Postal urine specimens: are they a feasible method for genital chlamydial infection screening?

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SUMMARY

Background. *A United Kingdom (UK) screening programme for Chlamydia trachomatis has recently been announced. Pilot projects involving the opportunistic testing of women attending health facilities are due to commence in several sites. There is a danger that this approach will fail to obtain adequate population coverage. The alternative — true systematic population screening — is generally assumed to be unfeasible. Studies in Denmark using postal urine specimens have challenged this assumption. No such studies have been reported from the UK.*

Aim. *To assess the potential of urine specimens sent by post as the basis for a UK population screening strategy for genital chlamydial infection.*

Method. *Two hundred patients (100 men, 100 women) aged 18 to 45 years were randomly sampled from the list of one urban group practice. Subjects were mailed an explanatory letter, a urine sample container, a sexual lifestyle questionnaire, and a prepaid return envelope. Non-responders were contacted by telephone; persistent non-responders were visited at home. Samples were tested for Chlamydia by DNA amplification and enzyme immunoassay.*

Results. *Sixty-four (32%) subjects were no longer living at their GP registered address. Of the remaining 136, 126 (93%) responded to the survey and 113 (83%) accepted the request for a urine sample and completed a questionnaire. Acceptance rates were similar for men and women and across age groups. Four samples (3%) were Chlamydia positive.*

Conclusion. *Home mailed urine specimen collection in conjunction with a self-completed postal questionnaire is feasible. This could provide a viable basis both for determining population Chlamydia prevalence and for a UK Chlamydia population screening strategy. Overall cost effectiveness of such a strategy will depend on the cost of the test used. Comparative performance characteristics of the different currently available tests in this setting have yet to be fully determined.*

Keywords: Chlamydia trachomatis; postal questionnaire; postal urine specimen collection; population screening.

Introduction

GENITAL infections caused by *Chlamydia trachomatis* are the commonest acute non-viral sexually transmitted infection in the United Kingdom (UK).[1] Lower genital tract infection is thought to affect 3–5% of the sexually active population.[2-4] If untreated, up to 30% of women will go on to develop pelvic inflammatory disease (PID) and 10% will experience ectopic pregnancy.[5] Over 50% of infertility is related to *Chlamydia*. Yet antibiotic treatment is simple, cheap, and effective at preventing all these complications. The fact that *Chlamydia* continues to be an important cause of morbidity is a reflection of the shortcomings of current control strategies, focusing on the treatment of symptomatic cases and their contacts. However, lower genital tract infection is usually asymptomatic in women and frequently so in men.[3] Unrecognized and untreated infection sustains transmission within the community and explains why chlamydial infection and its sequelae continues to cost UK health services over £50 million annually.[6] A further complication is that prevalence estimates are based on voluntary clinic and laboratory reporting, which is known to be incomplete. Thus, since community prevalence is not known, underlying disease trends and the potential impact of therapeutic intervention is difficult to assess.

Chlamydia trachomatis has been proposed in the UK as a disease for which screening and treatment during the detectable preclinical phase could reduce both short- and long-term morbidity.[5] Following the recent report of the Expert Advisory Group to the Chief Medical Officer, pilot projects involving the opportunistic testing of women attending primary health care facilities in two English regions have been announced.[7,8] Experiences in Sweden and North America suggest that screening can be effective in reducing rates of both PID and ectopic pregnancy.[9-11] This screening has generally been selective and opportunistic in its approach and, in North America, confined to women. Some studies have been prone to methodological problems, making assessment of the validity of their conclusions difficult.[12] In addition, results from these settings may not be generalizable to the UK.

As *Chlamydia trachomatis* is an obligate intracellular organism, diagnostic tests have generally depended on the collection of cellular material using invasive intimate procedures. Urinary testing by enzyme-linked immunosorbent assay (EIA) has been demonstrated to provide a non-invasive alternative of adequate sensitivity in men.[13] Recently developed molecular techniques suggest that urinary testing in both women and men is feasible.

