresses/km^2); AAD3 moderate urban (1,000-1,500 addresses/km^2); AAD4 low urban (500-1,000 addresses/km^2); AAD5 rural (<500 addresses/km^2).

				Univariable			Multivariable		
	Yes	No*	Percent	OR	95% CI	P	OR	95% CI	P
Sex						0.050			
Male	45	102	44.1	1.0					
Female	111	198	56.	1.6	1.0 - 2.6				
Ct result						0.000			0.000
Positive	57	71	80.3	5.3	2.8 - 10.1		4.0	1.8 - 8.6	
Negative	99	229	43.2	1.0			1.0		
Age group						0.000			0.000
15-19 yrs	49	70	70.0	3.5	1.9 - 6.6		6.9	2.9 - 16.2	
20-24 yrs	60	112	53.6	1.7	1.0 - 2.9		2.9	1.5 - 5.8	
25-29 yrs	47	118	39.8	1.0			1.0		
AAD #						0.050			
AAD1	51	89	57.3	2.6	1.2 - 5.7				
AAD 2-4	92	173	53.2	2.2	1.0 - 4.5				
AAD5	13	38	34.2	1.0					
Ethnicity						0.288			
Dutch	141	275	51.3	1.0					
Non-Dutch	15	24	62.5	1.6	0.7 - 3.7				
Education						0.006			
Low	41	72	56.9	2.1	1.1 - 3.8				
Intermediate	73	123	59.3	2.3	1.3 - 3.9				
High	39	100	39.0	1.0					
Age at first sex (years)						0.000			
≤15	56	80	70.0	5.6	2.7 - 11.6				
16-18	81	155	52.3	2.6	1.4 - 4.9				
19+	18	61	29.5	1.0					
Symptoms previous 4 weeks						0.015			
Yes	63	102	61.8	1.8	1.1 - 3.0				
No	93	198	47.0	1.0					
No. of lifetime partners						0.000			0.000
1	30	90	33.3	1.0			1.0		
2-5	71	139	51.1	2.1	1.2 - 3.6		2.0	1.0 - 4.0	
6 or more	53	67	79.1	7.6	3.6 - 15.8		6.8	2.7 - 17.4	
No. of partners previous 6 months						0.000			
0 or 1	109	242	45.0	1.0					
2 or more	47	58	81.0	5.2	2.6 - 10.5				
New contact previous 2 months						0.000			
Yes	42	51	82.4	5.8	2.7 - 12.5				
No	101	227	44.5	1.0					
Condom use al last sexual contact									
Yes	12	565	2.1%						
No	27	1428	1.9%						
Anticonceptie laatste contact									
Ja	32	1678	1.9%						
Nee	7	278	2.5%						
Condom use al last sexual contact						0.988			
Yes	30	58	51.7	1.0					
No	112	217	51.6	1.0	0.6 - 1.8				
Ever had STD						0.001			
Yes	16	18	88.9	8.2	1.8 36.1				
No	139	281	49.5	1.0					
Duration relationship						0.000			0.004
No relationship	52	80	65.0	1.0			1.4	0.7 - 2.7	
0-6 months	32	36	88.9	2.9	1.7 - 5.0		5.7	1.8 - 18.1	
>7 months	72	184	39.1	12.4	4.2 - 36.5		1.0		
Previously tested for Ct						0.000			0.019
Yes	28	35	80.0	4.4	1.9 - 10.5		3.2	1.2 - 8.7	
No	124	261	47.5	1.0			1.0		

Discussion

Acceptability Screening Method

The unsolicited STI test offer by the MHS as well as the method of screening by urine collection at home was generally well accepted. It was appreciated to have easy access to testing and to collect urine at home in privacy at a convenient time like described before.[11] In previous studies, the home-based screening method was also shown to be well-accepted.[12-14] In The Netherlands, the public is familiar with the MHS and our participation rate was comparable with the study in Amsterdam where the invitation was sent by the GP.[15] In The Netherlands, STI test results are usually communicated personally, and not having a face-to-face discussion about a positive result could be a disadvantage. Receiving the STI result by mail was perceived as acceptable, provided that questions concerning the result could be answered.

Experiences With Test Results of Chlamydia Screening

It is to be expected that infected participants experience their result less positive than those who are not infected do. Twenty percent of those infected, however, expressed reassurance, indicating that now something could be done about their infection. The paradox is that damage may well be present at diagnosis and that treatment cannot always reverse this. A noninfected person with high-risk behaviour may unjustly feel reassured by the absence of a chlamydia infection. The importance of taking up or continuing safe sex behaviour should be emphasised. Having an STI might evoke distress, self-disgust, and worry, as was described previously.[6,17] The fear of stigma after diagnosis of an STI could be a barrier to testing.[18] Fortunately, a considerable number of the infected persons did not report these feelings. The need of supporting counselling is obvious, especially as this concerns unexpected STI results.

Although the majority of the consultations at the GP or a sexually transmitted disease (STD) clinic were experienced as pleasant, some participants felt annoyed. A feeling of uneasiness might reflect their own uncertainty about the diagnosis, but apparently not all healthcare workers were able to make their patients feel comfortable and gain their trust. This is a serious signal and continuous training in STI counselling as part of screening activities is necessary. Openness is a prerequisite for partner notification and the need for training of GP's has been emphasised before.[19-21]

It is encouraging that a majority of the participants discussed STI testing and results in their social environment and experienced supportive reactions. Nevertheless, those who were infected were confronted with negative reactions more often. This underlines the importance of health education to reduce a stigma of having an STI.[11,22]

Effects of Screening

Infected persons, and particularly women, often have negative expectations about the reaction of their partners. The positive reactions of partners of both noninfected and infected are encouraging, but suspicion and fear for infection in partners of positives deserve attention.

Potential infertility is a concern for both women and men, and understandably more so for infected women. The asymptomatic nature of the infection creates uncertainty about the duration of infection. An assumed long duration may lessen fears about a partners' infidelity, but could also increase anxiety about possible reproductive morbidity. These issues should be addressed explicitly during counselling.

Besides some critical issues regarding screening, we have also observed positive effects of this screening program: increase of knowledge and awareness about condom use. Infected participants reported more often the intention to use condoms. Knowledge and intention are a prerequisite for behavioural change, yet not sufficient.[23] The question whether participants would indeed engage in more safe behaviour is beyond the scope of our study.

Motivation for Participation and Willingness to be Tested in the Future

We motivated people to participate by emphasising the possibility of treatment in case of infection. In our study, the majority indeed took part in order to know their result, but only a minority of those perceived themselves to be at risk. Seeking certainty of not being infected was decisive to participate in more than one fourth of the participants, and those who turned out to be infected doubted the result. This suggests that risk perception is not adequate. This is exemplified by the fact that 27% had no idea where their infection was acquired.

Because we have performed a single screening round, the crucial question is whether participants would be willing to be tested repeatedly. Among the participants, 50% wanted to be tested regularly in the future, the readiness is higher in persons who can be regarded having an elevated risk for Ct infection. Unsurprisingly, persons who just found out to be infected are more motivated to be tested regularly. We also showed that a history of earlier testing is an indicator for willingness to be tested in the future, independent of the STI result. Persons without a current or with short-term relationships, or with multiple lifetime partners were more likely willing to be tested. It is encouraging that the two younger age groups are motivated for testing. For persons in long-term monogamous relationships, there is not a great need for chlamydia testing. It remains to be seen whether the nonresponders of our study would show the same level of willingness to be retested.

The majority of the participants who wanted to be screened regularly preferred to be invited by the MHS, underlining the acceptance of our screening method. It also emerged clearly from our data that a very low threshold for getting test material is a prerequisite for testing.[16,18] A matter of concern is the lower response in men. Shared responsibility in stopping transmission between partners requires testing of men and women.

Limitations of Our Study

A limitation of our data is that this study includes only participants of the Ct Pilot and the response rate was 50%. There might be a selection bias towards motivated participants with favourable opinion, as they took part both in the original screening and in the acceptability study. Unfortunately, it was not feasible to approach nonresponders of the PILOT Ct Study for this study. Among the participants of the PILOT Ct Study, non-Dutch persons were underrepresented, and possibly a different approach is needed to motivate them.[24]

In conclusion screening for Ct by the MHS through urine collection at home, outcome notification by mail, and treatment by regular health services is well-accepted by the target population of 15-29 year old women and men. The method can be used in future screening of the general population, as well as for selective screening of high-risk groups. Access to personal counselling is essential, with focus on unintended effects of positive results, especially in women. Training of health care workers in STI counselling should be strengthened. Motivation of men to get tested deserves special attention. Participants with a high risk for chlamydia infection were willing to be tested regularly. Interventions for stimulating active testing among non-Dutch high-risk groups combined with methods to increase risk perception should be developed.

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8

Chlamydial infections in multi-ethnic urban youth: a pilot combining STD health education and outreach testing in Rotterdam, Netherlands

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Abstract

Objectives

Screening for *Chlamydia trachomatis* (Ct) is less accepted in migrants compared to native Dutch people. We offered additional Ct and gonorrhoea testing through our outreach STD-prevention programme for migrants to determine whether this intervention strategy is feasible and efficient.

Methods

Outreach workers offered test kits to women and men aged 15-29 years, in group and field-based settings and in a vocational training school. Demographic and behavioural data and characteristics of non-responders were assessed. DNA was isolated (using the MagNA Pure LC system) from pooled urine and tested using the Cobas Amplicor test. Urine from positive pools was re-tested individually.

Results

Among sexually active persons, the test rate differed by venue (groups 80% [74/93], school 73% [49/67], street 17% [49/287]; $p<0.001$); sex (female 53% [99/187], male 28% [73/260]; $p<0.001$), and ethnicity (Dutch 63%[44/70], Surinamese/Antillean 32% [80/251], other 41% [47/115]; $p<0.001$). Surinamese/Antillean women were more likely to get tested than Surinamese/Antillean men (45% vs. 22%; $p<0.001$). Ct prevalence was 14.5% (25/172), [95% CI 10.0-20.6]), women 20.2% versus men 6.8% ($p=0.01$). The highest prevalence was detected in Surinamese/Antillean women (25.5%). Most efficient was testing in group and school settings.

Conclusions

The acceptance of Ct testing in group settings was higher than in street outreach and systematic home-based screening. The test rate of migrant women was higher than in migrant men, and higher than found previously. The prevalence found indicates that we have indeed accessed high-risk persons, that outreach testing is feasible and that efficiency is satisfactory in school- and group settings.

Introduction

Chlamydia trachomatis (Ct) infection, the most prevalent bacterial STI in developed countries, can progress to pelvic inflammatory diseases (PID) in women with sequelae such as ectopic pregnancy, infertility and chronic pelvic pain.[1] Improved detection methods of Ct in urine allow community based testing in both sexes, including home based testing[2-10], school based screening[11,12] and tailored community outreach testing[13-21].

In a home based Ct screening project targeting 25-29 year olds, we found non-Dutch ethnicity, particularly Surinamese/Antillean origin a predictor for infection.[9,22] Participation in screening was less in people of non-Dutch ethnicity compared to Dutch ethnicity (31% versus 42%, $p<0.001$).[9,22]

Rotterdam is a multiethnic city; 45% of the inhabitants are of non-Dutch, and 27% of these are of Surinamese/Antillean origin. We were therefore interested to develop alternative strategies to reach people of non-Dutch ethnicity for chlamydia testing, and conducted a pilot screening project for 15-29 year old youths as part of our community STI prevention programme in Rotterdam. This 'STI prevention PLUS' project also included gonorrhoea testing. We aimed to determine whether the intervention strategy of outreach testing is feasible, and technically efficient (response rate and Ct positivity) in various outreach settings.

Methods

The Municipal Health Service (MHS) in Rotterdam has outreach projects targeting populations at high risk for STI/HIV. Youths, particularly of non-Dutch ethnicity, are approached by outreach workers in three separate venues: group settings (e.g. projects for Surinamese/Antillean immigrants, Surinamese/Antillean and African women, teenage dropouts of all ethnicities), street settings (e.g. street corners, parks and underground stations; majority men and non-Dutch ethnicity), and sessions at vocational training schools. Outreach workers belonging to the ethnic groups concerned discuss STIs and distribute prevention materials such as condoms in group and street settings. STI nurses provide STI education at the schools.

Project design and data collection

In this project additional confidential testing for gonorrhoea and Ct infection was offered to sexually active persons, but others were not excluded. In addition to a verbal explanation, a leaflet was provided about chlamydia and gonorrhoea and the procedure of testing, including a waiver consent form and safe sex information. Participants received a urine sampling kit, a 13-item questionnaire concerning demographic characteristics (age, sex, education, self assigned ethnicity), sexual behaviour, symptoms of STI and history of STI-testing, and risk perception for having a STI. As incentive, all participants received a small backpack to carry the test material home. Participants could either provide first void

urine on location, or mail urine later in a postage free plastic envelope. The coded questionnaire and a card with ID number, personal data (at least name and telephone number) and preferred way of receiving the result (mail, email or sms) were left with the outreach worker. Information was collected systematically to assess participation and reasons for refusal. The time spent to approach all persons, including those sexually non-active, was registered. Technical efficiency, the optimal utilisation of given resources,[23] was assessed by the time required per person approached, to reach one person to discuss testing, to obtain one urine sample, and to detect one infected person.

Detection of *Chlamydia trachomatis* and gonorrhoea

Urine specimens were collected by the outreach workers and kept at room temperature until transport the next working day (maximal 60 hours) to the laboratory. Specimens collected at home were mailed to the laboratory, where they were stored refrigerated. DNA was isolated from urine specimens using the MagNA Pure LC system and tested using the Cobas Amplicor test (Roche Diagnostics, Almere, The Netherlands).[24]

Notification of results and treatment

ID coded results were linked to personal data at the MHS. Non-infected subjects received their result according to their choice, together with a telephone number for inquiries. Those tested positive for Ct were phoned by the nurse, and offered the choice to be treated by the MHS or by their general practitioner (GP), and were advised to bring their current partner along. Directly observed treatment was according to current standards (Ct: single-dose Azithromycin 1 g; gonorrhoea: Ciproxin 750 mg single-dose) and provided free of charge. Partners in the last six months were assessed, and offered assistance in partner notification.

Data analysis

Participation rate was defined as the number of persons who accepted a test kit, and test rate as the actual number who supplied urine of those who discussed testing with the outreach worker. Non-response was analysed by comparing participants with those who declined a test kit. Univariate logistic regression analyses for sexually active participants were performed with screening venue and demographic factors as independent variables and participation and test rate as well as diagnosis of Ct as the dependent variable. 95% confidence intervals (CI) were calculated. The Chi square statistic was used to compare proportions. Statistical significance was considered to be $p < 0.05$. Data were analysed with SPSS statistical software version 10.0 (SPSS, Inc., Chicago, Illinois).

The medical-ethical committee of the Erasmus MC stated that there was no objection against the study.

Results

From September to December 2004, 28 street outreach sessions were held (average 10, range 1-27 persons per session), 14 group sessions (average 10, range 4-20 persons), and 13 school sessions (average 10, range 3-15 persons). In street outreach, approximately 30% of those approached discussed testing. The study population included 556 individuals.

Participation- and test rate

The overall participation rate was 43% (239/556) and the test rate 34% (190/556). Determinants for participation were sexual activity (47% versus 16%, p <0.001) and venue (street 27%, group 79%, school 52%). In street outreach, 16% (14/88) of the interested persons delivered urine at the venue, and 51% (38/74) of those who took the kit home got tested. In the groups and at the school 90% (135/151) used the urine kit at the venue and 19% (3/16) of those who intended to mail the specimen did so.

Among those who indicated to be sexually active, 38% (172/447) were actually tested (Table 8.1). The test rate was determined mainly by venue (street 17%, groups 80%, school 73%). The test rate by sex and ethnicity differed significantly only in the street setting (female 23% versus male 15% [p=0.02]; Dutch 44%, Surinamese/Antillean 13%, other 19% [p= 0.002]). There was no significant difference in test rate by sex and ethnicity in the other settings, nor was there a sex difference within ethnicities (data not shown).

