Health Technology Assessment 2007; Vol. 11: No. 8

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March 2007

Health Technology Assessment
NHS R&D HTA Programme
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Declared competing interests of authors: none

Published March 2007

This report should be referenced as follows:

Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*. Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection. *Health Technol Assess* 2007;**11**(8).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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The research reported in this monograph was commissioned by the HTA Programme as project number 97/32/31. The contractual start date was in August 2000. The draft report began editorial review in August 2005 and was accepted for publication in May 2006. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection

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Objectives: To investigate epidemiological, social, diagnostic and economic aspects of chlamydia screening in non-genitourinary medicine settings.

Methods: Linked studies around a cross-sectional population-based survey of adult men and women invited to collect urine and (for women) vulvovaginal swab specimens at home and mail these to a laboratory for testing for *Chlamydia trachomatis*. Specimens were used in laboratory evaluations of an amplified enzyme immunoassay (PCE EIA) and two nucleic acid amplification tests [Cobas polymerase chain reaction (PCR), Becton Dickinson strand displacement amplification (SDA)]. Chlamydia-positive cases and two negative controls completed a risk factor questionnaire. Chlamydia-positive cases were invited into a randomised controlled trial of partner notification strategies. Samples of individuals testing negative completed psychological questionnaires before and after screening. In-depth interviews were conducted at all stages of screening. Chlamydia transmission and cost-effectiveness of screening were investigated in a transmission dynamic model.

Setting and participants: General population in the Bristol and Birmingham areas of England. In total, 19,773 women and men aged 16–39 years were randomly selected from 27 general practice lists.

Results: Screening invitations reached 73% (14,382/19,773). Uptake (4731 participants), weighted for sampling, was 39.5% (95% CI 37.7, 40.8%) in women and 29.5% (95% CI 28.0, 31.0%) in men aged 16–39 years. Chlamydia prevalence (219 positive results) in 16–24 year olds was 6.2% (95% CI 4.9, 7.8%) in women and 5.3% (95% CI 4.4, 6.3%) in men. The case-control study did not identify any additional factors that would help target screening. Screening did not adversely affect anxiety, depression or self-esteem. Participants welcomed the convenience and privacy of home-sampling. The relative sensitivity of PCR on male urine specimens was 100% (95% CI 89.1, 100%). The combined relative sensitivities of PCR and SDA using female urine and vulvovaginal swabs were 91.8% (86.1, 95.7, 134/146) and 97.3% (93.1, 99.2%, 142/146). A total of 140 people (74% of eligible) participated in the randomised trial. Compared with referral to a genitourinary medicine clinic, partner notification by practice nurses resulted in 12.4% (95% CI –3.7, 28.6%) more patients with at least one partner treated and 22.0% (95% CI 6.1, 37.8%) more patients with all partners treated. The health service and patients costs (2005 prices) of home-based postal chlamydia screening were

£21.47 (95% CI £19.91, 25.99) per screening invitation and £28.56 (95% CI £22.10, 30.43) per accepted offer. Preliminary modelling found an incremental cost-effectiveness ratio (2003 prices) comparing screening men and women annually to no screening in the base case of £27,000/major outcome averted at 8 years. If estimated screening uptake and pelvic inflammatory disease incidence were increased, the cost-effectiveness ratio fell to £3700/major outcome averted.

Conclusions: Proactive screening for chlamydia in women and men using home-collected specimens was feasible and acceptable. Chlamydia prevalence rates in men and women in the general population are similar. Nucleic acid amplification tests can be used on first-catch urine specimens and vulvovaginal swabs. The administrative costs of proactive screening were similar to those for opportunistic screening. Using empirical estimates of screening uptake and incidence of complications, screening was not cost-effective.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Proactive screening A population is proactively invited to be screened. Also known as register-based systematic, cyclical or call–recall screening. Non-selective proactive screening is equivalent to Wilson and Jungner's description of mass screening.

Chlamydia Genital *Chlamydia trachomatis* infection caused by strains D–K.

Incremental cost-effectiveness ratio Measure of cost-effectiveness.

