Comparison of two methods of screening for genital chlamydial infection in women attending in general practice: cross sectional survey

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Abstract

Objectives: To estimate the prevalence of *Chlamydia trachomatis* in asymptomatic women attending general practice; to assess the potential of the ligase chain reaction as a screening tool; and to evaluate selective screening criteria.
Design: Cross sectional survey.
Setting: Four general practices in northeast London.
Subjects: 890 women aged 18-35 years attending general practice for a cervical smear or a "young well woman" check between October 1994 and January 1996. The women were tested for *C trachomatis* with confirmed enzyme immunoassay (endocervical specimens) and ligase chain reaction assay on urine specimens.
Main outcome measures: Prevalence of *C trachomatis* infection in women aged 18-35 on the basis of each test; sensitivity and specificity of both tests in this population.
Results: Prevalence of confirmed infection was 2.6% (95% confidence interval 1.6% to 3.6%) in all women. Prevalence on the basis of enzyme immunoassay was 1.6% (0.8% to 2.7%), with a sensitivity of 60% and a specificity of 100%. Prevalence on the basis of ligase chain reaction was 2.5% (1.5% to 3.9%), with 90% sensitivity and 99.8% specificity. Screening all women aged ⩽25 and all women who had had two or more partners in the past year would have detected 87% (20/23) of infections.
Conclusion: Ligase chain reaction on urine samples performs at least as well as enzyme immunoassay on cervical specimens in this low prevalence population. It offers potential as a non-invasive screening tool. A simple selective screening strategy might be appropriate and would be able to detect most cases of infection. However, a rigorous economic evaluation of possible screening strategies is needed first.

Introduction

Chlamydia trachomatis is the commonest sexually transmitted bacterial pathogen in Britain.[1] It causes urethritis and epididymitis in men, and cervicitis, salpingitis, and endometritis in women. Symptoms of lower genital tract infection in both sexes can be mild or non-specific. Up to 70% of infections in women may be asymptomatic and are thus unlikely to be treated.[2-4] Untreated women may develop pelvic inflammatory disease, which can also be asymptomatic and can lead to chronic pelvic pain, infertility, and ectopic pregnancy. These complications occur in up to 25% of cases of chlamydial pelvic inflammatory disease[5] and are a major personal, social, and health service burden.

The prevalence of chlamydial infection in women in Britain has not been accurately determined,[6] largely because of the asymptomatic nature of infection and the need for endocervical swabs to establish the diagnosis. Recently the ligase chain reaction assay for the detection of *C trachomatis* has become available and shows high sensitivity and specificity when used for urine testing in high prevalence populations.[7-9] Little work has been done, however, on its use in low prevalence populations.[10]

We report a study designed to establish the prevalence of chlamydial infection in women aged 18-35 years who were due for a cervical smear or who were invited for a "young well woman" check during the 16 months between October 1994 and January 1996. We also compared the use of a confirmed enzyme immunoassay on an endocervical swab with the use of ligase chain reaction on urine samples collected at the same time. This has enabled us to establish the performance characteristics of ligase chain reaction in a population with low prevalence of *C trachomatis* and thus determine its usefulness for future screening programmes. In addition, we collected data on possible risk factors for infection to evaluate the appropriateness of a selective approach to screening.

Methods

We invited all (n = 30) general practices with three or more partners in Camden and Islington and City and East Family Health Service Authorities to take part in

this study. Four practices agreed to participate; they had a joint list size of 37 000 patients.

All women aged 20-35 who were due for a routine cervical smear test between October 1994 and January 1996, as part of the national screening programme, were eligible to participate. They were invited by letter to attend for cervical screening. All those who attended for a smear test at clinics where the study nurse was present were invited to participate. In addition, some women were recruited directly by nurses or general practitioners when they attended for a smear test. After giving written informed consent, the women were asked to complete a brief questionnaire requesting demographic details, history of urogenital symptoms, and information on sexual behaviour in the past five years. Women attending for follow up of previous abnormal smears were not included unless they had returned to routine recall. Women who had taken antibiotics in the past two weeks were asked to return at a later date.