Reasons for refusal

Of 316 persons declining a test kit, 19% stated never to have been sexually active, 20% perceived they would not have any or only a small risk, 37% was not interested or did not have time, 5% was tested for chlamydia in the past months, and 19% stated other reasons. Of the 180 declining men, 50% said not to be interested. Among the 136 women who declined, sexual non-activity was the most common reason (42%).

Characteristics of the sexually active participants

In the sexually active group, 57% of the women had 2-5, and 10% more than 5 lifetime partners. For men these percentages were 27% and 66% respectively. These distributions were also found in the 15-19 year olds. Recent partner change in the last 2 months was reported by 26% of the women and 53% of the men. More women than men had ever been tested for STIs (31% versus 17%; p= 0.037), and of those tested, 28% of the women and 36% of the men reported a history of STI (Ct and Gonorrhoea). In total 48% of the women and 13% of the men indicated having complaints compatible with a STI.

Table 8.1: Participation rate, test rate and Ct positivity among 447 sexually active participants at outreach testing by demographic determinants and venue

		N	Partici-pants	Partici-pation rate	p	Urine collec-tion	Test rate	p	No pos	% pos	95% CI
Street											
Total		**287**	**79**	**28%**		**49**	**17%**		**6**	**12.2%**	**5.7-24.2%**
Sex											
	Male	205	47	23%	0.006	30	15%	0.02	2	6.7%	1.8-21.3%
	Female	82	32	39%		19	23%		4	21.1%	9.8-39.5%
5 years age group											
	15-19	136	38	28%	ns	23	17%	ns	3	13.0%	4.5-32.1%
	20-24	110	33	30%		20	18%		1	5.0%	0.8-23.6%
	25-29	38	7	18%		5	13%		2	40.0%	3.6-62.4%
Ethnicity											
	Dutch	25	15	60%	0.001	11	44%	0.002	2	18.2%	5.1-47.7%
	Sur/Ant	175	42	24%		23	13%		3	13.0%	4.5-32.1%
	Other	77	22	29%		15	19%		1	6.7%	1.2-29.8%
Group											
Total		**93**	**76**	**82%**		**74**	**80%**		**7**	**9.5%**	**4.6-18.3%**
Sex											
	Male	47	37	79%	ns	37	79%	ns	3	8.1%	2.8-21.3%
	Female	46	39	85%		37	80%		4	10.8%	4.3-24.7%
5 years age group											
	15-19	37	33	89%	ns	33	89%	ns	2	6.1%	1.7-19.6%
	20-24	42	30	71%		29	69%		4	13.8%	5.5-30.6%
	25-29	12	11	92%		10	83%		1	10.0%	1.8-40.4%
Ethnicity											
	Dutch	17	14	82%	ns	14	82%	ns	1	7.1%	1.3-31.5%
	Sur/Ant	53	44	83%		42	79%		3	7.1%	2.5-19.0%
	Other	23	18	78%		18	78%		3	16.7%	5.8-39.2%
School											
Total		**67**	**53**	**79%**		**49**	**73%**		**12**	**24.5%**	**14.6-38.0%**
Sex											
	Male	8	6	75%	ns	6	75%	ns	0	0.0%	0-39.0%
	Female	59	47	80%		43	73%		12	27.9%	16.7-42.6%
5 years age group											
	15-19	59	46	78%	ns	43	73%	ns	12	27.9%	16.7-42.6%
	20-24	7	6	86%		6	86%		0	0.0%	0-39.0%
	25-29	0	0	-		0	-		0	-	-
Ethnicity											
	Dutch	28	22	79%	ns	19	68%	ns	2	10.5%	2.9-31.4%
	Sur/Ant	23	16	70%		15	65%		7	46.7%	24.8-69.8%
	Other	15	14	93%		14	93%		2	14.3%	4.0-39.9%

		N	Partici-pants	Partici-pation rate	p	Urine collec-tion	Test rate	p	No pos	% pos	95% CI
All											
Total		**447**	**208**	**47%**		**172**	**38%**		**25**	**14.5%**	**10.0-20.6%**
Sex											
	Male	260	90	35%	<0.001	73	28%	<0.001	5	6.8%	3.4-13.4%
	Female	187	118	63%		99	53%		20	20.2%	14.4-27.6%
5 years age group											
	15-19	232	117	50%	0.039	98	42%	0.036	17	17.3%	11.1-26.0%
	20-24	159	69	43%	(trend)	55	35%		5	9.1%	3.9-19.6%
	25-29	50	18	36%		15	30%		3	20.0%	7.0-45.2%
Ethnicity											
	Dutch	70	51	73%	<0.001	44	63%	<0.001	5	11.4%	4.9-23.9%
	Sur/Ant	251	102	41%		80	32%		14	17.5%	10.7-27.3%
	Other	115	54	47%		47	41%		6	12.8%	5.9-25.2%

Infection rates

With 25 cases among 172 sexually active participants, Ct-positivity was 14.5 % (95% CI: 10.0-20.6%), and higher in women (20.2%) than in men (6.8%; p=0.01). Ct-positivity was highest at school (24.5%), and among Surinamese/Antillean participants (17.5%) (Table 8.1). We found two cases of gonorrhoea (1.2%; 95% CI: 0.3-4.1); one Ct co-infected female and one male.

Notification of results, treatment and partner notification

All but two non-infected participants could be notified of their results; 88% by sms, 4% by telephone, 4% by email, and 3% by mail. After receiving the sms message, 6 participants called the STI-nurse for further information. All 26 infected participants were informed by phone and 25 were treated at the MHS. Of the infected persons, 5 (19%) stated not to have a GP, 9 (35%) consented and 11 (42%) withheld consent for the MHS informing their GP.

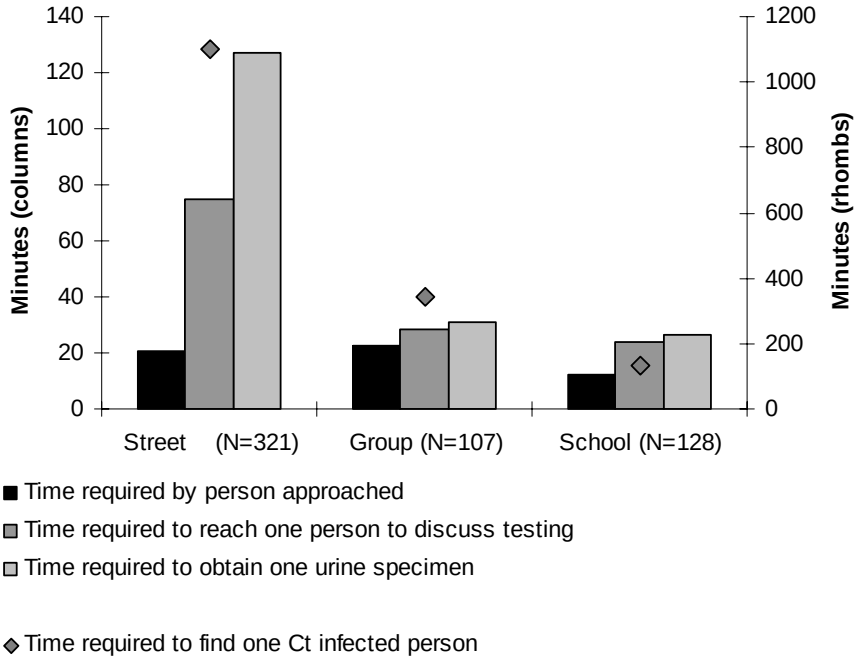
The 26 infected persons named 45 partners (mean 1.7) in the previous 6 months. The median number of partners of infected men during the last 6 months was 1.5 (1-3), while for women this was 1.0 (1-6). Notably, of 20 infected women (five of them native Dutch), 19 (95%) had partners of non-Dutch ethnicity.

Ten partners were anonymous, and 35 partners could be notified. Eighteen index cases (69%) had a current partner at the time of testing; of those 2 (11%) tested negative, 12 (67%) were treated, and 4 were referred by the index to their physician.

Efficiency

From the response rates at different venues it shows that the efficiency of community based testing varies considerably by venue. Figure 8.1 shows the time required (in minutes) to approach one person, to find a person who is willing to discuss testing, to ultimately obtain one urine specimen, and to find one infected person by venue.

Figure 8.1: Efficiency in the STI outreach testing project – depicted as the time required by person approached, to reach one person to discuss testing, to obtain one urine sample, and to detect one infected person.



Time required includes approaching all (including sexually non-active) persons.

Discussion

The test rate of *Chlamydia trachomatis* was high in the group and school settings (73-80%) compared to the street setting (17%). A crude Ct prevalence of 14.5% indicates reaching a high risk group for Ct infection, with the highest Ct prevalence (24.5%) at the school.

To our knowledge this is the first report of a study combining health education and outreach testing in Europe. An additional feature is the innovative use of sms as a communication tool. The main determinant of test uptake was the setting. The low street based test rate (17%) is in line with field based projects elsewhere [15,17] and can be explained primarily by the unexpected approach of people. The test rate at the school was similar to the comparable school based study of Cohen (59-67%).[12] A higher test rate of women compared to men was found only in the street setting. Notably, in the group and school settings the test rate among non-Dutch ethnicity was similar for both men and women to that of ethnic Dutch (65-80%). This is contrary to population based postal screening, where the test rate for men and non-Dutch ethnicity was lower than in women and Dutch ethnicity.[9,25] It should be kept in mind, however, that our data have the limitation of a small sample size and short study duration.

Compared to the Ct prevalence found in Rotterdam during a population based screening, Ct rates were higher in the present study in Dutch participants (11.4% versus 3.1%), Surinamese/Antillean participants (17.5% versus 12.6%), and other ethnic groups (12.8% versus 3.7%).[9,25] This indicates that we have succeeded in finding a high risk group. The Ct prevalence is comparable to that of the Rotterdam STI clinic in 2004 (overall 10%, and 16% in Surinamese/Antillean visitors). The most striking Ct-positivity level was 24.5% at the vocational training school. Whether such infection rates would be found repeatedly in school screening at larger scale remains to be seen; in the US in routine school based Ct screening the rates were between 8 and 20%.[11,12,26-29] Our gonorrhoea rate was lower (1.2%) than in field based testing in the US (2.5-4.9%).[16,17,30] The rate of Ct-Gonorrhoea co-infection was 4% (1/25). This rate suggests that Chlamydia infected persons should be advised to be tested for other STIs as well.

Community based testing includes challenges such as motivation of persons who do not actively seek care, confidentiality, communication of results, and treatment of those infected. Maintaining privacy is important, especially for adolescents living with their parents. We therefore asked the participants how they would like to receive results. Most preferred sms. The treatment rate in outreach testing varies from 61% to 100% [13,15-19,30] and only two studies from the US reported partner treatment rates (56 and 77%).[15,18] Our treatment rate of index cases was 100%. In total 78% (14/18) of the current partners were either tested negative or treated at the MHS. Participants preferred not to consult their GP. This suggests lack of trust in confidentiality during STI consultation, and the need of youth friendly sexual health care.

Outreach workers experienced the combination of prevention activities with a test offer as enriching. They reported more in-depth discussions in the field, but it remains to be seen whether increased interest in sexual health has a positive effect on safe sex behaviour of the high risk group.

Currently there is no Ct screening programme in the Netherlands, but a policy exists of offering active STI testing to high risk groups. The current study was performed to explore the application of such policy targeting a hard to reach risk group. The street setting was least efficient, but as many of these young people might not access health care otherwise, this service may provide a safety net offered by the MHS.[29,31] In group and school settings the offering of Ct testing was most efficient in terms of persons tested and infections found, compared to time investment (and thus costs). Our findings are in line with cost-efficiency reports of school based screening [12], with recent reports of community tailored outreach testing projects [16,21,32], and the less favourable outcomes in street settings.[15] However, a cost-efficiency analysis including effects on population level cannot be performed at this micro-level of activity.

Only a limited number of people can be contacted by outreach group activities. Our MHS may reach about 1000 people per year. Assuming a Ct-positivity of 10%, this means that 100 infections would otherwise probably remain undetected. Of course the individuals concerned may benefit from such a test offer, but this will not influence Ct prevalence in the population in any significant way. The settings described are individual testing facilities and cannot replace a systematic Ct screening programme. When looking at public health effects, it seems that targeting the vocational schools could reach large number of students (40,000), representing all ethnic groups of the Rotterdam population. If Ct screening would be adopted in the Netherlands, schools may offer opportunities to increase participation as alternative testing facility for those who are hard to motivate by postal screening. This deserves further study.

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9

Prediction of *Chlamydia trachomatis* infection - application of a scoring rule to other populations

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Abstract

Background:

Active case finding is crucial to reduce transmission and consequences of *Chlamydia trachomatis* infections. We previously proposed the use of a prediction rule for Ct infection for selective screening of high-risk individuals in a population. To support such an application, the prediction rule needs to be validated in other populations.

Methods:

We studied participants aged 15 to 29 years in a population based study in Amsterdam (n = 1788) and an outreach screening project among high-risk youth in Rotterdam (n=172). Validity was indicated by discriminative ability (area under the receiver operating characteristic curve [AUC]) and by calibration, which was visualized in plots and tested with the Hosmer-Lemeshow [H-L] goodness-of-fit test. Cut-offs of predicted risk were examined for their effect on sensitivity and the fraction of participants that would need to be screened.

Results:

Discriminative ability was reasonable, both for the Amsterdam study (AUC 0.66, 95% confidence interval 0.58-0.74) and for the Rotterdam study (AUC 0.68, 95% CI 0.58-0.79). The observed Ct prevalence was lower than predicted in Amsterdam (H-L p=0.02), and non-significantly higher in Rotterdam (H-L p=0.20). By screening 77% of the Amsterdam population, 93% of the cases would have been detected, while in the Rotterdam study no cases would be missed by screening 75%.

Conclusion:

The chlamydia prediction rule showed a reasonable external validity in 2 studies. These findings support the use of the rule as a tool for selective chlamydia screening, although only a limited fraction of participants can be excluded when a high sensitivity is required.

Introduction

Chlamydia trachomatis (Ct) infection, the most prevalent bacterial STI in developed countries can progress to pelvic inflammatory diseases (PID) in women and epididymitis in men and may lead to sequelae such as ectopic pregnancy, infertility and chronic pelvic pain.[1] Active case finding and early treatment are crucial strategies to reduce transmission and consequences of infection. Systematic screening of women has been shown to reduce the incidence of PID and ectopic pregnancy.[2,3] Improved detection methods of Ct in urine allow for community based testing in both sexes, including home-based testing [4-9] and tailored community outreach testing.[10]

Universal screening is not likely to be cost-effective in a population with relatively low Ct prevalence. Selective screening, based on risk assessment, may improve the cost-effectiveness and confronts fewer individuals with an unnecessary test. However, it could lead to a substantial proportion of missed infections (low sensitivity).

We previously developed a prediction rule for Ct infection, which performed satisfactorily at internal validation.[11] The prediction rule was regarded as a promising tool for selective Ct-screening at population level and to guide individuals in their choice of participation. Independent validation on other data is however essential before using the prediction rule in practice. When tested on data that were used for model development, the apparent performance may be excellent, but the performance in other populations may be considerably poorer.[12] Selective Ct screening criteria for both sexes showed poor performance when applied to another population in earlier studies[13-16], and have not led to practical guidelines for selection of high-risk individuals.[14,17]

We aimed to assess the validity of the previously developed prediction rule in participants of a systematic chlamydia screening project in Amsterdam[14,18] and in a community outreach Ct screening project in Rotterdam.[19]

Methods

Prediction rule

The Ct Pilot was a large population-based chlamydia screening project in 2002-03 covering rural and urban areas in the Netherlands. Demographic, behavioural, clinical, and geographic risk factors in 6303 15-29 year old sexually active women and men were measured by a self-administered questionnaire. These data were used to develop a prediction rule for the probability of Ct infection among participants.[11] The rule included as predictors age (15-19 years), area address density (urban), ethnicity (Surinamese/Antillean), education (low/intermediate), and urogenital symptoms in the previous 4 weeks (women (post)-coital bleeding; men frequent urination), lifetime sexual partners, a new sexual partner in the last 2 months, and no condom use at last sexual contact. Predictors were assigned scores based on logistic regression coefficients (Table 9.1).