Index case The person in a couple, chain or network of sexual partners who was first diagnosed with a sexually transmitted infection.

Non-selective Proactive or opportunistic screening involving a whole population or all health service attenders.

Nucleic acid amplification test A group of diagnostic tests for chlamydia that detect small amounts of chlamydial genetic material. Specific tests include polymerase chain reaction and strand displacement amplification.

Opportunistic screening People attending a healthcare setting for any reason are offered a screening test. Described by Wilson and Jungner as case-finding. Can be selective or non-selective.

Partner notification The process of informing the sexual partners of people with sexually transmitted infections of their potential exposure to infection, ensuring their evaluation and/or treatment, and providing advice about preventing future infection.

Screening Screening is a public health service where members of a defined population are asked a question or offered a test to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risks of a disease or its complications.

Selective Proactive or opportunistic screening involving only people with specified risk factors for disease including age.

List of abbreviations

CI	confidence interval
ClaSS	Chlamydia Screening Studies
CMO	Chief Medical Officer
DFA	direct fluorescent antibody
EIA	enzyme immunoassay
F	female
FP	family planning
GUM	genitourinary medicine
ICER	incremental cost-effectiveness ratio
LCR	ligase chain reaction
LE	leucocyte esterase
M	male
MOA	major outcome averted
NA	not applicable
NAAT	nucleic acid amplification test
Natsal 2000	National Survey of Sexual Attitudes and Lifestyles (2nd survey, 2000)
NGZ	negative grey zone
NICE	National Institute for Health and Clinical Excellence
ONS	Office for National Statistics
OR	odds ratio
PCR	polymerase chain reaction
PCT	primary care trust
PID	pelvic inflammatory disease
PSSRU	Personal and Social Services Research Unit
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SD	standard deviation
SDA	strand displacement amplification
STD	sexually transmitted disease
STI	sexually transmitted infection
TMA	transcription-mediated amplification

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Screening for genital chlamydial infection is being introduced across England in a National Chlamydia Screening Programme. This opportunistic programme, whose main focus is young women attending contraceptive clinics, is planned to cover all primary care trusts by March 2007. The organisation and focus of the screening programme were based on recommendations of an Expert Advisory Group to the Chief Medical Officer, which summarised the available evidence in 1998. The Expert Advisory Group also identified gaps in the evidence about the cost-effectiveness of chlamydia screening, the performance of new diagnostic techniques, methods for reaching the sexual partners of infected people, and possible criteria for targeting screening. These questions have been addressed in this multidisciplinary project, the Chlamydia Screening Studies (ClaSS) project, through a variety of research methods.

Objectives

The objectives of the report were to address the areas raised by the Expert Advisory Group as part of their work in the proposed National Chlamydia Screening Programme. These were categorised as follows.

- Chlamydia screening survey: to establish the prevalence of genital chlamydia in men and women in the general population.
- Social research: to determine the social, emotional and psychological effects of screening and partner notification for genital chlamydia.
- Laboratory studies: to find the best test and specimen to use for screening for genital chlamydial infection in men and women.
- Partner notification: to establish the most effective methods of accessing partners of infected patients for the diagnosis and treatment of genital chlamydial infection.
- Case–control study: to find the most cost-effective criteria for targeted screening and which outcomes should be measured.
- Economic evaluation: to determine how to maximise the cost-effectiveness of screening for genital chlamydial infection in non-genitourinary medicine (GUM) clinic settings.

Methods

Design

A multicentre multidisciplinary series of linked studies was conducted. The core study was a cross-sectional population-based chlamydia screening survey. Adult men and women were invited by post to collect self-taken urine and (for women) vulvovaginal swab specimens at home, and to post these to a laboratory for testing for *Chlamydia trachomatis*. People with positive tests provided a confirmatory specimen after receiving results and a third specimen 6 weeks after treatment.

Questionnaires about anxiety, depression and self-esteem were sent before, at and after screening to random samples of survey participants testing negative. In-depth semi-structured interviews were also conducted during screening and partner notification with participants, non-participants and staff.