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Urinary ligase chain reaction (LCR) has achieved sensitivities of around 95% in women tested in specialist clinics,[14,15] although this sensitivity may fall in the community setting.[16] Urinary EIA is generally felt to be inadequately sensitive in women. The performance of EIA on other non-invasive test substrates has yet to be fully evaluated; for example, self-collected vulvo-vaginal material (using a variety of sampling techniques) may prove a useful alternative.[16,17] Direct comparison of invasive (culture and EIA on cervical swabs) with non-invasive (ligase and polymerase chain reaction on urine) techniques has suggested that performance of the non-invasive tests was superior.[18] Generally, the question of which test applied to which type of specimen in men and in women is most appropriate for use in a *Chlamydia* screening programme remains unanswered.[19]

A non-invasive test is likely to be preferable to patients. If testing is not dependent on attendance at a health facility, then compliance with a testing programme is likely to be further enhanced. *Chlamydia* screening directed exclusively at women is likely to have minimal population impact, as unrecognized and untreated male infection will sustain community transmission.[20]

The feasibility of *Chlamydia* testing based on home-mailed urine specimens has been demonstrated in women who had previously been examined in a community clinic in Denmark.[16] We assessed the feasibility of community-based *Chlamydia* testing of both men and women, independent of their attendance at a health facility, based on mailed urine specimens from subjects identified from general practice lists. We attempted also to determine whether a home-mailed questionnaire is a viable method for collecting information about the risk markers on which a targeted screening strategy could be based.

Method

Our study was undertaken in August to November 1996 on a random sample of 200 patients aged 18–45 years from the list of one urban group practice in Bristol. Local ethical committee approval was obtained. Subjects were sent a package containing a covering letter from their GP with a brief description of the study, a 'fact sheet' on *Chlamydia*, a short questionnaire on aspects of their sexual lifestyle (and recent use of antibiotics), and a urine specimen container to be returned with the questionnaire in a prepaid envelope also enclosed. Instructions for collecting a first void urine specimen were provided.

After three weeks, subjects who had not responded were sent a package identical to the first but with a modified covering letter. At each point of postal contact, subjects were given the opportunity to state a wish not to participate in the study and not to be recontacted. Both packages were sent by recorded delivery. One month after being sent the second package, an attempt was made to contact, by telephone, those subjects who had still not responded. If attempted telephone contact was unsuccessful, or if no telephone number was available, subjects were visited at home. Subjects were classified as no longer living at their registered address on the basis of either the return of an unopened package marked 'not known at this address' or confirmation by either a neighbour or current occupant that the subject had moved. Subjects for whom no confirmation of having moved was obtainable were classed as non-responders.

On receipt, mailed specimens were divided into 2 ml aliquots, which were frozen at −20ºC before being tested by LCR (Abbot Diagnostics Ltd). A further 15 ml aliquot was tested by an enzyme linked immunoassay (EIA) (Ideia [Dako UK Ltd]). Both tests were conducted according to the manufacturer's instructions. A spun deposit was prepared for direct fluorescent antibody (DFA) testing from each aliquot of specimens either LCR- or EIA-positive. The DFA test in the Bristol laboratory is more sensitive than culture, and this sensitivity is not significantly reduced with previously frozen specimens (unpublished data). Tests were all undertaken blind. Subjects identified as *Chlamydia*-positive were offered treatment in the local department of genitourinary medicine.

Results

Response rates

Figure 1 shows the distribution of responses of the 200 people surveyed. At the time of the study, 32% (36 men, 28 women) were not living at their GP registered address, leaving an effective sample of 136 (64 men, 72 women). Responses were received from 93% (126/136) of these people: 91% of men (58/64) and 94% of women (68/72). Eleven people declined to participate, and two people who offered to participate were considered ineligible because they were living outside the UK at the time of the study.