Validation populations

A population based screening project was organized by general practitioners in Amsterdam in 1996/97 ('Amsterdam study').[14,18] Men and women aged 15-40 years were invited to fill in a questionnaire and collect urine at home. Samples were tested by Ligase chain reaction (Lcx). Participation rate among women was 51%, and 33% among men. The overall prevalence of Ct infection among the participating women and men was 2.8% and 2.4% respectively. Selective screening criteria were developed for 75% of the sexually active participants. Determinants for Ct infection in women were Surinamese/Antillean origin, being unmarried and not cohabiting and a partner change in the last 2 months. For men Surinamese/Antillean origin and painful micturition were predictive for chlamydial infection.[14] For women aged 15-40 years the discriminative ability in the development group had been calculated as an area under the receiver-operating characteristic curve (AUC) of 0.67 (0.65 – 0.69), which decreased to 0.58 (0.54-0.61) at validation in a random part of the Amsterdam population. For men in this age category the AUC in the development group had been 0.59 (0.55-0.60), which decreased to 0.53 (0.48-0.57) at validation.[14]

The questionnaire of the Ct Pilot had been adapted from the questionnaire of the Amsterdam study. Therefore most variables were the same in both studies. Only one predictor variable was modified: In the Ct Pilot condom use at last sexual contact was inquired, while in the Amsterdam study the question was phrased: do you and your partner use a condom always - sometimes - never. The answer "always use condom" was substituted by "condom use at last sexual contact - yes", the remaining answers were coded as no condom use.

In a community outreach-testing project in Rotterdam in 2004, youths aged 15-29 years and expected to be at high risk (low education, Surinamese/Antillean ethnicity) were offered urine testing for chlamydia during STD prevention activities. Participants filled in a written questionnaire. In this project urine samples were tested by PCR Amplicor and by a test with higher sensitivity.[19] For this validation study the Ct results of the PCR Amplicor were used as this was the test used in the Ct Pilot. Test rate among sexually active men was 28% (73/260) and 53% (99/187) among women. Ct prevalence was 11% (19/172). For 152 participants, including all 19 Ct infected cases (13%), the score could be calculated (Table 9.1).

Performance of models

We calculated the predicted probability for Ct infection for participants aged 15-29 years according to the predictor score. Mean and median risk scores were calculated for each population. The performance of the models was assessed with respect to discrimination and calibration.[20,21] The prediction rule's ability to discriminate between participants with or without a chlamydial infection was quantified by using the AUC. [22] A model with an AUC of 0.5 has no discriminative power, while an AUC of 1 reflects perfect discrimination. Ninety-five percent confidence intervals around these AUCs were calculated. Calibration is the ability of a model to produce unbiased estimates of the

probability of outcome, e.g. if participants with certain characteristics are predicted to have a 10% risk for Ct infection, the actually observed prevalence should also be 10%. Calibration was assessed graphically by plotting observed frequencies of chlamydial infection against predicted probabilities. Calibration was further tested with the Hosmer-Lemeshow goodness-of-fit test, which assesses agreement between predicted and observed risks. The ratio of the means of the predicted and actual Ct prevalence was calculated.

Imputation of missing values based on correlations between predictors was performed as a secondary analysis.[23,24] We compared the regression coefficients between the development and validation studies to explain differences in performance. Hereto, logistic regression models were used for each validation study that included the log odds of the predicted outcome (also known as linear predictor) as an offset variable, and Ct infection as dependent variable[25]. The predictors were added to this model one at a time to test the significance of the deviation of the predictive effect in the validation study from the development study.[25]

Results

Characteristics of validation populations

From the Amsterdam study data of 1788 sexually active participants aged 15-29 years were available and the score could be calculated for 1413. Among these, 52 were Ct infected (3.7%). Due to missing data the score could not be calculated for 21%, where the Ct prevalence was 3.2% (12/375, p=0.65). In the Amsterdam study 8.4% of the population was under 20 years compared to 23% in the Ct Pilot and 58% in the Rotterdam study (Table 9.1). Frequency of Surinamese/Antillean ethnicity and intermediate/ low education was high in the Rotterdam study population and lowest in the Ct Pilot study. Recent partner change and condom use at last sexual contact was most frequent in the Rotterdam study, and comparable in the two population based studies.

External validity

The prediction rule had an AUC of 0.79 (0.76-0.84) in the Ct Pilot study.11 Validation showed a lower AUC in both the Amsterdam study (0.66 [95% CI 0.58-0.74]) and the Rotterdam study (0.68 [95% CI 0.58-0.79]). The mean risk score of both external studies were higher than in the Ct Pilot. The standard deviations were smaller, indicating less spread in predictions (Table 9.2). This reflects the higher homogeneity in risk factors; for example all participants in the validation studies were living in a very high urban area (Table 9.1).

Table 9.1: Characteristics of screened populations and performance of predictor score for Chlamydial infection in 15-29 year old participants

Table 9.1	Predictor score		Ct-Pilot		Amsterdam		Rotterdam	
Participants	Women	Men	6303		1788		172	
Missing values for score			2.6%		21%		12%	
Participants with score			6141		1413		152	
CT result								
negative			5997	98%	1361	96%	133	88%
positive			144	2%	52	4%	19	13%
Sex								
Women			4195	68%	913	65%	91	60%
Men			1946	32%	500	35%	61	40%
Age group								
15-19	1	1	1386	23%	118	8%	87	58%
20-24	0	0	2307	38%	440	31%	51	34%
25-29	0	0	2448	40%	855	61%	12	8%
AAD *								
rural (AAD 5)	0	0	1418	23%	0	0%	0	0%
low/intermed./high urban	2	2	3414	56%	0	0%	0	0%
very high urban (AAD 1)	3	3	1309	21%	1413	100%	152	100%
Ethnicity								
Dutch or other	0	0	6031	98%	1284	91%	81	53%
Surinamese/Antillean	2	2	110	2%	129	9%	71	47%
Education †								
Low or intermediate	2	2	4009	65%	708	50%	146	96%
High	0	0	2132	35%	705	50%	6	4%
Urogenital symptoms #								
Women								
no	0		4017	96%	870	95%	84	92%
yes	1		178	4%	43	5%	7	8%
Men								
no		0	1851	95%	480	96%	59	97%
yes		1	95	5%	20	4%	2	3%
Lifetime sexual partners								
1	0	0	2160	35%	248	18%	34	22%
2-5	3	2	2904	47%	529	37%	66	43%
6 or more	5	3	1077	18%	636	45%	52	34%
New partner previous 2 months								
No	0	0	5404	88%	1232	87%	96	63%
Yes	1	1	737	12%	181	13%	56	37%
Condom use last contact								
Yes	0	0	1288	21%	285	20%	61	40%
No	1	1	4853	79%	1128	80%	91	60%

Legend Table 9.1: The predictor score was developed in the Ct Pilot and validated in the Amsterdam study and the Rotterdam study
* AAD1 - very high urban (>2,500 addresses/km2); AAD2 - high urban (1,500-2,500 addresses/km2); AAD3 - moderate urban (1,000-1,500 addresses/km2); AAD4 - low urban (500-1,000 addresses/km2); AAD5 - rural (<500 addresses/km2).
† Low – primary school, lower vocational or lower general secondary education; Intermediate – intermediate vocational education, intermediate or higher general secondary education; High – higher vocational education or university education
# urogenital symptoms Women: (Post)coital bleeding previous 4 weeks; Men: Frequent urination previous 4 weeks

Table 9.2: Performance of the Ct predictor score at development and at external validation

Population	Development	External validation	
	Ct Pilot	Amsterdam	Rotterdam
Mean score (S.D.)	6.3 (2.4)	8.1 (2.1)	9.8 (2.0)
Median score	6	8	10
Discrimination			
AUC ¶	0.79	0.66	0.68
95%CI	0.76-0.84	0.58-0.74	0.58-0.79
Predicted mean prevalence	2.3	4.7	8.9
Actual mean prevalence	2.3	3.7	12.5
Ratio	1.0	1.27	0.71
Calibration			
HL-test §	0.51	0.02	0.20

¶ AUC = Area under the receiver operating curve
§ Hosmer-Lemeshow goodness-of-fit test, low p-values indicate poor goodness-of-fit

Figure 9.1a shows the calibration plot for the Ct Pilot, where the prediction rule was developed. The calibration was good, especially for Ct prevalence under 10% (Hosmer-Lemeshow goodness of fit test p=0.51). The predictions for the Amsterdam study were systematically too high, with a ratio between mean predicted and actual prevalence of 1.27. The p-value of 0.02 for the Hosmer-Lemeshow goodness of fit test also indicated poor calibration (Figure 9.1b). Calibration for the Rotterdam study was acceptable (p=0.20). The predicted prevalence was generally lower than the actual prevalence, for example a predicted prevalence of 5% according to the score was actually around 10%. The ratio between mean of predicted and actual prevalence was 0.71 (Figure 9.1c).

The effects of the predictors were generally similar across the 3 studies. However, low/intermediate education had a significantly lower effect in the Amsterdam population compared with the Ct Pilot (p 0.02). Remarkably, having a new partner in the previous 2 months seemed to have a protective effect in the Rotterdam study (p=0.04). Repeated analyses with imputation of missing values in the Amsterdam population led to similar results (data not shown).

Figure 9.1: Observed frequencies of C.trachomatis infection against predicted probabilities

Figure 9.1a: Calibration plot of Ct Pilot [11] *

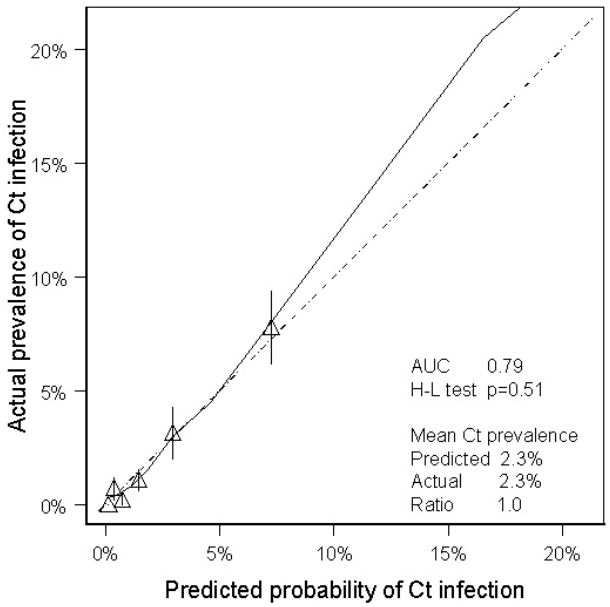


Figure 9.1b: Calibration plot of Amsterdam study

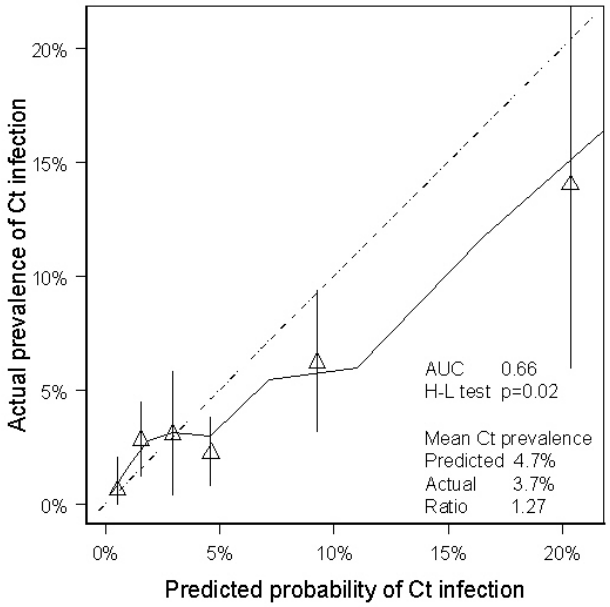
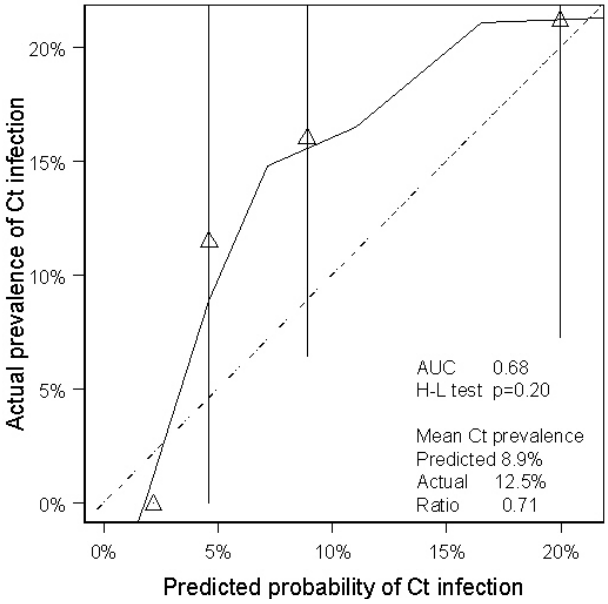


Figure 9.1c: Calibration plot of Rotterdam outreach study



Legend Figure 9.1: AUC = Area under the ROC curve; H-L-test = p value of the Hosmer-Lemeshow goodness-of-fit test; Vertical lines depict the 95% confidence interval around the actual Ct prevalence of the various studies; * This figure has been published on the internet of STI (ref.11) Permission for reproduction has been received.

Application of the prediction rule for screening

The prediction rule might be used for selective screening of individuals with relatively high scores (Table 9.3). The first row gives the scenario of screening all participants (sensitivity 100%). Screening all sexually active participants in the Ct Pilot with a sum score ≥ 7 would reduce the fraction to be screened to 45%. However, 13% of the cases would then be missed (sensitivity 87%). The expected prevalence in the screened group would be 4.5%, in contrast to 2.3% on average. Using the same cut-off score in the Amsterdam study would detect 94% of the cases by screening 77% of the population, with an expected prevalence of 4.5%. In the high-risk population of the Rotterdam study 94% would then be advised to be screened, no cases would be missed and the expected prevalence would be 13%. Figure 9.2 depicts the fraction of detected Ct cases (sensitivity) in relation to the fraction to be screened for various cut-off points of the sum score.

To reach a sensitivity of 93% in the Ct Pilot, 62% of the population would have to be screened and the expected prevalence would be 3.5%. To reach the same sensitivity in the Amsterdam study 77% of the population would have to be screened and a higher prevalence would be found (4.5%). In the Rotterdam study no cases would be missed when screening 75% of the population and the expected prevalence would be 16.5%.

Table 9.3: Test characteristics of using the prediction rule for screening for C. trachomatis in 15-29 year old participants of the development population (Ct Pilot) and in the Amsterdam and Rotterdam studies *

	Ct Pilot				Amsterdam				Rotterdam			
Cut off sum score *	Sens †	Spec ‡	Fraction pos §	PPV ||	Sens †	Spec ‡	Fraction pos §	PPV ||	Sens †	Spec ‡	Fraction pos. §	PPV ||
≥ 3	100%	5%	96%	2.5%	100%	0%	100%	3.7%	100%	0%	100%	12.5%
≥ 4	99%	14%	86%	2.7%	100%	1%	99%	3.7%	100%	0%	100%	12.5%
≥ 5	94%	23%	77%	2.9%	98%	7%	93%	3.9%	100%	0%	100%	12.5%
≥ 6	93%	38%	62%	3.5%	98%	10%	90%	4.0%	100%	1%	99%	12.6%
≥ 7	87%	56%	45%	4.5%	94%	23%	77%	4.5%	100%	7%	94%	13.3%
≥ 8	79%	68%	33%	5.7%	75%	40%	61%	4.6%	100%	15%	87%	14.4%
≥ 9	59%	83%	18%	7.8%	65%	51%	49%	4.9%	100%	28%	76%	16.5%
≥ 10	42%	92%	9%	11.4%	48%	79%	22%	8.1%	84%	45%	59%	18.0%
≥ 11	28%	97%	4%	17.5%	29%	86%	14%	7.5%	58%	65%	38%	19.0%
≥ 12	12%	99%	1%	20.5%	19%	96%	5%	14.1%	37%	81%	22%	21.2%
≥ 13	4%	100%	0%	31.6%	10%	99%	2%	20.8%	11%	93%	7%	18.2%

* Cut off-sum score: selection criterion for screening
† Sensitivity: the percentage of Ct positive participants screened under the given selection
‡ Specificity: percentage of Ct negative participants not screened under the given selection
§ Fraction positive: percentage of the total population that is eligible for screening under the given selection
|| PPV: Prevalence in the screened population (predictive value of selection criterion)
* Part of this this table has been published in STI (ref. 11). Permission for reproduction has been received.