All specimens were used in laboratory evaluations of the performance of different diagnostic tests on individual specimens. Male urine and female vulvovaginal swab specimens were used to examine pooling groups of four and eight specimens. Specimen stability in female urine and vulvovaginal swab specimens was assessed from GUM clinic attenders not involved in ClaSS.

After receiving results and treatment at their general practice, chlamydia-positive cases were invited into a randomised controlled trial (RCT) comparing partner notification carried out by the practice nurse with referral to a specialist health adviser at a GUM clinic. Positive cases and two matched negative controls per case were asked to complete a detailed risk factor questionnaire before receiving their results.

A systematic review of economic evaluations of chlamydia screening was conducted, as were time and motion studies in laboratories and patient cost questionnaires. In addition, primary data were collected on costs of screening invitations, reminders, consultations and telephone follow-up. Finally, a dynamic model of chlamydia transmission was developed using discrete event simulation. The primary data were then used to

determine the cost-effectiveness of proactive chlamydia screening.

Setting
The study was conducted among the general population in the Bristol and Birmingham areas of the UK.

Participants
In total, 19,773 men and women aged 16–39 years randomly selected from 27 general practice lists were eligible.

Interventions
The invitation was sent to men and women to collect a specimen of early-morning first catch urine and for women to take a first catch urine specimen and a vulvovaginal swab at home and post specimens to a laboratory to be tested for *C. trachomatis*. Specimens were tested by enzyme immunoassay (EIA) and/or nucleic acid amplification tests (NAATs). Practice nurse-led partner notification, including a sexual history and patient referral, was carried out with ongoing support from a health adviser or by specialist referral to a sexual health adviser and partner notification at a GUM clinic. Health advisers conducted telephone follow-up for both.

Main outcome measures
For the chlamydia screening survey, the main outcome measures were coverage of the postal screening invitation, uptake of chlamydia screening and chlamydia prevalence. From a social research perspective, the outcome measures were the qualitative data about the emotional effects of chlamydia screening, anxiety, depression and self-esteem scores before and after screening. In the laboratory studies, performance characteristics of diagnostic tests for *C. trachomatis* on self-taken first catch urine and vulvovaginal swab specimens were used. When considering partner notification, the number of people with at least one sexual partner treated and cost of partner notification were the main outcome measures. Odds ratios for associations between risk factors and chlamydia were considered for case–control study aspects. The economic evaluation considered the health service and patient costs of chlamydia screening at 2005 and cost per major outcome averted in 2003 (costs were in UK pounds).

Results

Screening invitations reached 73% (14,382/19,773) of eligible people. Overall, 4731 men and women participated in the cross-sectional screening survey. Uptake rates were 39.5% [95% confidence interval (CI) 37.7 to 40.8%] in women and 29.5% (95% CI 28.0 to 31.0%) in men. Uptake was lower in more deprived areas. There were 219 people with positive chlamydia results. Prevalence in 16–24-year-olds was 6.2% (95% CI 4.9 to 7.8%) in women and 5.3% (95% CI 4.4 to 6.3%) in men. Chlamydia prevalence was not strongly associated with any demographic or practice level factors. The number of new partners in the past 12 months was the strongest predictor of infection. During the screening study an estimated 68.8% (95% CI 67.3 to 69.9%) of 16–24-year-old patients had attended their own general practice (75% of women and 60% of men).

Being invited to post home-collected specimens to a laboratory was well accepted by those who took part and did not adversely affect anxiety, depression or self-esteem. Reasons for not taking part in screening included low perception of personal risk or relevance, and not wanting to take responsibility for their own or their partner's health. Some women found taking a vulvovaginal swab unpleasant and this put some off from participating in screening.