The women who failed to respond to the first invitation for a smear test were sent a specific invitation in addition to the routine follow up invitation from their practice. Women who did not respond to this specific invitation were sent a further letter by recorded delivery inviting them to participate in the study or return a completed questionnaire. A stamped addressed envelope was enclosed. If a recorded delivery letter was returned undelivered the woman was considered to have moved and was not eligible to enter the study.

Women aged 18-19 are not included in the national cervical screening programme but are at risk of chlamydial infection if they are sexually active. All women in this age group were sent letters inviting them to a young well woman check with the study nurse. At the check, general health concerns were discussed, including smoking, diet, exercise, contraception, and safer sex. All these women were invited to participate in the study. Those agreeing to participate were asked for written consent and completed the same questionnaire as the older women. If they had ever been sexually active a cervical smear and samples for chlamydia testing were taken. Women who had taken antibiotics in the past two weeks were asked to return at a later date. Those younger women who did not respond to the first invitation were sent two further invitations by the study nurse, the last of which was sent by recorded delivery. This invited them to participate or to write back declining to participate. If recorded delivery letters were returned undelivered the women were excluded from the study.

All the women testing positive for chlamydial infection were contacted directly by the study nurse, who arranged treatment and contact tracing in either a genitourinary medicine clinic or in general practice.

Samples of the first 20-30 ml of the urine stream were collected from women before a speculum was passed into the vagina. The urine was stored at 4°C and transported to the laboratory, where it was frozen at −70°C until it was batch processed when ligase chain reaction testing became available in February 1996. The study nurse trained all doctors and practice nurses to take endocervical swabs in the following way: the cervix was visualised and a smear taken using an Ayre's spatula; the cervix was then cleaned with a large headed swab, and a further cotton swab was rotated in the endocervix for 30 seconds according to the manufacturer's instructions and placed immediately in transport medium supplied by the manufacturer. The specimens were kept at 4°C and tested within seven days of collection. Clinicians recorded their examination routinely for use in the analysis of risk factors.

Endocervical specimens were tested on a routine basis with enzyme immunoassay and confirmatory blocking test (Chlamydiazyme Abbott Laboratories, Chicago, Illinois). Urine samples were tested with a plasmid based ligase chain reaction (Abbott Laboratories, Chicago) according to the manufacturer's instructions.[10]

When the results of cervical enzyme immunoassay did not accord with those of the urine ligase chain reaction further testing was performed immediately. When the ligase chain reaction was positive and the enzyme immunoassay was negative a direct immunofluorescence (Syva Microtrak, Syva Company, San Jose, CA) was performed on the cervical specimen. Urine samples that were persistently positive with ligase chain reaction when enzyme immunoassay and direct immunofluorescence on the cervical specimen were negative were further evaluated with a major, outer membrane-based protein ligase chain reaction (performed by Abbott Laboratories, Chicago). All discrepant analyses were performed in a blinded fashion. If the enzyme immunoassay was positive and the ligase chain reaction was negative, ligase chain reaction was repeated, first with neat urine and then at a 1:4 dilution to reduce the effect of any inhibitors. If samples were found positive in this way the original ligase chain reaction result was considered to be a false negative. In addition, direct immunofluorescence was performed on the urine. A true positive was defined as positive on both enzyme immunoassay and ligase chain reaction, or two positive unrelated tests (enzyme immunoassay with confirmatory blocking test; direct immunofluorescence; plasmid based ligase chain reaction; or major, outer membrane-based protein ligase chain reaction) on one or both specimens.

To determine the generalisability of our findings we compared women in our sample with women living in central London in the same age range (18-35) who completed the British sexual attitudes and lifestyle survey[11] in 1990-1 and reported having sexual intercourse with men. We compared age at first intercourse, proportion with two or more male partners in the past year, and reported condom use in the past year.

Statistical methods

Groups of women found to be positive and negative were compared with the χ^2 test for binary variables, the *t* test for age, and the Mann-Whitney test for number of sexual partners. Multiple logistic regression was performed in the statistical software SPSS to assess the effect of several factors simultaneously on chlamydial status.