Discussion

This study showed a reasonable discriminative ability of a chlamydia prediction rule in a population-based Ct screening study from Amsterdam (n=1413, AUC 0.66) and in a small study among high-risk groups in Rotterdam (n=152, AUC 0.68). The observed Ct prevalence was lower than predicted in the Amsterdam study, but higher in the Rotterdam study. When comparing the population based studies, a higher fraction had to be screened in the Amsterdam population compared with the Ct Pilot to reach the same sensitivity. The Rotterdam study selected high-risk youths, and efficiency of screening would hence be higher than in the Amsterdam study.

Prediction rules for Ct infection have developed before, but we used more advanced statistical methods in a relatively large population, and report here on a thorough external validation. Development and validation of the score were done in Dutch populations. Predictions of the score can probably not directly be used in other countries without further validation. Most predictors included in our prediction rule are however well-known from previous research. [13,16,26-31] Since all are readily available from questionnaire data or interviews, practical application is well possible.

The Amsterdam screening study was carried out in the general population, similar to the Ct Pilot. Due to resembling questionnaires used in the two validation studies, calculation of the predictor score was possible for both studies, a prerequisite for external validation. Despite the similar questionnaire we had a considerable amount of missing values in the Amsterdam study, but this did not to affect the validation results. Since the percentage missing score in the Ct Pilot was low, there is no indication that participants would be unwilling to provide information needed for the decision to be screened.

Although direct comparison is not possible because of different age-ranges, it seems that the performance of the predictor score was somewhat better than that of sex-specific models which were previously developed from the Amsterdam study.[14] This may be explained by the inclusion of a different and more extensive set of predictors in our prediction rule.

In a re-evaluation of screening criteria among women in the US Pacific Northwest a benchmark for selective screening was stated as 90% sensitivity by screening 60% of the population.[29] This benchmark was reached in our development population (52% to be screened), almost in the Rotterdam study (62%), but not in the Amsterdam study (72%, Figure 9.2).

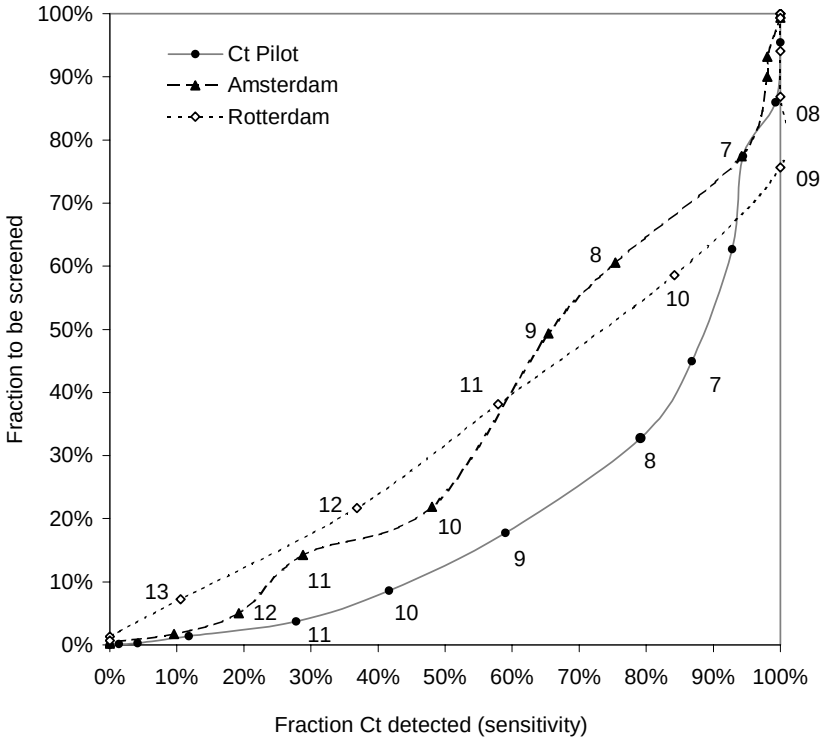
External validation of prognostic models is essential to assess generalizability, and for fair comparisons of alternative models. Models often perform less at external validation [12,20] and this can have several reasons. The predictor score was developed in a multi-centre study, with a rather large sample size and advanced statistical approaches, e.g. bootstrap validation techniques were used.[21] As a rule of thumb, the number of predictors should be less that 1/10 of the number of events.[23] In the Ct Pilot the ratio of predictors to Ct cases was 8/144 = 1/18. Therefore, overfitting was unlikely, and generalizability and calibration of predictions in new screenees was expected to be good.[23,32,33]

In the Amsterdam study the discriminative ability was reasonable, but lower than we had expected. Use of models in other populations requires similar prognostic relationships in these populations. We assessed differences in effects of variables between the Ct Pilot and the validation studies, but these comparisons were limited by the small size of the latter studies.

While the Ct Pilot and Amsterdam study population were similar in design, the Amsterdam population was less heterogeneous, especially because all participants were living in a very high urban area (higher mean score). Further, having a low/intermediate education equals 2 score points in the prediction rule, but this predictor had no predictive

effect in the Amsterdam participants. Hence, the score – and the predicted risk of Ct infection – were too high.

Figure 9.2: Fraction of detected Ct cases (sensitivity) in relation to the fraction to be screened for various cut-off points of the predictor score.



Dots represent cut-off values for predictor score in the respective studies; examples of cut-off levels are shown in the figure.

The Rotterdam study was targeted at high-risk youths within a highly urbanized area, and consequently this population was rather homogenous. This may partially explain the relatively low AUC of 0.68. Another reason may be that the study was too small to perform a reliable external evaluation, as is apparent from the wide confidence intervals of the predicted prevalences.[34,35]

A low performance of a predictive model may be due to missing determinants of infection, which are unequally spread in the respective populations. We have included well-known risk factors in our score that are easily measured by a questionnaire. We did however not inquire about concurrent partnerships, nor do we have data on age or ethnicity of the partner. Partner characteristics are obviously a component of the sexual network persons participate in. This is exemplified by the fact that some of the young infected women were with their first partner, and that those partners were members of high risk ethnic groups.[19] Those missing network determinants may form part of the explanation for the suboptimal performance of the score in the Rotterdam study. This indicates that the prediction rule has to be validated and adapted further. For example, when using the predictor score questions in a Ct screening program, partner characteristics should preferably be included, and performance be evaluated.

An individual may mainly be interested in her/his own risk and the need to get tested. Agreement of the predicted risk with the actual risk is then important (calibration). When participants from the Rotterdam study with a certain score and a corresponding predicted prevalence are advised to get tested, the actual prevalence would even be higher. This does not undo the advantages of the prediction rule. When screening persons with a score ≥7 in the Amsterdam study, this corresponds with a predicted prevalence of 4.5%. The actual prevalence would however only be 3%, which is a critical point in the use of the score.

A score ≥7 as cut off point would detect 87% of the cases in the Ct Pilot by screening 45%, the optimal threshold of the benchmark of 90% sensitivity by screening 60% would be reached.[29] In the Amsterdam study this cut-off would imply testing 77% to find 94% of the cases. This implies a reduction of persons to be screened of 23% compared to screening the whole population, and we consider this reduction to be sufficient to support use of the prediction rule. Finally in the Rotterdam study no cases would be missed but one would have to screen 94% of those high-risk persons. With an expected prevalence in the screened population above 13% there is no reason to oppose this. The Rotterdam study was approaching high-risk youth in its design, consequently it was inherent to screen a large fraction. We therefore believe that the score could be used to motivate individuals for testing despite statistical less than optimal results.

In conclusion, these findings support the use of the prediction rule as a tool for selective Ct screening. However, when a high sensitivity is required, only a limited fraction of participants can be excluded from screening.

Acknowledgement

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10

Discussion

The scope of this thesis was to study how Ct screening can best be implemented and who in particular should be targeted. The results of our studies will be discussed in the light of the five research questions formulated in the introduction. We will end with conclusions and recommendations for further research.

Answering the research questions

Question 1: What difficulties are encountered in monitoring Ct prevalence?

Prevalence trends derived from population based surveillance do not necessarily reflect the actual population trends in Chlamydia prevalence because of the following reasons. The number of cases reported in surveillance systems is influenced by changes in diagnostic tests, changing in policies towards testing and changes in focus high-risk versus general population testing. Also incident and prevalent infections cannot be distinguished, in a surveillance system.

Comments:
An increase in the number of detected Ct cases can be due to an increase in incident infections, finding more prevalent cases due to active searching, using more sensitive tests and therefore detecting more infections, or of focussing testing of high-risk groups. Monitoring Ct prevalence is performed by surveillance systems, in some countries like Sweden and the UK by obligatory notification of cases, in other like the Netherlands through a sentinel surveillance system. Surveillance data should lead to action when necessary. An apparent increase of number of cases reported may lead to additional action to control chlamydia, while a stable or decreasing number of cases may reassure us that we are doing well in the control of chlamydia. In any case, the reliability of surveillance data is crucial for the interpretation of changing trends.

The number of detected and notified cases should be related to the population at risk and to the reason for testing. In passive surveillance systems trends are monitored through tabulations of infections reported to the public health authorities, and population data are used as denominators. That this can be misleading was shown in our paper, which discussed the increase in notifications of Ct in Sweden (Chapter 2). Both the absolute number of cases detected and the Ct rates by 100 000 person years were stable in the period 1994 - 1997. However, we found a decreasing number of tested persons in this period, and consequently there was an increase in Ct positivity. From 1997 onwards both the number of tested persons and Ct positivity increased. We showed that the increasing use of tests with higher sensitivity could only partially explain the increase of Ct prevalence, thus a real increase was most likely ongoing.

Fine *et al.* recently evaluated the increase in Ct positivity among women attending family planning clinics in the US, in an opportunistic screening programme from 1997-2004. The increase of Ct positivity was associated with increasing use of NAATs rather than shifts in risk profile or prevalence of clinical signs. However the possibility of additional, unmeasured factors affecting chlamydia positivity could not be excluded.[1]

Monitoring screening coverage, outcomes (infections found and treated), and impact (reduction of complications) is of key importance for any screening programme to ensure that there is a public health benefit. For chlamydia screening the impact has been formulated in terms of cost-effectiveness, declines in prevalence over time, and decreases in incident cases of PID. Of importance is that precise measuring and monitoring of prevalence in the community through a national Ct screening programme is difficult. A principal limitation is that not all sexually active persons are tested, and thus the Ct infection status of untested persons remains unknown. At best, prevalence estimates can be made only for the population tested, and only if individuals can be uniquely identified to track multiple testing and/or infection episodes. Only then prevalence can be defined as the number of persons screened Ct positive divided by the total number of persons screened. Monitoring such level of prevalence in a large screening programme would require immense efforts.[2] Another indicator is Ct positivity, calculated as total positive tests divided by total tests. Whether Ct positivity is valid as an approximate for prevalence is the question. Ct positivity would overestimate prevalence if a high proportion of the population was tested frequently, and underestimate prevalence if there was a high percentage of repeat tests that were positive.[3] In clinic based screening programmes in the US, Ct positivity has been used as surrogate measure for prevalence and has been shown to be a useful tool in monitoring programme performance.[4] In a recent evaluation of data from a opportunistic screening pilot project in the UK, LaMontagne found only slight differences between positivity and prevalence, regardless of geographic area, health care setting, age, or reason for testing and concluded that positivity can be used as a proxy for prevalence.[2] This will lower the reporting burden and allow for rapid assessment of populations affected and changes in burden of disease.

Conclusions regarding screening coverage have often been based on surveys of health care provider or facility screening practices, but such surveys do not consider persons who do not seek care at these facilities or who seek care at more than one facility. Levine *et al.* developed a method to estimate the proportion of sexually active females aged 15-19 years screened for chlamydia in several US states by using national data on chlamydia positivity, estimates of sexual activity from the National Survey of Family Growth, and chlamydial infections reported to the Centers for Disease Control and Prevention.[5]

At the start of a Ct screening programme more cases will be detected, many of these may reflect more long-lasting, prevalent infections and thus delay appreciation of measurable decreases in chlamydia prevalence in the community. Bachmann et al. demonstrated that the success of expanded opportunistic chlamydia screening was more accurately reflected by systematic prevalence (Ct- positivity) monitoring in sentinel sites than by passive reporting.[6] They showed that during a number of years of screening there was an increase of the number of cases detected, while chlamydia prevalence (the number of positives among those tested) decreased.

In conclusion, surveillance systems for chlamydial infections need to register the number of persons tested and cases found, and type of tests used. To evaluate a Ct screening programme, population coverage should be estimated, and Ct positivity may be used as a proxy for prevalence.

Question 2: What is the prevalence of Ct infection in the Netherlands?

The Ct prevalence among 15-29 year olds is 2% (2.5% in women and 1.5% in men). The prevalence differs between rural and urban areas (0.6% versus 3.2%). Prevalence also varies by age group. In women, highest prevalence is in ages 15-19 years (4.3%); in men in ages 25-29 years (4.1%).

Comments:
In the Ct Pilot study we found a Ct prevalence of 2% among all (including not sexually active) participants (Chapter 3). Comparable rates between 2% and 3.9% in population based studies in the same age group were found in the UK and the US [7-9] Marked differences were seen between rural areas, where prevalence was under 1%, and highly urban areas where prevalence was 3.2%. A difference between rural areas and inner-city areas was also seen in an opportunistic screening study among Belgian GPs and in the Natsal 2000 study in the UK.[7,10] In women living in highly urban areas the Ct rate was 3.5% and in men 2.9%, rates comparable with those found in a population of the same age group, which was screened systematically by GPs in Amsterdam (women 3.3%, men 2.9%). Like other studies we found the highest rates in adolescent women.[7,8,11] A surprising finding was that the Ct rates did not decline in the oldest age-group, which is consistent with results from recent studies in Belgium and Finland.[10,12] In men the highest prevalence (4.1%) was found among 25-29 year olds.

In clinic based studies more Chlamydia infections were found in women than in men. This has been attributed to the fact that women seek health care more often and that opportunistic screening is also performed in family planning clinics. Therefore sex differences in population-based studies are of interest. Ct prevalence in the Ct Pilot was only slightly higher in sexually active women than in men, (2.6% versus 2.0%). In other European population based studies, Ct prevalence was 2.2-2.8% in men and 1.5-3.6% in women.[7,8,13] In the Ct Pilot in highly urban areas the prevalence found in 25-29 year old men was higher than in women of the same age (4.1% versus 3.3%). This was also found in a British probability sample survey (Natsal 2000), where Ct prevalence in the older age group (25-23 years) was higher in sexually active men than women (3.0% versus 1.7%).[7] These studies suggest that the prevalence of asymptomatic undiagnosed chlamydial infections is probably not lower in men compared to women.[7]

It has been suggested that systematic screening is not cost-effective when Ct prevalence is lower than 3%.[14] Based on this criterion three important conclusions regarding Ct screening in the Netherlands can be drawn: Firstly, nation-wide Ct screening is not warranted in view of the low prevalence in rural areas. Secondly, omitting the age group 25-29 years in screening would not be justifiable, and thirdly focussing chlamydia screening initiatives predominantly on women is not justified in view of the prevalence in men in specific settings like highly urbanised areas.