The sensitivities of PCE EIA with negative grey-zone testing on male first catch urine and female vulvovaginal swab specimens were 75.0% (24/32, 95% CI 56.9 to 88.5%) and 66.4% (97/146, 95% CI 58.2 to 74.0%). Testing male urine using Cobas polymerase chain reaction (PCR) identified all positive specimens (32/32, 95% CI 89.1 to 100%). The relative sensitivities of female urine and vulvovaginal swabs were 91.8% (134/146, 95% CI 86.1 to 95.7) and 97.3% (142/146, 95% CI 93.1 to 99.2%), respectively. Inhibition was present by Cobas PCR in 2% (19/1003) of male urine, 13% (192/1476) of female urine and 16% (232/1269) vulvovaginal swab specimens, and by Becton Dickinson strand displacement amplification (SDA) in 7% (85/1269) female urine specimens and one swab. Compared with individual testing (£137.35 per positive urine, £104.10 per swab), pooling urine specimens in groups of four required 50% (969/1936) of the number of tests and cost £70.93 per positive, but missed 8.5% (9/106) of positive specimens; pooling swab specimens in groups of four required 60% (637/1062) of the tests and cost £42.66 but missed 5.3% (4/76) of positive specimens. The performance of Cobas PCR on female urine and vulvovaginal swab specimens stored at room temperature for 24 and 48 hours was equivalent.

A total of 140 people (74% of those eligible) participated in the randomised trial. Of patients referred to the GUM clinic, 31% (21/68) did not attend. In intention-to-treat analysis, compared with referral, the practice nurse strategy resulted in 12.4% (95% CI –3.7 to 28.6%) more patients with at least one partner treated and 22.0% (95% CI 6.1 to 37.8%) more patients with all partners treated. The strategies cost the same (£34.48 per index case for the practice nurse strategy and £34.55 for specialist referral) and qualitative research showed that patients preferred to be seen at their practice.

A total of 148 chlamydia-positive cases and 246 negative controls took part in the case–control study (response rate 69%). Among cases, 68.6% (70/102, 95% CI 58.7 to 77.5%) of women and 73.9% (34/46, 95% CI 58.9 to 85.7%) of men were asymptomatic. The case–control study did not identify any additional independent factors that would help to target screening.

The health service and patient costs (2005 prices) of home-based postal chlamydia screening were £21.47 (95% CI £19.91 to 25.99) per screening invitation and £28.56 (95% CI £22.10 to 30.43) per accepted screening offer. About 30% of the costs were incurred by the patient. Most published economic evaluations of chlamydia screening suggest that both population-based and opportunistic screening are cost-effective but use static models, which do not capture the effects of interaction between individuals, and use estimates of the incidence of chlamydial complications that may be overestimated. In a transmission dynamic model using discrete event simulation in a population of 50,000 with 60 runs over 15,000 simulated days, the incremental cost-effectiveness ratio comparing screening women only annually with no screening at 8 years was £29,000 per major outcome averted, and for screening men and women annually compared with no screening £27,000 per major outcome averted (with uptake in women 39%, uptake in men 29% and risk of pelvic inflammatory disease in women with chlamydia 8.9% by the age of 35 years). Results were sensitive to uptake and incidence of sequelae. The cost of screening men and women annually by 8 years with 60% uptake in women and 40% in men was £17,000 per major outcome averted, with pelvic inflammatory disease incidence 25% £6800, and with 60% uptake in men and women and 25% pelvic inflammatory disease £3700 per major outcome averted.

Conclusions

Proactive screening for chlamydia in women and men under 25 years of age using home-collected specimens was feasible and acceptable, but the uptake of this method was lower than had been expected from an early pilot study.

The ClaSS project approach to screening included features that could enhance the uptake of opportunistic screening. Mixed models of chlamydia screening should be evaluated to see if they achieve higher consistent levels of screening uptake than either active or opportunistic screening alone.

Practice registers could be used by central chlamydia screening offices to optimise the process. Home-based specimen collection can be offered by post as an alternative to clinic-based screening.

The examination of risk factors for chlamydia in the prevalence and case–control studies did not find any factors, other than young age, that would help to target screening more easily. Men should be targeted more intensively for chlamydia screening, as prevalence in young men was the same as in young women. As nearly two-thirds of men aged 16–24 years (and three-quarters of women) attended their general practice in 1 year, this would be the best setting for opportunistic screening.