Results

Recruitment

In all, 3638 women aged 20-35 were eligible to participate. Of these, 597 (16.4%) who no longer lived at their

Table 1 Comparison of performance of ligase chain reaction testing on urine with that of enzyme immunoassay of endocervical specimens in 765 women aged 18-35

	Ligase chain reaction		Enzyme immunoassay	
	No of women	% (95% CI)	No of women	% (95% CI)
Prevalence	19/765	2.5 (1.5 to 3.9)	12/765	1.6 (0.8 to 2.7)
Sensitivity	18/20	90 (68 to 99)	12/20	60 (36 to 81)
Specificity	744/745	99.9 (99.2 to 100)	745/745	100 (99.5 to 100)
Predictive value of positive result	18/19	95 (74 to 100)	12/12	100 (74 to 100)
Predictive value of negative result	744/746	99.7 (99 to 100)	745/753	98.9 (97.9 to 99.5)

stated address were excluded, leaving 3041 (83.6%) women in this age group. After two invitations and a recorded delivery letter, 2051 (67.4%) women attended their general practice for a cervical smear during the study period and 65 returned a questionnaire but did not want to be tested. Of those attending, 672 (32.8%) were invited to participate because they attended clinics run by the study nurse, and 186 (9%) were invited to participate by general practitioners and practice nurses. Of those invited, only 17 (2.0%) declined to participate; 14 (1.6%) were taking antibiotics and so were excluded.

Of 322 women aged 18-19 who were eligible to participate, 118 (36.6%) were excluded as they no longer lived at their stated address. Of the remaining 204 women, 130 (63.7%) attended an appointment with the study nurse, of whom 105 (80.8%) agreed to participate, but 42 (40%) of these had never been sexually active and were therefore excluded.

Prevalence of infection

Of the 890 women in whom an endocervical swab was taken, 765 also provided sufficient urine for ligase chain reaction testing. In all, 23 women had a confirmed positive result for chlamydia on at least one sample, giving an overall prevalence of 2.6% (95% confidence interval 1.6% to 3.6%). Sixteen of the women aged 20-35 had positive results (1.9% (1% to 2.8%)), as did seven of the women aged 18 and 19 (11% (3.2% to 19%)).

Table 2 Demographic and behavioural characteristics of 879* women participating in study—comparison of those positive for chlamydia infection with those negative for infection

Risk factor	% (No) of women with positive result	Odds ratio
Age group (n=848):		
≤20	10.6 (9/85)	8.64 (2.28 to 32.8)
21-25	3.8 (8/210)	2.89 (0.76 to 11.0)
26-30	0.9 (3/331)	0.67 (0.13 to 3.34)
≥31	1.4 (3/222)	1
Marital status (n=822):		
Married	0.6 (1/170)	0.19 (0.02 to 1.45)
Cohabiting	3.1 (8/260)	1.00 (0.41 to 2.49)
Single	3.1 (12/392)	1
No of partners in past year (n=812):		
0-1	1.7 (11/630)	1
≥2	4.9 (9/182)	2.93 (1.19 to 7.18)
One or more new partners in past 3 months (n=782):		
No	2.4 (16/671)	1
Yes	4.5 (5/111)	1.93 (0.69 to 5.38)
Ever had sexually transmitted disease (n=818):		
No	2.3 (14/616)	1
Yes	3.5 (7/202)	1.54 (0.61 to 3.88)
Ever had termination of pregnancy (n=831):		
No	2.6 (15/575)	1
Yes	2.7 (7/256)	1.05 (0.42 to 2.61)
Genitourinary symptoms at present (n=807):		
No	2.4 (11/467)	1
Yes	3.2 (11/340)	1.33 (0.53 to 2.99)

*Total is not always 879 owing to missing data.

Performance of ligase chain reaction and enzyme immunoassay

Overall, 765 women provided both urine and endocervical samples. In this group the performance of ligase chain reaction on urine and of enzyme immunoassay on endocervical specimens was compared with the number of true positives as defined in the methods section. In total, 20 samples were found to be true positives. Ligase chain reaction identified 18 of these, whereas enzyme immunoassay detected only 12 of them. One specimen positive on ligase chain reaction testing could not be retested with major, outer membrane-based protein ligase chain reaction and was recorded as an assumed false positive. No false positive results occurred with enzyme immunoassay testing. Table 1 compares the performance of the two tests.