Application of the prevalence data to the region of the Municipal Public Health Service Rotterdam
How many chlamydia infections do we miss in the region of the MHS Rotterdam? The percentage of undiagnosed infections in the MHS Rotterdam can be estimated by extrapolating the Ct pilot prevalence rates to the population aged 15-29 and compare this with the number of diagnosed cases in our region in one year (assuming a mean duration of infection of one year). The MHS Rotterdam receives aggregated chlamydia test data from all laboratories in the area. Main test applicants are GPs, some samples are from specialist clinics. Ct-positivity among persons tested in those laboratories varies from 6.1% - 10.2%, indicating that persons at higher risk than the general population are tested. Age, sex and reason for testing are not available for analysis. In 2004, 1900 Ct cases have been diagnosed in the regional laboratories. This includes all cases diagnosed in the STD clinic at the Erasmus MC. As Table 10.1 shows, this would be 26% of the expected cases. Of course these figures are crude estimates, some of the infections diagnosed are from other age categories, and not all cases at the STD clinic are living in our area. However, the percentage of detected cases would be even lower taking these factors into account. Treatment of current partners will increase the number of infections removed from the pool of infections, but this will be counteracted by reinfections through untreated partners. In conclusion, currently around 70% of the Ct infections remain undetected in the infectious pool in the area of the Rotterdam public health service.

Table 10.1 Percentage diagnosed Ct infections as extrapolated from Ct Pilot prevalence, 2004

	MHS Rotterdam	Ct-Pilot prevalence	Population (15-29 yrs)	Expected cases	Diagnosed	% diagnosed
Rotterdam city	AAD* 1	4.4%	132 166	5815	unknown	
Surrounding communities	AAD* 2	2.1%	38 332	805	unknown	
Total population			170 498	6620	1700	26%

* Area address density

Question 3: Can a prediction rule for the risk of Ct infection, based on risk factors, be developed?

We developed a prediction rule which uses easily established risk factors. The validity of the rule was good in our own population. In other study populations the validity was moderate.

Comment:
Predictors for chlamydial infection were high urbanisation, young age, non-Dutch ethnicity, low or intermediate education, multiple lifetime partners, a new sexual contact in the previous two months, no condom use at last sexual contact, and complaints of (post) coital bleeding in women and frequent urination in men (Chapter 4). We developed a prediction rule by regression modelling which had adequate discriminative ability for Ct infection (AUC 0.78).

Our prediction score consists of varying combinations of risk factors, mirroring the probability of infection. Every risk factor receives a certain number of points. The points are added to a risk score. The height of the score reflects the probability of infection. By choosing a certain risk score as cut-off level for screening, the number of persons to be screened will be reduced, and the prevalence in the screened population will be higher than in the general population.

When for example in the population of the Ct Pilot, screening would be advised for people with a score of 7 or above, 87% of the cases could be detected by sceening only 45% of the population. In the screened population Ct prevalence would be 4.5% compared with 2.3% on average. When only considering the screened population, 95.5% of the screened population would be tested negative. However, one has to look at the whole population. Of all non-infected persons, 56% would justly not be screened. The 95.5% screen-negatives are 44% of all non-infected persons.

By targeting screening in this way, efficiency of screening in population-based programmes may be improved. The prediction rule has potential for application on individual level in areas with lower prevalence, and can also be used for selection and motivation of people living in high-prevalence areas.

We evaluated the performance of the prediction rule in a population based screening study performed by GPs in Amsterdam. The performance of the predictor score was moderate with an AUC of 0.66. The predicted prevalence was lower than the actual prevalence, and a higher proportion has to be screened to reach the same sensitivity as in the Ct Pilot (Chapter 9). The less optimal results than in the Ct Pilot are partially caused by a less heterogeneous population in Amsterdam, a highly urbanised area. This indicates that the prediction rule has to be adapted with regard to association between risk factors and the risk for infection.

The scenario of selective screening is to increase sensitivity (percentage of cases detected), and to increase efficiency (decrease the percentage of the population to be screened). Categories of selection criteria usually include demographic variables, clinical (signs and) symptoms and behavioural factors. Our data confirm that local adaptation of screening criteria is needed. Age under 25 is a screening criterion used in the US and the UK.[15-17] Applying this to our study population would require screening of 60% of our population but only detect 58% of the cases.

Symptoms - while possibly not leading to health care seeking behaviour – contribute to the sum score and are therefore valuable in home based screening. Surinamese/Antillean (Black Caribbean) ethnicity was a strong risk factor in the Ct Pilot, as found before in the Netherlands[13,18] and in other (European) studies.[17,19,20] We assume the independent character of this variable to reflect risks involved in sexual partner choice: in case of unsafe sex, acquisition of *C.trachomatis* infection is related to *C.trachomatis* prevalence background rates within particular sexual networks, which are clearly different in various educational and ethnic categories, as demonstrated in our study. This is in line with a recent population based UK study which concluded that individual sexual behaviour is a key determinant of STI risk, but alone does not explain the varying risk across ethnic groups.[19]

The predictor 'area address density', a geographic factor, clearly showed variation in prevalence within and between regions and also illustrated the different sexual networks persons enter. In our study behavioural factors were important predictors of infection, which is consistent with recommendations for screening criteria in opportunistic[12,21] and systematic[7,8,11] screening. Remarkably, in a recent evaluation of screening criteria in the US, behavioural factors were not found to add efficiency as selective factor.[22] The authors wondered if the right questions were asked to the target group. A limitation of our study is that we did not inquire about concurrent partnerships, nor do we have data on age, ethnicity or symptoms of the partner. Questionnaires and also a risk score chart have to be as simple as possible, and are as such no comprehensive studies of sexual behaviour. However, partner characteristics are obviously a component of the sexual network persons participate in. We suppose that the lack of partner characteristics in the risk score is partly explaining the less than optimal performance of the score in the high-risk outreach screening pilot. This is exemplified by the fact that 20% of the young infected women were with their first partner, and that all those partners were members of high-risk ethnic groups (Chapter 7). Rothenberg demonstrated in social network studies that the immediate social network is the key determinant for STI risk. In groups with high risk, partner concurrency is higher, even though the number of partners over time may be similar. This leads to more efficient transmission of STIs within a social network.[23]

Practical considerations for the use of the prediction rule:

When applying screening in other regions, the score for urbanisation takes care of differences in prevalence. Using age in the prediction rule is not expected to cause problems. However, using education and ethnicity in a decision rule might give rise to concerns about stigma and discrimination. This would need careful attention and explanation of network effects. Behavioural factors are the most direct risk indicators and probably the most generalizable predictors. We would regard asking questions on sexual behaviour in a screening programme for STI acceptable, especially if this can be done at home. Creating awareness about STI symptoms may stimulate health care seeking. We believe that the predictor score can be used in informed choice for individuals who are offered screening. This can be applied in low prevalence areas for selection, and in high-risk areas to increase motivation. The use of a personal score chart for risk evaluation may increase risk perception, awareness and motivation for testing in people who are most likely to benefit. We expect that such a personal test tool accompanying the invitation for screening, could be experienced as 'cool' and may attract the adolescents for chlamydia testing.

In conclusion the prediction rule based on risk factors found in a population based screening offers avenues for risk assessment in Ct screening. One could consider screening all young women and men universally in settings with high prevalence, whereby the score may motivate the target group, or apply the predictive score in regions with lower prevalence. Even when the optimal results in the Ct Pilot cannot be repeated, selection using the prediction rule may contribute to more efficient screening. However, validation by application and adaptation of the prediction rule including characteristics of partners is necessary.

Question 4: How should population based chlamydia screening in the Netherlands be organized?

Organising population-based chlamydia screening by home-based urine collection by the MHS was feasible. A purpose made computer programme facilitated the process and outcome evaluation. The response rate was 41% in the general population, and lower in men and persons with non-Dutch ethnicity. Participants favoured home-based urine collection and high-risk persons were willing to be tested regularly. Co-operation between the public health system (MHSs) and regular curative care proved to be possible.

Comments:
Organisation:
We have shown that organisation of population based screening by MHSs is feasible. In large scale screening a central organisation is necessary. MHSs have capacities for regional organisation of screening activities and are a familiar organisation for the population. The invitation for systematic screening could also be done by GPs, however co-ordination and evaluation need to be done at regional level. The purpose made computer software was of immense help, both during the process (duration of screening round / avoidance of errors) and for outcome evaluation.

Our participation rates were comparable with other population based studies where test kits were mailed.[8,11,24] It is an important challenge for organisers of screening to increase participation of high-risk groups. Especially worrying is the lower participation rate of men, and of persons belonging to non-Dutch, particularly Surinamese/Antillean (Black) ethnicity. We achieved a substantial increase in participation by sending a reminder, which we could show would be most efficient after 4 weeks. Due to reminders an increase in uptake from 22% to 31% in non-Dutch people could be effectuated (Chapter 5).[25] Furthermore this low response in high risk migrant groups was the starting point to develop an alternative strategy to reach migrants for chlamydia testing, which will be discussed under question 5.

Sending test kits as reminder was effective in terms of uptake rate, but from the point of view of cost effectiveness it may not be feasible to send test kits to non-responders twice.

Sending a postal invitation and request of test-kits by participants (either by mail, telephone or Internet) is an option, which should be investigated. This will not necessarily decrease response much[24] and could potentially be much cost-saving. Internet is currently used for syphilis testing.[26] Encouraging women to learn about chlamydia and use a home-sampling kit via the Internet was recently piloted in the US. Ct positivity was 10%, but the uptake rate among all internet hits was not reported.[27] Inviting people by mail in population based screening and attract them to a website where they can request a test kit would be a method adequate for the 21st century. A small Ct screening study among men in Sweden achieved an uptake rate of 39%. Invitation for screening was by mail, the result could be obtained through the Internet. The positivity rate however, was low with 1.1%, indicating that men outside the risk groups have responded.[28] As we argued in Chapter 3,

instead of perpetuating the imperative of maximising response, selective non-response in systematic screening based on informed choices may yield higher prevalences.

Test material in community based screening:
It has been established since several years that home-based testing is technically feasible. Self-sampling was acceptable and preferred in many situations.[29-31] Our data show once again that urine processing does not impair diagnosis of chlamydia (Chapter 4). Sending urine by mail requires specific handling of specimens both for mailing and in the laboratory.[32] Vaginal or vulval swab can be shipped dry, which is an advantage compared to urine. Sensitivity and specificity are comparable or even higher than testing urine with NAATs.[33-36] Combination of first catch urine and vulval swabs was shown to have the highest sensitivity.[35,37] Preference for urine has been found in some studies.[38,39] Test characteristics on various specimens, logistic factors and women's preferences should be well thought-out when deciding which specimen to use in large scale screening.

Outcome evaluation:
A treatment rate of 91% is acceptable and comparable to other studies, but not optimal. In large scale screening in general, not treating 9% of the cases found is undesirable, especially in view of a 95% cure rate of azithomycin.[40] In addition, it was problematic that a reminder was needed to increase the treatment rate from 80 to 91%. Feedback of treatment has to be organised in order to direct reminders. Lower treatment rates in groups with high risk are worrying, a personal approach (by phone) like in the STI prevention PLUS study can increase treatment rate. Focus group discussions to investigate reasons for not seeking treatment may be needed. Access to youth friendly sexual health services as alternative for general practitioners is a prerequisite. Whether giving specific consultations for screenees would break down barriers for treatment remains to be seen. We have shown that co-operated efforts of the organising MHSs with regular curative care are possible. GPs are unburdened from a major work load, and can concentrate on treatment of infected participants. Obviously, with screening the number of cases detected will increase initially. The use of alternative treatment facilities including STD nurses for treatment may support this process.

Partner notification:
Traditional methods of partner notification are index referral (the patient notifies the partner), provider referral (the health care worker notifies), and contract referral (a combination of index and provider-referral). Our advise was direct treatment of current partners without diagnostic testing. With quite some effort we managed to evaluate partner notification rates. We treated 57% of current partners and 50% of all named partners, which was in the range reported in other screening studies, yet not very satisfactory. Studies in the US showed that index referral is the most commonly used strategy.[41,42] Daily practice in the Netherlands is similar.[43] Many, and perhaps most, such partners do not receive treatment after their partner's diagnosis.[44,45] As we have emphasised the need for partner treatment in the Ct Pilot and asked for follow up, possibly partner treatment rates are even lower in daily practice.

STI-modelling studies have stressed the impact of partner notification for effects on prevalence within screening programmes. Kretzschmar found that even treating only 50%

of partners has a marked effect on Ct prevalence.[46] When screening men and women, the additional effect of partner notification is smaller than in a screening programme for women only.

The question is if higher treatment rates can be achieved by the traditional way of referring the partner to another health care worker. All methods of partner notification (index referral, provider referral, contract referral) and new methods like delivering test-kits to partners or patient delivered therapy depend on the co-operation of the index patient in naming partners. Partner notification is increased among persons with higher levels of self-efficacy and in relationships with stronger affiliative and emotional ties.[47] Our study also showed that current partners are more likely to be notified than ex partners. Niccolai has shown that knowledge about treatment of the current partner in a previous episode of STI was associated with lower risk for STI.[48] From the view of reinfection by a current partner it is particularly important to treat the current partner. In the Netherlands, GPs sometimes prescribe medication without testing to the current partner if he/she is enrolled in their practice.[49] In the US, in recent years the practice of expedited partner therapy has been expanded.[42,50-53] Expedited treatment for partners can be given to patients directly or provided without examination by health care workers to the partners. In a recently published randomised controlled trial, Golden et al. found that expedited treatment of sex partners reduced the rates of persistent or recurrent chlamydial infection.[54] Potential disadvantageous effects as discussed by the authors (adverse events of medication, treatment compliance, concurrent STIs, legal barriers) have to be investigated thoroughly. Expedited partner therapy may increase the efficiency of partner notification for this common STI in the Netherlands and needs advocacy and investigation.

Acceptability:
One of the criteria of Wilson and Jungner is that a screening test should be acceptable for the target group. When we started the Ct Pilot, there were no studies known which had assessed acceptability of home based screening, and it would have been a missed opportunity not to investigate this issue in the Ct pilot. A limitation was that it was not feasible to include non-responders in this acceptability study. Nevertheless it has given us some valuable insights. An unsolicited test offer is received well by the majority of the participants of Ct screening; the procedure of urine collection and mailing specimen is well accepted, as is receiving the result by mail. As became clear from the outreach testing study in Rotterdam, receiving the result by short message service (sms), a very individual way of approaching participants was very popular. Including sms, email and Internet for invitation and communicating results in large scale screening activities may be useful. A personal consultation remains of importance for those infected.

The majority of those who were willing to be tested in the future preferred to be invited by the MHS. Although there might be some selection bias in this answer, it was clear that participants favoured the test kit at home instead of going to a clinic. This is also found by other authors.[31,55-57] It was encouraging to find out that those at highest risk were willing to be tested in the future, as long as test material was easily available.

Critical issues:

Some critical issues emerged from the acceptability study. Firstly, the reassurance of Ct negatives, which may be false reassurance, after all being non-infected cannot be equated with not having been at risk. A repetition of the safe sex message within the media campaign about the screening should not be omitted. Secondly, as we had expected, some infected participants experienced negative feelings and stigma, but on the other hand they felt reassured as something could be done now. Women more often experienced worries and fear than men did, consequently sex-differences should be taken into account when counselling. This was also concluded in a Danish study about psychosocial consequences of Ct testing.[58] Although there is a dilemma in counselling as nobody can guarantee that there is not yet irreversible damage in an infected woman, she should indeed be assured that not having detected the infection could continue causing damage. Complication rates after the first infection are lower than after repeated infections,[59] and it should be stressed that preventing further infections is important. There are worries of negative effects of screening, when due to a programme many people would be exposed to unexpected STI results. But then again chlamydia is an easily treatable disease, and consequences of abnormal findings in for example cancer screening cannot be compared with consequences of screening for this infectious disease.