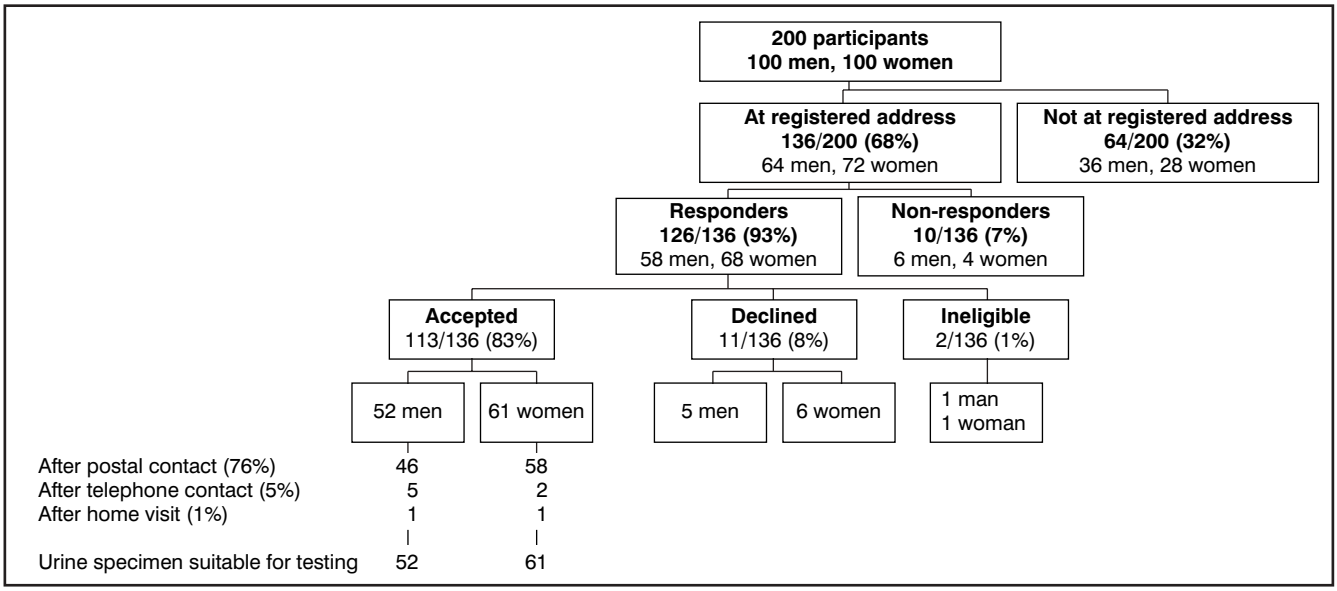

Figure 1. Responses to postal survey.

After two postal contacts, 76% of the 136 people surveyed agreed to provide a urine specimen (72% of men: 46/64; 81% of women: 58/72), rising to 82% after telephone contact (80% of men: 51/64; 83% of women: 60/72) and 83% after a home visit (81% of men: 52/64; 85% of women: 61/72). Acceptance rates tended to be slightly higher among women, but the differences were not statistically significant.

Response rates according to age group are shown in Table 1. There was a tendency for younger members of the sample to be less likely to be living at their registered address than older people, although this difference was not significant (χ^2 for linear trend against age group = 1.71; $P = 0.19$ for proportion not being at registered address compared with remainder of sample). For sample members who apparently lived at their registered address, there was little association of response rate with age (χ^2 for linear trend = 0.47, $P = 0.50$). All participants who returned a urine specimen also returned the questionnaire. As the aim of this study was to determine feasibility and acceptability of a method, specific responses were not analysed.

Reasons for declining participation

Nine of the 11 people declining participation could be contacted by telephone or home visit. Six of these felt that *Chlamydia* was not an issue for them and were not persuaded by explanations about protecting the public health. Two people declined for emotional reasons involving sexual health problems in themselves or their partners, and one was annoyed by the postal request for intimate information.

Test results

Of the 113 urine specimens tested, four (one male, three female) were positive for *Chlamydia trachomatis*. The aim of the present study was not to measure population *Chlamydia* prevalence, as sample size was clearly inadequate. Of the positives, one female was positive by LCR only, one female was positive on all tests, and two subjects (one male, one female) were positive by EIA (confirmed by DFA).

Discussion

This is the first UK study to assess the feasibility of a population-based strategy for *Chlamydia* testing. Results were encouraging in terms of population coverage achieved; however, several logistical issues were highlighted.

Deficiencies in the population register

As noted above, 32% of the initial study sample were no longer at their GP registered address at the time that the study was undertaken. There are several possible reasons for this: UK population registers are known to be incomplete and GP lists generally include a number of 'ghost' patients.[21,22] This phenomenon was likely to have been amplified in our particular practice, as a large number of students and single, young professionals were included on the practice list. By focusing on young adults, the study concentrated on the section of the population likely to be most mobile. Table 1 shows a tendency for a greater proportion of younger subjects to have moved from their registered address, although this association was not statistically significant. Some subjects in the present study may have changed address while remaining patients of the practice, and should arguably be included in the denominator for the purpose of response rate estimation (despite having no opportunity to respond), thus reducing response rate estimates. In an actual screening programme, these subjects would be picked up when their new address is recorded with the practice. Another study of *Chlamydia* screening strategies, carried out contemporaneously in North East London, found that 16.4% of patients were not living at their registered address, with this figure rising to 36.6% in the under-20s.[4]