Comparison with sexual attitudes and lifestyle survey

Median age at first sexual intercourse among women in this study was 17 years, compared with 18 years among women of the same age who completed the sexual attitudes and lifestyle survey.[11] Women in this study were more likely to have had two or more partners in the past year (22% *v* 16%), and a higher proportion (62% *v* 43%) reported condom use in the past year.

Selective screening strategies

Questionnaire data on demographic characteristics, and medical and sexual history were examined in univariate analysis—we compared the 23 women with a positive result for chlamydia on either test with those who had a negative result (table 2). Those with a positive result were significantly younger ($P < 0.001$) and had had significantly more partners in the past year ($P = 0.02$) than those with a negative result. No other potential risk factor showed a significant association with infection.

With multivariate analysis, age and having two or more partners in the past year were each found to be associated with infection after the other was controlled for. We therefore went on to test possible combinations that might be used as screening strategies. If all women aged 25 or less had been screened, 17 of 23 infections would have been detected among 295 (35%) women tested. If all women aged 29 or less had been screened, 20 of 23 infections would have been detected among 566 (67%) women tested. If all women aged 25 or less and all women who had had two or more partners in the past year had been screened, 20 of 23 infections would have been detected among 401 (49%) women tested. No selective strategy detected all the cases of infection.

Discussion

In this study the estimated prevalence of *Chlamydia trachomatis* in asymptomatic sexually experienced women aged 18-35 was 2.6%. This figure may be an underestimate because both ligase chain reaction on a single urine sample and enzyme immunoassay on an endocervical swab have been shown to have suboptimal sensitivities.[12 13] Our estimate of the prevalence of chlamydia is consistent with recent work in general practices in south London, where the prevalence (based on enzyme immunoassay testing) was 3% among women aged 17-35 in whom cervical smears were taken,[14] and with results from Fife, Scotland, where the prevalence (based on direct immunofluorescence) was 2% among women aged 15-40 in whom a smear was taken.[15] The prevalence of infection in women aged under 20 in our study was 11%; the numbers in this group, however, are small and the confidence intervals wide. Further work is needed to make a more reliable estimate. Previous studies showing a higher prevalence have focused on subgroups of women at risk—for example, those seeking termination of pregnancy, complaining of genitourinary symptoms, or of social class III, IV, or V.[16-20] Lower estimates are likely to be more reflective of the population as a whole.

Performance of ligase chain reaction

We have shown that the performance of the ligase chain reaction assay on urine in a population with a low prevalence of *C trachomatis* is at least as good as that of enzyme immunoassay on cervical specimens, and may be superior. Some doubt has been expressed recently about the use of discrepant analysis to assess the performance of new tests.[21] In this study, however, we treated both tests in the same way and limited the number of additional tests performed. The cost of performing all tests on all samples is too great to make this a practical option for screening in a low prevalence population. In addition to detecting some 50% more cases in this study, ligase chain reaction has the major advantage of using a urine sample that is far easier to collect. Although the benefits of ligase chain reaction testing in high prevalence populations have been shown, this appears to be the first study to define its performance in a low prevalence population. Its high sensitivity and specificity and the ease of taking samples make it a suitable test for community based screening. The positive predictive value of 95% reflects the fact that one sample result could not undergo further testing; this was likely in fact to have been a true positive, in which case the positive predictive value of ligase chain reaction would approach 100%.

Viability of screening

Chlamydial infection fits most of the criteria for screening given by Wilson and Junger.[22] We have shown that a pool of asymptomatic infection is unlikely to be detected without a screening programme. In view of the relatively low prevalence of infection it may be more appropriate to consider selective screening than universal testing. Selective screening for chlamydial infection on the basis of age, ethnic group, having two or more partners in the past year, and being unmarried has reduced the incidence of pelvic inflammatory disease in a large study in the United States.[23] Our data suggest that simple criteria could be used, possibly only age and number of partners in the past year, to limit the number of women who need to be screened (the addition of other screening questions, particularly about marital status, does not improve the detection rate in this study). Such screening would identify a population with a prevalence of infection of about 5%. The information needed could be elicited easily in routine consultations in all primary care settings and could also be part of a wider awareness campaign in the media.