Some infected participants experienced stigma and embarrassment. Stigmatisation of STI's may lead to test barriers and avert STI control.[55,60,61] Tebb found in a clinic based study among adolescents that only 22% would seek any STI screening if asymptomatic. Adolescents who worried about having an STI were more likely to favour home-based urine collection instead of visiting a clinic.[31] To increase youth participation in screening programmes, it will be necessary to address their concerns, dispel misconceptions, and provide more information about chlamydia. The need to make sexually transmitted disease screening services more private and confidential was stressed in focus groups.[55] A positive finding was that participants shared their experience and test result with acquaintances and partner, and most did not experience rejection or other unsupportive reactions. The less positive experiences with some health care workers underline the need of training in counselling attitudes and appropriate management of feelings of stigma and embarrassment.[61,62] Asthon *et al.* found that overall, STI-related attitudes were more positive among physicians who were female, worked in clinic settings, and received adequate training in STIs.[63] This stresses the need of training health care workers. Barriers for testing can be found in the target group, but also in health care workers. Barriers to opportunistic chlamydia testing and screening were lack of knowledge of the prevalence of chlamydia, the benefits of testing, when and how to take specimens, lack of time, worries about discussing sexual health, and lack of guidance.[64,65]

Risk perception about being infected was found to be poor. Within health educational programmes it could be investigated if personal risk perception, motivation for and actual test acceptance will change after being confronted with the prediction rule. We found an increase of knowledge about chlamydia and raised intention to use condoms. The effects of a screening programme on safe sex behaviour are worth investigating.

In conclusion home-based systematic chlamydia screening organised by municipal health services is feasible, treatment of index cases and partners can be provided and evaluated

in co-operation with curative care. Response optimisation by innovative approaches especially among men and high-risk groups is needed. Vaginal swabs instead of urine may be used if preferred. Home-based screening is acceptable for participants, and those with an elevated risk are interested in screening as long as test kits are easily available. Counselling with focus on effects of Ct especially in women is essential, and training of health care workers is a prerequisite for their co-operation in screening. Expedited partner therapy may increase the efficiency of partner notification for this common STI in the Netherlands.

Question 5: Can participation of high-risk groups to Ct screening be improved?

Besides systematic Ct screening with risk-selection there are other ways to approach risk groups separately. Offering Ct testing was shown to be most efficient in vocational training schools and groups receiving STD education, where participation was >73%. Outreach screening in street settings (participation 17%) is feasible and may to some extent reach marginalized migrant groups who may not seek care anywhere. Ct prevalence found was >9% in all settings. From a public health point of view school setting offers potential as additional screening site in systematic screening.

Comments:
Traditional Ct screening within clinics is limited to the people seeking health care. Non-invasive testing provides opportunities to develop screening strategies targeting those at risk and missed by traditional control efforts. Identifying patients with risk behaviour and locating them is important, not only because they are vulnerable to reinfection and need counselling, but also from a public health point of view, since they play a disproportionate role in transmission.[66] Groups at risk are not necessarily in one single social context. The next step is to think of alternative strategies to approach them and to encourage testing. Communicating test results while protecting privacy to those who agree to be tested by self-collected specimens could be difficult. Infected people may chose to forgo treatment in a conventional clinic, and alternatively field based therapy could be provided.[67,68] This however, could limit follow-up counselling and testing for other STI's as well as partner notification. Furthermore legal rules about consent to testing apply for all community-based settings where youth under 16 years is approached.

In the Ct pilot, an example of community based testing, we found lower response rates in highly urban areas and particularly among people of non-Dutch ethnicity. On the other hand people of some ethnic groups have been shown to be at highest risk for chlamydial infection. People of non-Dutch ethnicity are from different cultural and religious backgrounds and specific approaches may be needed for each of them. Home based testing is limited by non-personal approach and lack of openness about sexual health matters in the family. Offering testing should be done in a context of activities carried out by those groups. The first hurdle to take is to access those communities. Only after gaining confidence, issues like safe sex and testing can be discussed.

In schools large groups of adolescents can be approached for health education and additional testing. Schools may serve as setting for systematic screening additional to

postal screening. Within an opportunistic screening strategy schools could serve as a location for screening outside health care.

As the Rotterdam MHS has several projects ongoing for STI health education, it was logical to try that path and include a test offer. Outreach workers offered test kits to women and men aged 15-29 years, in group and field-based settings. From the beginning it was clear that using the street setting is time intensive, as individuals or small groups who hang out on the street have to be accessed. They do not expect to discuss sexual health issues. The alternative to offer testing in groups who gather with the purpose of sexual health education is attractive.

Our test rates illustrate these expectations. In the street setting the test rate was ultimately only 17%. On the other hand we know that we reach drop out youth at those places that might not be reached by any other activity. Test rates in group setting and at school was above 73%, which is much higher than in the Ct Pilot and resembles test rates in opportunistic screening. Notably in these settings where persons were approached personally, we found no difference in test rate between sexes and between peoples of various ethnic background.

A sensitive issue is approaching Turkish and Moroccan youth, as their cultural background (Islamic religion) prohibits sexual activities before marriage. Getting tested implies sexual activity and compromises the person in question. Social control might limit testing. At school we have tried to avoid this problem by offering testing to all students, including those not sexually active.

It is apparent that we reached high-risk groups by this selective approach as the prevalence found was above 9% in all settings. This alternative strategy is of advantage when the risk group is already reached by other activities like health education. The strength lies in the combination of discussing safe sex and testing and offering it directly to both women and men. Other approaches described are offering test-kits in pharmacies, retail outlets or community centers.[69]

In conclusion, a personal approach of high-risk groups, particularly migrants, linked to STI prevention activities is feasible, and can achieve higher test rates than postal screening, especially in migrant women. High-risk groups can be tested and treated. Outreach based screening is most efficient in group/school settings compared to street settings. School-based screening has potential impact on Ct prevalence in the population. This may form an additional approach in large-scale screening.

Findings of this thesis in the context of the discussion about chlamydia screening in the Netherlands

The title of this thesis is 'Screening for chlamydia: whom and how?'. We have shown that systematic home-based screening is feasible and acceptable, but the opportunistic screening approach as a strategy has not been studied in this thesis. Most opportunistic screening programmes target women only. The goals of Ct screening programmes can be considered from individual and population perspective. At an individual level, identification and treatment of chlamydial infection in a women presenting for routine health care will reduce her risk of PID. Contact tracing and treatment of her current partners will reduce the risk of reinfection and complications. Consequently opportunistic screening should benefit many individual women. But will it make a meaningful difference in the population?

Opportunistic screening usually has a higher yield in cases than systematic screening, as is exemplified in the opportunistic screening project by GPs in Amsterdam (6.6% prevalence in 15-29 year olds)[18] and programmes abroad (Belgium GPs women 5% [10]; UK National Chlamydia Screening Programme in England: women 10% [93% of all tests]; men 13% [17]). Reported participation rate is apparently higher in opportunistic than in population based systematic screening. This is usually the proportion of participants tested among those who have been offered screening. It is the question whether all eligible patients who enter a clinic are offered testing. The Amsterdam study reported a 95% participation rate, without mentioning the number of eligible persons consulting the GPs.[18] Furthermore only a part of the population visits the clinics and population coverage is lower than participation rate. The effective screening rate is the proportion of people actually tested of the total attending population. Substantial differences have been demonstrated by Pimenta *et al.* in the pilot project for opportunistic screening which found 76% participation rate among 66% of the eligible population who was offered testing, leading to an effective test rate of 50%. Effective test rates varied much between clinic types (7-59%).[70] From GP side it was commented that a structured incentive system and a public and professional awareness campaign would be required to raise the effective screening rate in the UK.[71] Therefore population coverage may be similar to systematic screening which has a seemingly lower test rate.

Up till now there are no systematic, register based Ct screening programmes. A controlled trial which evaluated postal and opportunistic screening strategies for women organised by GPs, found a coverage of 21% in the opportunistic group and 48% in the postal group.[72] This was however a small study (N=600) limited by opting out of 21% of the participants.

In addition to effects for individuals, a Ct screening programme should reduce the prevalence of Ct in the population and thereby reducing the risk of acquiring chlamydia.[73] Which lessons can we learn from countries which have adopted an opportunistic screening policy since several years? In the USA, the current screening programmes appear unable to achieve and sustain this desirable outcome. Population based prevalence now is 4.2% in 18-26 year olds.[74] After implementation of screening in family-planning

clinics, Ct prevalence declined, but this trend has not been sustained, nor replicated in other regions of the country.[1,75]

In Sweden opportunistic screening of women and mandatory partner notification for chlamydia have been undertaken since the 1980's.[76] Although rates of diagnosed chlamydia initially declined, chlamydia rates doubled between 1997 and 2003 to pre-screening levels.[77,78] In a linkage study it was found that by the age of 35 years, an estimated 71% of women had been screened at least once, but nearly half were only tested once. The annual screening coverage in 15-24 year old women was 10-20%, which is insufficient to control ongoing transmission. Men were mainly tested through partner notification which is only done in less than 50% of the cases. Ectopic pregnancy rates in 15-19 year olds are increasing.[79,80] A Danish study showed testing women for Ct did not reduce the prevalence of chlamydia infections. During 5 years, the coverage achieved was only 19% per year, an additional factor may be that screening was not offered to men.[81] These examples demonstrate the difficulties of attaining and sustaining adequate coverage through opportunistic screening.

All systematic screening studies mentioned were cross-sectional prevalence studies, at only one point in time and only in a selected part of the eligible population. Effects of screening, both prevention of complications in individuals and decrease of transmission of Ct at population level will only be visible and measurable after repeated screening rounds. The optimal screening interval remains to be determined, usually yearly screening is recommended. We performed a reinfection study one year after the initial screening [82] and found that re-infection rate was higher in previously screen-positives (9.6%) than in screen-negatives (2.6%). This indicates that a differentiation in recommended screening intervals should be advised, which is congruent with recommendations abroad.[83]

The question remains in which way periodic, programmatic and large scale screening could be introduced, which participation rates would be achieved among persons invited for screening, how motivation of professionals particularly in opportunistic screening could be sustained, and what cost effectiveness would be calculated for the various approaches. Needless to mention is that the complication rates of Ct infection need further study. Chlamydial infections have become endemic in a large part of the Netherlands. Waiting for optimal evidence and not actively offering testing and treating these infections will worsen the situation. There is sufficient evidence that systematic screening is an effective intervention in the prevention of PID.

Conclusions and recommendations

Conclusions

- Surveillance systems for chlamydial infections can be used optimally to interprete trends in chlamydia prevalence when they register the number of persons tested and cases found, and type of tests used.

- When systematic Ct screening is performed, calculating screening coverage is essential, and Ct positivity may be used as a proxy for prevalence in evaluating the programme.
- In view of the low prevalence in rural areas nation-wide Ct screening in the Netherlands is not necessary. The recommended age group for screening is 15-29 years. Focussing chlamydia screening initiatives predominantly on women is not justified in view of the high prevalence in men in specific settings such as highly urbanised areas.
- The prediction rule for Ct infection can be used for risk assessment in Ct screening. Even when the good results in the Ct Pilot cannot be repeated, selection using the prediction rule may contribute to more efficient screening.
- Home-based systematic chlamydia screening organised by municipal health services and treatment of index cases and partners in co-operation with regular curative care is feasible.
- Home-based screening is acceptable for participants, as long as test kits are easily available.
- Personal approach of high-risk groups, particularly migrants, linked to health education activities, is feasible and most efficient in group and school settings.

Recommendations

- Ct screening should be implemented in highly urban areas during several years, with evaluation of outcome (Ct positivity, treatment rates and screening coverage). This should be organised by MHSs, which are responsible for regional STI control.
- The prediction rule should be used for motivating high-risk groups when screening in areas of high prevalence. Evaluation and adaptation of the prediction rule, including partner characteristics, is necessary.
- Selective screening using the prediction rule may be implemented in areas with lower Ct prevalence (AAD 2-4).
- The effect of potential cost saving methods (test-kits on request) and use of modern technologies for invitation, reminders and result notification (Internet, sms) ought to be field trialed.
- Optimisation of participation and treatment rate by innovative approaches, especially among men and migrants, is necessary. Expedited partner treatment ought to be strengthened.
- Counselling with focus on adverse effects of chlamydia, especially in women, needs to be strengthened, and training of health care workers is a condition for their co-operation in screening.
- Both systematic and opportunistic screening could be implemented in various high-risk regions during some years, in order to compare the outcome of both approaches in long term perspective and in the current situation of the health care system in the Netherlands.

- Implementing Ct screening in schools in high-risk areas in addition to other screening activities needs to be investigated, as a large proportion of high-risk groups can thus be approached directly.
- Monitoring of PIDs, both hospital- and primary care-based, associated with Ct infections, and of ectopic pregnancy and infertility should be attempted.
- Dynamic modelling, including use of the prediction rule, and sensitivity analysis of complication rates and partner notification should be performed, to determine which chlamydia screening approaches are cost-effective in preventing morbidity in individuals and in reducing infection in the population.

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Summary

This thesis addresses the question whom and how to screen for *Chlamydia trachomatis,* and the monitoring of chlamydia trends.

Chapter 1 introduces *Chlamydia trachomatis* (Ct) infection, the most common bacterial sexually transmitted infection, and pathogenesis of infection which is characterised by damage of tissue and inflammatory responses. It is often asymptomatic and can be persistent for prolonged periods. Chlamydial infections range from self limiting disease to complications like pelvic inflammatory disease (PID), chronic pelvic pain, ectopic pregnancy, and reduced fertility in women. Repeated Ct infections increase the risk of such complications. The availability of sensitive detection methods (NAATs) on urine/vaginal swabs and effective single-dose treatment has made home-based screening for infections with Ct feasible. Using more sensitive tests like NAATs hampers interpretation of surveillance data.

In screening of infectious diseases the individual benefits, but as transmission is interrupted, incidence of the infection will be reduced also. It has been shown that screening reduces Ct prevalence and PID. Whether to screen for chlamydia in the Netherlands is under debate. Unanswered questions regarding the screening criteria of Wilson and Jungner include history of infection and complication rates, population prevalence, the acceptability of screening by the target population, cost-effectiveness and feasibility of various screening methods. When modelling effects of a Ct screening programme, a dynamic approach is needed to account for transmission dynamics and the impact of screening on Ct incidence during longer periods.

Recruitment for screening can be done by an opportunistic approach (offering screening to people attending health care) or systematically (actively searching the population to be screened). The population targeted can be universal within a certain age-range, or selective. Selection criteria have to be validated in other populations than those from where they were developed. High-risk groups for chlamydia are the priority to be tested, as they play a major role in transmission. Opportunistic screening usually targets women only, and screening men as transmitters is preferably as it makes them part of the problem. Whether organisation of screening by GPs in the present situation would be feasible is doubtful, municipal health services can play a role in systematic screening.

In this thesis we address the following research questions: 1) What are the difficulties encountered in monitoring Ct prevalence; 2) What is the prevalence of Ct infection in the Netherlands; 3) Can a prediction rule for the risk of Ct infection, based on risk factors, be developed; 4) How should population based chlamydia screening in the Netherlands be organized and 5) Can participation of high-risk groups to Ct screening be improved?

In **Chapter 2** we address difficulties in interpreting trends of chlamydial infections in Sweden, a country performing opportunistic screening. Based on clinical and laboratory surveillance data, trends in rates of genital Ct infections in Sweden from 1991 to 1999 and the influence of changes in laboratory methods on the reported infections were analysed.

After a decrease in the incidence rate of infection by 36% between 1991 – 1994, followed by a stable level, a 20% increase was observed from 1997 to 1999 (157 to 189/100,000). The incidence rates started to increase in 1994 in the 15-19 year olds of both sexes. Crude Chlamydia positivity increased from 4.1% (of 352,050 tested persons) in 1994 to 5.4% (of 305,946 tested persons) in 1999. The increase in Chlamydia positivity was seen both in laboratories that had changed to more sensitive methods and in those that had not. Changes in laboratory methods could therefore only partially explain the increase in notified cases. Increased screening of men may have contributed, but rising incidence rates in all young age groups of both sexes suggests a true increase in prevalence.