In an actual screening programme, patient mobility may be less of an issue. Practices with more stable lists will also be represented. Some subjects will have registered with other practices and will be identified through their lists. Others are likely to be identified as partners and contacts of those that are diagnosed positive. Generally, some 'hard to reach' populations may be at higher risk of chlamydial infection and may only be amenable to opportunistic screening undertaken in a variety of primary care settings including general practice.[23]

Screening test

Previous studies have suggested that sensitivity of molecular *Chlamydia* assays may be compromised in the community setting.[16] This may result from an inability to maintain a 'cold chain'. In addition, the issue of their specificity also has to be resolved. Published estimates have frequently been based on 'discrepant analysis' (where apparent false-positives are subject to a battery of tests including other molecular assays, and, if found positive on any of these, are reclassified as true-positives). This inevitably inflates estimates of both sensitivity and specificity.[24-26] In our study we were unable to confirm one LCR-positive test. All subjects diagnosed as positive by EIA in our study were confirmed by DFA, two of these were negative by LCR. It has been suggested that LCR sensitivity may be compromised by hormonal 'inhibitors' present in urine.[27] These would not be expected to influence the performance of EIA or DFA, which is dependent on the absolute quantity of chlamydial material present.

Suboptimal performance characteristics of a test in the community, as opposed to the specialist clinic setting, may not preclude its usefulness in a screening programme. The Danish study, suggesting reduced LCR sensitivity in the community, still found this test to be as sensitive as any other community-based test used in the same population.[16] In addition, the sensitivities reported were comparable with those of tests used in other screening programmes; for example, cervical cytology.[28]

Table 1. Distribution of survey responses according to age.

Age	Living at registered address	Not at registered address n (% at registered address)		Total sample n (% of total sample)	n
	Accepted	Declined, ineligible, or no response			
18–24 years	17 (81)	4 (19)		16 (43)	37
25–34 years	52 (81)	12 (19)		27 (30)	91
35–45 years	44 (86)	7 (14)		21 (29)	72
All ages	113 (83)	23 (17)		64 (32)	200

Feasibility and cost effectiveness of screening

Population screening aims to provide benefits both to the individual screened and to the population. Individual benefits are influenced by the screening strategy and the instruments used. Low response rates in a screening programme for an infectious disease will not reduce future service costs nor reduce the pool of circulating infection. Results from a comparative study of two approaches to opportunistic screening in women attending primary care showed that the overall response rates were below 30%, even after excluding 'ghost' patients.[4] In our population, overall response rates were relatively high. Different population characteristics may explain part of this difference. In addition, a request made in the privacy of a person's home, and supported by written information, may be more likely to elicit a positive response than one included in the already crowded agenda of the typical primary care consultation, particularly when the patient perceives that the intimate issues involved are unrelated to those motivating their attendance.

Future research

The important question of whether a chlamydial screening programme should be universal or targeted at 'high-risk' individuals identified by risk markers, was not addressed in this study. We have demonstrated that the collection of information on sexual behaviour, through which risk status could be assigned by postal questionnaire, is feasible. Only one subject in this study reported offence at our request for intimate information. Our limited questionnaire would have provided sufficient information to determine risk based on marital status, age, sexual activity, and contraceptive method. A more detailed questionnaire may have deterred participation and reduced our response rate.

Other future research priorities in this area should include studies to determine baseline population prevalence more accurately, whether opportunistic screening of patients presenting in primary care would pick up the majority of cases and whether screening is cost effective. The latter consideration is likely to depend on the cost of the screening instrument used: EIA is considerably cheaper than molecular diagnostic assays. Rigorous comparison of the performance of the various non-invasive *Chlamydia* tests in the community setting is needed.

A further issue relates to problems in providing an unsolicited, unexpected diagnosis of a sexually transmitted infection to men and women identified through population-based screening. In this study, two of the four individuals identified as being *Chlamydia* positive reported being in monogamous relationships, and the diagnosis caused some concern.

In summary, a postal request for a urine specimen and a self-completed sexual risk behaviour questionnaire is feasible, and appears to be acceptable to patients in the community. This method should now be used to determine the prevalence of *Chlamydia* in populations in Britain so that the impact of future screening programmes can be assessed. The method may also prove useful as the basis for a screening programme.

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