Previous studies have suggested that screening becomes cost effective at a prevalence of about 6% or more.[5 24 25] This estimate needs to be re-evaluated, however, in the light of new tests with higher sensitivity and the possibility of single dose treatment—for example, with azithromycin, which is associated with improved compliance.[26] Reducing the prevalence of chlamydial infection has the potential for reducing the incidence of serious, long term complications, which are costly both personally and financially. We have shown that a potential exists for non-invasive screening for genital chlamydial infection in Britain. Before screening is introduced, however, a rigorous economic evaluation is needed to assess the most cost effective strategy.

Key messages

- *Chlamydia trachomatis* causes a common sexually transmitted infection, which is often asymptomatic but may lead to pelvic inflammatory disease, ectopic pregnancy, and tubal infertility in 10%-25% of infected women
- Over 1 in 20 women aged 18-25 years attending general practice may have undiagnosed infection
- New screening tests that do not require a cervical sample should improve the prospects for community based screening for chlamydia
- Rigorous evaluation of the cost effectiveness of such screening is now a priority

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Conflict of interest: None.

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A memorable patient

Out of Africa: a rash occurrence

"Mgongwa kwa ndui," said the breathless African forerunner. The last word misled me into expecting a patient with leopard bites, a condition not uncommon in that remote part of Africa in 1963. However the Swahili dictionary showed "ndui" as smallpox, a leopard being "chui."

Sure enough 10 minutes later a man covered in pustules was wheeled down the dirt track towards our little 60 bed hospital; "wheeled" because he was on a makeshift bamboo carrier on the back of a bicycle. Local tribal beliefs reserved stretchers for the dead. Rashidi had been pushed about 40 miles by his brother. The patient, an estimated 55, was able to give an accurate account of the fever that started 10 days earlier; he had presumed it to be the usual and widespread subacute endemic malaria, until on the fifth day the rash appeared. He came from Liwale, where medical and nursing facilities were virtually non-existent. The spots presented no diagnostic difficulties to the locals who had seen ndui before and in whom the milder form, alastrim, occurred sporadically. The characteristic umbilicated pustules, about 5-8 mm across, had started on his hands and feet and spread classically centripetally, heavily clustering now on the face and body. He was only moderately toxic with mild dehydration and a temperature of 39°C.

Obviously a patient with smallpox is not great news in an overcrowded small hospital where there were many non-immune contacts (in spite of our periodic vaccination clinics). What to do?

Luckily, months before, my mentor—a wise Scot with 30 years' experience of African doctoring—had briefed me on this very subject. Accordingly, I instructed the relatives, with the help of our sage male nurse, to construct a bamboo and grass isolation hut in the deeper bush about half a mile from the hospital and off all the main paths. The directions included leaving his drinks and uji, a maize gruel, at the door, within reach of the bed loaned from the wards. A sensible, previously vaccinated male relative was deputised to "drop" the victuals and act as auxiliary and messenger, otherwise "no visitors please." The nurse and I would visit him in his splendid isolation. Our crash vaccination programme started two hours later and was much more popular than usual.

My return after four hours revealed an impressive shelter but a lot of chatter within. The hubbub was due to a cluster of friends, well wishers, and their children—all gathered round the bed. The gallimaufry was expelled vehemently, which caused great amusement to all—except me. Rashidi, who looked better for being in bed rather than on a bike, asked me if he could go out that evening to a local beer party. I thought not. Walking back, I mused on how the international community would have reacted if such a patient had flown into Heathrow from Dar es Salaam. The patient improved slowly but cheerfully, with minimal scarring over the next 14 days. The only treatment given was calamine lotion, oral tetracycline (for secondary infection), antihistamines, and this ad hoc form of barrier nursing.

Not many years later—in 1977—the world was declared free of smallpox. I found myself wondering how the experts could really be so sure, reflecting on very isolated backwater bush areas such as Liwale. I felt privileged to see a rarity such as one of the last cases of variola on our planet and saddened as the camera was out of film.

Richard Dreaper, *semiretired general practitioner in Winchester now practising complementary medicine*

We welcome filler articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.