In **Chapter 3** we describe the results of a Ct screening study (Ct Pilot) with regard to the prevalence of Ct infection among 15-29 year old men and women in rural and urban areas in the Netherlands. We performed a stratified national probability survey according to 'area address density' (AAD). The screening included invitation by the Municipal Public Health Service (MHS), home-based urine collection, PCR testing of pooled urine specimens, outcome notification by mail, and referral of Ct positive participants to regular curative health care services. Fourty-one percent (8383 out of 20,495) responded by sending in urine and questionnaire, 11% (2227) returned a refusal card. Non-responders included both higher risk (non-Dutch people) and lower risk (sexually not active people) categories. Chlamydia prevalence was significantly lower in rural areas (0.6%, 95% CI 0.1 to 1.1) compared to very highly urbanised areas (3.2%, 95% CI 2.4 to 4.0). Overall prevalence was 2.0% (95% CI 1.7 to 2.3): 2.5% (95% CI 2.0 to 3.0%) in women and 1.5% (95% CI 1.1 to 1.8) in men. These results suggest that nationwide systematic screening is not indicated in the Netherlands and that targeted approaches are a better option.

In **Chapter 4** analysis of risk factors for Ct infection is performed in the Ct Pilot study population. Selective screening, incorporating risk assessment, may increase the cost-effectiveness of screening and confronts fewer individuals with an unnecessary test. We describe the development of a prediction rule for estimating the risk of chlamydial infection as a basis for selective screening. Multivariable logistic regression in a model including both sexes was used to identify risk factors for Ct infection among 6303 sexually active participants, and the discriminative ability was measured by the area under the receiving operating characteristic curve (AUC). Internal validity was assessed with bootstrap resampling techniques. For the presence or level of each characteristic in the regression model, a score was calculated, based on the regression coefficients with rounding to simplify the calculation in practice. For each individual these scores were added into a sum score, the height of the score reflects the probability of Ct infection.

We found a Ct prevalence of 2.6% (95% CI 2.2-3.2) in women and 2.0 % (95% CI 1.4-2.7) in men. Chlamydial infection was associated with high level of urbanisation, young age, Surinamese/Antillean ethnicity, low/intermediate education, multiple lifetime partners, a new sex contact in the previous two months, no condom use at last sexual contact, and complaints of (post)-coital bleeding in women and frequent urination in men.

A prediction model with these risk factors showed adequate discriminative ability at internal validation (AUC 0.78). The prediction rule could be used for selection in Ct

screening. When screening is performed in all sexually active participants with a sum score ≥ 8 , the number to be screened in our study population would be reduced to 33%. However, 21% of the cases would then be missed (sensitivity 79%). The expected prevalence in the screened group would be 5.7%, in contrast to 2.3% on average. By lowering the cut-off from a sum-score ≥ 8 to ≥ 6, one would have to screen an additional 30% of the population to find 93% of the cases. The prediction rule has the potential to guide individuals in their choice of participation when offered chlamydia screening and is a promising tool for selective Ct-screening at population level.

In **Chapter 5** we describe lessons learned from the Ct pilot method. In the Ct pilot we used a computer programme which supported data flow from population sampling to informing participants of the result. The median periods between invitation and urine sampling, urine arrival at laboratory, sending out results and consultation of physician in case of infection were 7, 10, 17 and 24 days respectively. Ninety-five percent of the urine specimens arrived at the laboratory within 29 days from invitation and 4 (1-11) days after collection, indicating good specimen quality. A new test kit or a letter reminded non-respondents after 6 weeks. The 'urine response' was 34% (6877/20,495) after the first mailing and 12% (1462/12,185) after the reminder. The reminder contributed to 18% of the total response of 41%; this was more outspoken in people of non-Dutch origin (27%) than in Dutch people (17%). Test kits had a higher response than letters (15% versus 10%). These results indicate that reminders are necessary and effective after 4 weeks.

We had included fifteen year olds in the screening, and due to legal requirements written parental consent was required for them. Sexual activity corresponds with an increase in response of 15-19 year olds. Response in 15 year olds was 33%; with 2% Ct infected sexually active 15 year olds. Necessary parental consent for under 16 year olds should not be a deterrent to offer Ct screening to this age group.

Evaluation of management of 165 index cases and their partners in the Ct Pilot is described in **Chapter 6.** Infected participants were referred to regular curative services. The treating physician provided feedback on treatment and partner notification. Including the effect of a reminder, the treatment rate of all index cases was 91% (150/165); among persons with non-Dutch ethnicity 81% (25/31). The majority of cases (82%) consulted the general practitioner for treatment as opposed to STD/MHS clinics (18%). 85% of cases were treated within two weeks. The confirmed treatment rate of partners in the last six months was 49% (86/176); 57% (81/141) for current versus 14% (5/35) for other partners. Partner referral was advised in an additional 18% (25/141) of current partners and in 9% (3/35) of other partners. The necessity of a reminder to increase treatment rate and the lower treatment rate in non-Dutch high-risk groups deserve attention. Low confirmed treatment rate of current partners carries the potential of re-infection and expedited partner treatment should be expanded.

Chapter 7 addresses the acceptability of Ct screening for participants and their willingness to be screened in the future. Among all Ct-positives and 600 random sampled Ct-negatives, 74 infected and 266 noninfected participants took part in the acceptability study; 38% of the men and 59% of the women responded. The screening method was well accepted. Seventy percent (52) of the Ct positives were surprised about their result.

Infected women more often than men reported a feeling of being dirty and of anxiety about infertility. Curiosity for the Ct result was decisive for participation in 68% and perception of personal risk was poor. The willingness to be tested regularly was determined by present chlamydial infection, young age, multiple lifetime partners, short relationship, and earlier test for chlamydia. We concluded that Ct screening organised by the MHS is acceptable for future screening. Participants with an elevated risk are interested in screening as long as testkits are easily available. Counselling with focus on effects of Ct especially on women is essential. Alternative approaches are needed to motivate men and non-Dutch high-risk groups.

In **Chapter 8** we evaluated whether offering urine test kits in combination with STI prevention activities can increase testing particularly in high risk and hard to reach migrant populations (STI prevention PLUS project). Among sexually active persons, the test rate differed by venue (groups 80% [74/93], school 73% [49/67], street 17% [49/287]; $p<0.001$). There was no difference in test rate between group and school settings by sex or ethnicity. Ct-positivity was 14.5% (25/172); women 20.2% (20/99) versus men 6.8% (5/73); $p=0.01$. Ct-positivity was highest at school (24.5%[12/49]), and among Surinamese/Antillean people (17.5%[14/80]). The prevalence indicates that we have accessed high risk persons. Outreach testing and is feasible and most efficient in school and group settings. School screening may have impact on community prevalence of Ct infections.

In **Chapter 9** we evaluated the performance of the prediction rule developed in the Ct Pilot on data from a population based screening project in Amsterdam and the outreach screening project among high-risk youth in Rotterdam. Discriminative ability was reasonable, both for the Amsterdam study (AUC 0.66) and for the Rotterdam study (AUC 0.68). The observed Ct prevalence was lower than predicted in the Amsterdam study, but higher in the Rotterdam study. To detect 93% of the cases required screening of 77% in the Amsterdam study, while in the high-risk study in Rotterdam no cases would be missed by screening 75%. These findings support the use of the prediction rule as a tool for selective Ct screening, although only a limited fraction of participants can be excluded from screening when a high sensitivity is required.

Chapter 10 (Discussion) reviews the research questions and the results of the study in the context of past and recent literature, and puts this research in the context of the Chlamydia screening discussion in the Netherlands. The conclusions and recommendations that follow from the research for this thesis are formulated in the discussion chapter, and are described below.

Conclusions

- Surveillance systems for chlamydial infections can be used optimally to interprete trends in chlamydia prevalence when they register the number of persons tested and cases found, and type of tests used.
- When systematic Ct screening is performed, calculating screening coverage is essential, and Ct positivity may be used as a proxy for prevalence in evaluating the programme.
- In view of the low prevalence in rural areas nation-wide Ct screening in the Netherlands is not necessary. The recommended age group for screening is 15-29 years. Focussing chlamydia screening initiatives predominantly on women is not justified in view of the high prevalence in men in specific settings such as highly urbanised areas.
- The prediction rule for Ct infection can be used for risk assessment in Ct screening. Even when the good results of the Ct Pilot cannot be repeated, selection using the prediction rule may contribute to more efficient screening.
- Home-based systematic chlamydia screening organised by municipal health services and treatment of index cases and partners in co-operation with regular curative care is feasible.
- Home-based screening is acceptable for participants, and easily available test kits are a prerequisite for screening.
- Personal approach of high-risk groups, particularly migrants, linked to health education activities, is feasible and most efficient in group and school settings.

Recommendations

- Ct screening should be implemented in highly urban areas during several years, with evaluation of outcome (Ct positivity, treatment rates and screening coverage). This should be organised by MHSs, which are responsible for regional STI control.
- The prediction rule should be used for motivating high-risk groups when screening in areas of high prevalence. Evaluation and adaptation of the prediction rule, including partner characteristics, is necessary.
- Selective screening using the prediction rule may be implemented in areas with lower Ct prevalence (AAD 2-4).
- The effect of potential cost saving methods (test-kits on request) and use of modern technologies for invitation, reminders and result notification (Internet, sms) ought to be field trialed.

- Optimisation of participation and treatment rate by innovative approaches, especially among men and migrants, is necessary. Expedited partner treatment ought to be strengthened.
- Counselling with focus on adverse effects of chlamydia, especially in women, needs to be strengthened, and training of health care workers is a condition for their co-operation in screening.
- Both systematic and opportunistic screening could be implemented in various high-risk regions during some years, in order to compare the outcome of both approaches in long term perspective and in the current situation of the health care system in the Netherlands.
- Implementing Ct screening in schools in high-risk areas in addition to other screening activities needs to be investigated, as a large proportion of high-risk groups can thus be approached directly.
- Monitoring of PIDs, both hospital- and primary care-based, associated with Ct infections, and of ectopic pregnancy and infertility should be attempted.
- Dynamic modelling, including use of the prediction rule, and sensitivity analysis of complication rates and partner notification should be performed, to determine which chlamydia screening approaches are cost-effective in preventing morbidity in individuals and in reducing infection in the population.

Samenvatting

Dit proefschrift gaat over de vraag wie en hoe te screenen voor *Chlamydia trachomatis,* en het monitoren van trends in chlamydia infecties.

Hoofdstuk 1 introduceert *Chlamydia trachomatis* (Ct) infectie, de meest voorkomende bacteriële seksueel overdraagbare aandoening, en de pathogenese van de infectie welke gekenmerkt wordt door weefselbeschadiging en ontstekingsprocessen. Chlamydia infectie is vaak asymptomatisch en kan gedurende lange periodes persisteren. Chlamydia infecties variëren van een 'self limiting' infectie tot complicaties zoals 'pelvic inflammatory disease' (PID), chronische buikpijn, buitenbaarmoederlijke zwangerschap, en verminderde vruchtbaarheid bij vrouwen. Herhaalde Ct infecties verhogen het risico op zulke complicaties. De beschikbaarheid van gevoelige detectiemethoden (NAATs) op urine/vaginale uitstrijkjes en effectieve behandeling door één dosis antibiotica heeft thuis-screening op chlamydia haalbaar gemaakt. Het gebruik van sensitievere tests zoals NAATs belemmert de interpretatie van surveillance gegevens.

Screening op infectieziekten heeft voordelen voor het individu, en doordat de overdracht onderbroken wordt, zal de incidentie van de infectie ook verminderd worden. Het is aangetoond dat chlamydia screening het voorkomen van Ct en PID verlaagt. Of er in Nederland op chlamydia gescreend zal worden staat ter discussie. Er zijn nog onbeantwoorde vragen betreffende de screeningscriteria van Wilson and Jungner, zoals het natuurlijke beloop van de infectie en frequentie van complicaties, het voorkomen (prevalentie) in de bevolking, de acceptatie van screening door de doelgroep, kosteneffectiviteit en de haalbaarheid van diverse screeningsmethoden. Voor het modelleren van effecten van een Ct screening programma is dynamische modellering nodig om rekening te houden met transmissie dynamiek en de invloed van screening op Ct incidentie gedurende langere periodes.

Rekrutering voor screening kan door een opportunistische aanpak (aanbieden van screening aan personen die een gezondheidswerker [bijvoorbeeld een huisarts] consulteren, of systematisch (actief de populatie opzoeken die gescreend zou moeten worden). Men kan screening universeel aanbieden binnen een bepaalde leeftijdsgroep, of selectief. Selectieve screeningscriteria moeten gevalideerd worden in andere populaties dan degene waar ze ontwikkeld zijn. Hoogrisico groepen voor chlamydia hebben prioriteit om getest te worden, omdat zij een belangrijke rol spelen in transmissie. In opportunistische screening worden vaak alleen vrouwen getest, terwijl screenen van ook mannen als verspreiders de voorkeur verdient daar zij dan een deel van het probleem worden. Of organisatie van screening door huisartsen haalbaar is in de huidige situatie is twijfelachtig, gemeentelijke gezondheidsdiensten kunnen een rol spelen in systematische screening.

In dit proefschrift worden de volgende onderzoeksvragen behandeld: 1) Welke moeilijkheden (problemen) komen we tegen bij het registreren van Ct prevalentie; 2) Wat is de prevalentie van Ct infecties in Nederland; 3) Kan een predictie model (predictie regel) voor het risico op chlamydia infectie, gebaseerd op risicofactoren, ontwikkeld

worden 4) Hoe zou je bevolkingsonderzoek op chlamydia moeten organiseren en 5) Kan de deelname van hoogrisico groepen aan chlamydia screening verbeterd worden?

In **Hoofdstuk 2** behandelen we (aan de orde stellen) problemen in de interpretatie van trends van chlamydia infecties in Zweden, een land dat opportunistische screening uitvoert. Gebaseerd op klinische en laboratorium surveillance data, worden trends in het voorkomen van genitale Ct infecties per jaar in Zweden van 1991 tot 1999 en de invloed van veranderingen in laboratorium technieken op de gemelde infecties geanalyseerd. Na een daling van de infectie 'incidence rate' van 36% tussen 1991 en 1994, gevolgd door een stabiele fase, werd een stijging van 20% gevonden van 1997 tot 1999 (van 157 naar 189/100.000). De 'incidence rates' begonnen te stijgen in 1994 onder de 15-19 jarigen vrouwen en mannen. Chlamydia positiviteit steeg van 4.1% (van 352.050 geteste personen) in 1994 tot 5.4% (van 305.946 geteste personen) in 1999. De stijging was te zien zowel in laboratoria welke waren overgegaan op sensitievere methoden en in degenen die dat niet hadden gedaan. Daarom konden veranderingen in test methoden slechts gedeeltelijk de stijging van gemelde gevallen verklaren. Het vaker testen van mannen kan bijgedragen hebben, maar een stijgende incidentie rate in alle jonge leeftijdsgroepen van beide seksen duidt op een werkelijke stijging in prevalentie.

In **Hoofdstuk 3** beschrijven we de resultaten van een chlamydia screeningsonderzoek (Ct Pilot) betreffende de prevalentie van chlamydia infecties onder 15-29 jarige mannen en vrouwen in landelijke en stedelijke gebieden in Nederland. We voerden een gestratificeerde nationale 'probability survey' naar 'adressen dichtheid' (AAD) uit. De screening hield uitnodiging door de GGD in, thuis urine verzamelen, PCR testen op gepoolde urines, melden van uitslagen per post, en verwijzen van Ct-geinfecteerde deelnemers naar de reguliere gezondheidszorg. Eenenveertig procent (8383 van 20 495) deden mee door het insturen van urine samen met een vragenlijst, 11% (2227) stuurde een weigerkaart. Onder de niet-deelnemers (weigeraars) waren hoogrisico groepen (niet Nederlandse personen) en groepen met laag risico (seksueel niet actief). Chlamydia prevalentie was significant lager in landelijke gebieden (0.6%, 95% betrouwbaarheids interval 0.1 - 1.1%) vergeleken met hoog stedelijke gebieden (3.2%, 95% BI 2.4 - 4.0). Prevalentie was 2.0% (95% BI 1.7 - 2.3): 2.5% (95% CI 2.0 - 3.0%) in vrouwen en 1.5% (95% CI 1.1 - 1.8) in mannen. Deze resultaten laten zien dat systematische screening in het hele land niet aangewezen is en dat gerichte screening een betere optie is.

In **Hoofdstuk 4** wordt een analyse van de risicofactoren voor Ct infectie uitgevoerd in de CT Pilot onderzoekspopulatie. Selectieve screening, met gebruik van risico beoordeling, zou de kosteneffectiviteit van screening verhogen, en minder personen met een onnodige test confronteren. We beschrijven de ontwikkeling van een predictie model om het risico op chlamydia te schatten als basis voor selectief screenen. Multivariabele logistische regressie in een model voor beide seksen werd gebruikt om risicofactoren voor Ct infectie te identificeren onder de 6303 seksueel actieve deelnemers. Het discriminerende vermogen (onderscheid tussen geïnfecteerde en niet geïnfecteerde deelnemers) werd gemeten door de 'area under the receiving operating characteristic curve' (AUC). De interne validiteit werd gemeten met 'bootstrap resampling' technieken. Voor de aanwezigheid of de mate van iedere variabele in het regressiemodel werd een score berekend, gebaseerd op de regressiecoefficienten, en afronding om gebruik in de praktijk

te vereenvoudigen. Voor elke deelnemer werden deze scores opgeteld tot een som-score, de hoogte van deze score weerspiegelt de kans op Ct infectie.

We vonden een Ct prevalentie van 2.6% (95% BI 2.2-3.2) in vrouwen en 2.0 % (95% BI 1.4-2.7) in mannen. Chlamydia infectie hing samen met hoogstedelijke gebieden, jonge leeftijd, Surinaamse/Antilliaanse etniciteit, lage/middelbare opleiding, meerdere seks-partners in het leven, een nieuw seks contact in de laatste twee maanden, geen condoom gebruik tijdens de laatste seks, en klachten van (post)-coïtale bloeding in vrouwen en vaker plassen in mannen.

Een voorspellend model met deze risicofactoren liet adequate discriminatie zien bij interne validatie (AUC 0.78). Deze predictieregel zou je kunnen gebruiken voor selectie in chlamydia screening. Als je alle seksueel actieve deelnemers met een som-score ≥ 8 zou screenen, wordt het aantal te screenen personen verlaagd naar 33%. Dan zouden echter 21% van de chlamydia infecties gemist worden (sensitiviteit 79%). De verwachte prevalentie in de gescreende groep zou 5.7% zijn, in tegenstelling tot 2.3% gemiddeld. Als je de grens voor screenen verlaagt van een som-score ≥ 8 naar ≥ 6, zou je additioneel 30% van de populatie moeten screenen om 93% van de gevallen op te sporen. De predictieregel heeft het vermogen om individuen te ondersteunen in hun beslissing om deel te nemen als screening aangeboden wordt, en is een veelbelovend instrument voor selectieve screening op bevolkingsniveau.

In **Hoofdstuk 5** beschrijven we lessen die we leerden van de Ct Pilot. In deze studie gebruikten we een computer programma dat de gegevensstroom ondersteunde van steekproeftrekking tot het mededelen van het chlamydia resultaat aan deelnemers. De mediane periodes tussen uitnodiging en het verzamelen van urine, de aankomst van de urine bij het laboratorium, het verzenden van resultaten, en het consult bij de arts als de deelnemer een chlamydia infectie had, waren respectievelijk 7, 10, 17 en 24 dagen. Negenenvijftig procent van de urinemonsters kwamen binnen 29 dagen na de uitnodiging bij het laboratorium aan, en 4 (1-11) dagen na het verzamelen van de urine hetgeen duidt op een goede urine monster kwaliteit. Een nieuwe test kit of een brief herinnerde non – respondenten na 6 weken. De 'urine respons' was 34% (6877/20 495) na de eerste zending en 12% (1462/12 185) na de herinneringszending. De herinneringzending droeg bij aan 18% van de totale respons van 41%; dit was hoger in personen van niet Nederlandse origine (27%) dan onder deelnemers van Nederlandse etniciteit (17%). De respons op test kits was hoger dan degene op een herinneringsbrief (15% versus 10%). Deze resultaten duiden erop dat een herinnering nodig is en effectief is na 4 weken.

We hadden vijftienjarigen geincludeerd bij de screeningsuitnodiging, en volgens wettelijke bepalingen was een geschreven toestemming van hun ouders nodig voor deelname. Stijgende seksuele activiteit ging gepaard met een stijging in de respons van 15-19 jarigen. De respons onder 15 jarigen was 33%; waarbij 2% van de seksueel actieven onder hen geïnfecteerd was. De noodzaak van ouderlijke toestemming voor jongeren onder 16 jaar mag geen reden zijn om deze groep het aanbod van Ct screening te onthouden.

De evaluatie van het omgaan met de 165 index gevallen en hun partners in de Ct Pilot is beschreven in **Hoofdstuk 6.** Geïnfecteerde deelnemers werden verwezen naar de reguliere curatieve zorg. De behandelende arts verschafte feedback over de behandeling

en partnerwaarschuwing. Inclusief het effect van een herinnering was het percentage behandelde index gevallen 91% (150/165); voor personen van niet-Nederlandse etniciteit 81% (25/31). De meerderheid van de gevallen (82%) consulteerde hun huisarts in tegenstelling tot een SOA/GGD polikliniek (18%). 85% van de gevallen werd binnen twee weken behandeld. Het bevestigde behandel percentage van partners van de laatste 6 maanden was 49% (86/176); 57% (81/141) voor huidige versus 14% (5/35) voor andere partners. Partnerwaarschuwing werd geadviseerd in nog eens 18% (25/141) van de huidige en in 9% (3/35) van de overige partners. De noodzaak van een herinnering om het behandelpercentage te verhogen en het lagere behandelpercentage in personen van niet-Nederlandse etniciteit verdienen aandacht. Een laag percentage van bevestigde behandeling van huidige partners impliceert mogelijke herinfectie, en directe partnerbehandeling via de index of op andere manieren zonder diagnostiek zouden moeten worden uitgebreid.

Hoofdstuk 7 behandelt de acceptatie van chlamydia screening door de deelnemers en hun bereidheid om in de toekomst gescreend te worden. Van alle Ct-positieven en 600 random geselecteerde Ct-negatieven, namen 74 geïnfecteerde en 266 niet geïnfecteerde deel aan de acceptatie studie; 38% van de mannen en 59% van de vrouwen. De methode van screening werd goed gewaardeerd. Zeventig procent (52) van de Ct positieven waren verrast over hun resultaat. Geïnfecteerde vrouwen rapporteerden vaker dan mannen een gevoel van vies zijn en van angst voor onvruchtbaarheid. Benieuwd zijn naar de uitslag deed 68% besluiten tot deelname en perceptie van persoonlijk risico was matig. De bereidheid om regelmatig getest te worden werd bepaald door nu geïnfecteerd zijn, jonge leeftijd, multipele seksuele partners in het leven, korte relatieduur, en al eerder getest zijn voor chlamydia. Onze conclusie is dat chlamydia screening georganiseerd door de GGD acceptabel is voor toekomstige screening. Deelnemers met een verhoogd risico zijn geïnteresseerd in screening mits testmateriaal makkelijk verkrijgbaar is. Counseling met nadruk op de gevolgen van chlamydia vooral bij vrouwen is belangrijk. Een alternatieve aanpak is nodig om mannen en personen met niet Nederlandse achtergrond te motiveren.

In **Hoofdstuk 8** evalueerden we of een testaanbod in combinatie met SOA preventie activiteiten het testpercentage onder hoogrisicogroepen en moeilijk bereikbare migranten populaties kan verhogen (Chlamydia Voorlichting PLUS project). Onder seksueel actieve personen was het deelname percentage verschillend per setting (groepen 80%, school voor beroepsopleiding 73%, straat 17%). In groepen en op school vonden we geen verschil in deelname tussen mannen en vrouwen, in tussen verschillende etnische groepen. Ct positiviteit was 14,5% (25/172), vrouwen 20,2% (20/99) vergeleken met mannen 6,8% (5/73). Ct positiviteit was het hoogst op school (24.5% [12/49]), en in Surinaamse/Antilliaanse deelnemers (17.5% [14/80]). De gevonden prevalentie wijst erop dat we hoogrisico groepen bereikt hebben. Outreach testen is uitvoerbaar en het meest efficiënt in school en groepsverband. Ct screening op scholen kan de Ct prevalentie op bevolkingsniveau beïnvloeden.

In **Hoofdstuk 9** evalueerden we de prestatie van de predictieregel welke in de Ct Pilot ontwikkeld werd op data van een chlamydia bevolkingsonderzoek om Amsterdam en het outreach Ct screening project onder hoog risico jongeren in Rotterdam. Het discriminerend (onderscheidend) vermogen was redelijk, voor zowel de Amsterdam

studie (AUC 0.66) en de Rotterdam studie (AUC 0.68). De waargenomen Ct prevalentie was lager dan voorspeld in de Amsterdam studie, maar hoger in de Rotterdam studie. Om 93% van de gevallen te ontdekken zou 77% van de populatie van de Amsterdam studie gescreend moeten worden, terwijl in de hoogrisico studie in Rotterdam geen gevallen gemist zouden worden als 75% van deze populatie gescreend zou worden. Deze bevindingen ondersteunen de toepasbaarheid van de predictieregel als instrument voor selectieve screening, hoewel slechts een beperkt deel van de deelnemers geëxcludeerd kan worden van screening als een hoge sensitiviteit nodig is.

Hoofdstuk 10 (Discussie) geeft een overzicht van de onderzoeksvragen en de resultaten van de studie in de context van bekende en recente literatuur, en bespreekt dit onderzoek in de context van de chlamydia screening discussie in Nederland. De conclusies en aanbevelingen uit het onderzoek voor dit proefschrift zijn geformuleerd in het discussie hoofdstuk en worden hieronder nogmaals beschreven.

Conclusies

- Surveillance systemen voor chlamydia infecties kunnen optimaal gebruikt worden om trends in chlamydia prevalentie te volgen indien zij het aantal geteste personen en de gevonden gevallen registreren, evenals het type laboratorium test.
- Wanneer systematische chlamydia screening wordt uitgevoerd, is het van belang de dekkingsgraad van de screening te berekenen.Daarbij mag chlamydia positiviteit gebruikt worden als benadering voor prevalentie in de evaluatie van het screenings programma.
- Gezien de lage prevalentie in rurale gebieden is landelijke chlamydia screening in Nederland niet nodig. De aanbevolen leeftijdsgroep voor screening is 15-29 jaar. Het is niet gerechtvaardigd chlamydia screenings initiatieven voornamelijk op vrouwen te richten vanwege de hoge Ct prevalentie in mannen in specifieke omgevingen zoals grootstedelijke gebieden.
- De predictieregel voor chlamydia infectie kan gebruikt worden voor risico beoordeling in chlamydia screening. Zelfs als de goede resultaten van de Ct Pilot niet herhaald kunnen worden, zou selectie door middel van de predictieregel bij kunnen dragen aan meer efficiënte screening.
- Systematische chlamydia screening thuis, georganiseerd door GGDen en met behandeling van indexgevallen en partners in samenwerking met de reguliere curatieve zorg, is haalbaar.
- Thuis screening wordt geaccepteerd door deelnemers, mits de test kits gemakkelijk verkrijgbaar zijn.
- Een persoonlijke uitnodiging tot testen voor hoogrisicogroepen, in het bijzonder migranten, gekoppeld aan SOA voorlichting, is haalbaar en het meest efficiënt in groepen en scholen.

Aanbevelingen

- Chlamydia screening zou geïmplementeerd moeten worden in grootstedelijke gebieden gedurende meerdere jaren, met evaluatie van de uitkomst (Ct positiviteit, behandelpercentage en screening dekkingsgraad). Dit zou georganiseerd moeten worden door GGDen, die verantwoordelijk zijn voor regionale SOA bestrijding.
- De predictieregel zou gebruikt moeten worden om hoogrisico groepen te motiveren bij screening in gebieden met hoge prevalentie. Evaluatie en aanpassing van de predictieregel, met inclusie van partner karakteristieken, is nodig.
- Selectieve screening met gebruik van de predictieregel zou geïmplementeerd kunnen worden in gebieden met lagere Ct prevalentie (Omgevingsadressen dichtheid 2-4).
- Het effect van mogelijk kostenbesparende methoden (test kits op aanvraag) en het gebruik van moderne technieken voor de uitnodiging, herinneringsoproep en meedelen van de uitslag (Internet, sms) zouden in de praktijk getest moeten worden.
- Optimalisatie van deelname en behandelpercentage door innovatieve aanpak is nodig, in het bijzonder bij mannen en migranten,. Laagdrempelige, directe partner behandeling moet versterkt worden.
- Counseling met nadruk op complicaties van chlamydia infecties, vooral bij vrouwen, moet versterkt worden, en training van gezondheidswerkers is een voorwaarde voor hun medewerking in een chlamydia screeningsprogramma.
- Zowel systematische als opportunistische screening zou geïmplementeerd kunnen worden in gebieden met hoge prevalentie gedurende meerdere jaren, om de uitkomsten van beide methoden op langere termijn en in de huidige situatie van de gezondheidszorg in Nederland te vergelijken.
- Implementatie van chlamydia screening in scholen in hoogrisicogebieden in aanvulling op andere screeningsactiviteiten zou onderzocht moeten worden, omdat een groot deel van de hoogrisicogroepen zo persoonlijk en direct benaderd kan worden.
- Er zou getracht moeten worden om PIDs, die geassocieerd zijn met chlamydia infecties, in zowel in ziekenhuizen als in de eerste lijn, en van extra-uteriene zwangerschappen en onvruchtbaarheid te registreren. .
- Dynamische modellering, inclusief de predictieregel, en sensitiviteitsanalyse van complicatiecijfers en partnerwaarschuwing zou uitgevoerd moeten worden om vast te stellen welke screeningsmethoden kosteneffectief zijn in het voorkomen van ziekte in individuen en in de reductie van infecties in de bevolking.

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This thesis starts with work I have done in Sweden during my EPIET fellowship. Being responsible for the national chlamydia surveillance was a valuable experience, and cooperating with the co-authors was pleasant. Torvald Ripa was inspiring with his view on chlamydia control beyond the laboratory walls; Johan Lindbäck was making statistics funny. Karl Ekdahl should be acknowledged for his supervision. Malin Arneborn and Ragnhild Jansson — your friendship kept me going.

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Curriculum vitae

Hannelore Götz is geboren en getogen op de Schwäbische Alb, Zuid Duitsland. Na het gymnasium in Bad Urach, werk als verpleeghulp en reizen, begon zij in 1979 de studie geneeskunde aan de Vrije Universiteit in Amsterdam. Na drie jaar klinische assistentschappen gynecologie/ verloskunde en chirurgie vertrek naar de tropen. In Namibie, aan de grens met Angola heeft ze gedurende 3 jaar gewerkt als District Medical Officer.

Terug in Nederland (1995) werkte ze bij de GGD Stedendriehoek, beginnend bij diverse taken van de sociale geneeskunde (sociaal medische advisering, forensische geneeskunde, infectieziektebestrijding), maar de keuze voor infectieziektebestrijding was gauw gemaakt. De modules infectieziektebestrijding werkten verdiepend voor het dagelijkse werk.

In 1998 kreeg zij de kans om het 2-jarige EPIET programma (European Programme for Intervention Epidemiology Training) te volgen aan het 'smittskyddsinstitutet' in Stockholm, Zweden. Daar heeft ze zich naast uitbraak bestrijding en onderwijs geven vooral bezig gehouden met Soa/Chlamydia surveillance. Het geleerde kon in de praktijk gebracht worden bij de GGD Rotterdam e.o. waar zij sinds december 2000 als arts-epidemioloog infectieziektebestrijding werkt. Ze is lid van het LOI, de LOI redactieraad, en de osiris registratiecommissie. Ze studeerde af als Master of Public Health aan het NIHES in Rotterdam in 2004.

Onderzoek doen naast de dagelijkse werkzaamheden was tegelijkertijd voorwaarde en uitdaging voor de invulling van dit vak. Het Ct Pilot onderzoek en daarna uitgevoerde onderzoeken leidden uiteindelijk tot dit proefschrift.

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