Chlamydia screening has the potential to increase inequalities in sexual health. Postal screening invitations were less likely to reach people in areas with high numbers of residents from non-white minority ethnic groups, and the uptake of the screening invitation was lower in more deprived areas. Women with the highest prevalence of infection were the most difficult to engage in screening. Even if chlamydia prevalence did not vary by gender, ethnic group or socioeconomic deprivation, introducing a screening programme that is less available and accessible, and less acceptable to people from vulnerable and disadvantaged groups, could create or widen existing inequalities. This applies to opportunistic as well as active screening.

Nurse-led partner notification, with support from specialist health advisers, could be considered for implementation within the National Chlamydia Screening Programme. Practice nurse-led partner notification was as effective a strategy for ensuring treatment of the sexual partners of people

diagnosed with chlamydia in primary care as referral to a GUM clinic. The strategy was no more expensive than referral to a specialist GUM clinic and was preferred by patients. The strategy could be extended to nurses in family planning clinics, youth sexual health clinics and NHS walk-in centres. Home-based specimen collection could be offered to eligible patients as an alternative to clinic-based screening; and can be given to individuals diagnosed with chlamydia to improve partner notification rates.

EIAs, even when used with strategies to enhance their performance, were inadequate for performing chlamydia screening using male urine and female vulvovaginal swab specimens.

Female vulvovaginal swab specimens are likely to become more popular for screening women using NAATs. They had high sensitivity and specificity, and lower levels of inhibition than with urine specimens. Women were, however, unfamiliar with this type of specimen. Some confused it with a cervical smear, and others said that it had put them off taking part in the study altogether. More education of the public about the benefits of vulvovaginal specimens should improve the acceptability of these types of specimen.

Pooling of specimens for screening is not recommended if resources to carry out individual testing are available. Pooling of self-taken urine and vulvovaginal swab specimens reduces costs and workload, but misses an appreciable proportion of positive tests.

Active chlamydia screening was not cost-effective, based on a model of chlamydia transmission that assumed realistic, but lower, screening uptake and disease progression rates than other models. However, these assumptions are thought to be more realistic for studying the asymptomatic population in whom chlamydia is diagnosed by NAATs.

Recommendations for research

There is still a need for a large multicentre RCT of chlamydia screening to determine whether reducing female reproductive tract morbidity and chlamydia transmission are realistic long-term goals. Existing RCTs have only evaluated population-based (proactive) screening with a maximum follow-up of 1 year. No RCT has demonstrated any impact on the population incidence and prevalence of infection. Any new RCT would have to include opportunistic screening as one of the interventions, because this is current practice in the National Chlamydia Screening Programme, and would have to measure long-term primary outcomes.

Further research on the mathematical modelling of interventions to control chlamydia and other sexually transmitted infections is required. In addition, studies are needed to determine the best ways of engaging young men in chlamydia screening. Other areas to be addressed include the risks of reinfection following screening and treatment, the appropriate screening interval, the uptake of repeat screening, the effects of chlamydia screening on inequalities in sexual health, the performance of female urine and vulvovaginal specimens for *C. trachomatis* diagnosis, the likelihood of progression of chlamydial infection, and issues surrounding quality of life and long-term consequences.

Chapter 1
Introduction

Screening for genital chlamydial infection is being introduced across England in a National Chlamydia Screening programme.[1] The opportunistic programme, whose main focus is young women attending contraceptive clinics, is planned to cover all primary care trusts (PCTs) by March 2007.[2] The organisation and focus of the screening programme were based on recommendations of an expert advisory group to the Chief Medical Officer (CMO), which summarised the available evidence in 1998.[3] The expert advisory group also identified gaps in the evidence about the cost-effectiveness of chlamydia screening, the performance of new diagnostic techniques, methods for reaching the sexual partners of infected people, and possible criteria for targeting screening.[3] The National Centre for the Coordination of Health Technology Assessment (NCCHTA) then commissioned research to address these questions. A multidisciplinary project, the Chlamydia Screening Studies (ClaSS) project, which used a variety of research methods to investigate these wide-ranging questions in linked studies, was designed. This report presents the background to the project (this chapter), the overall design and component studies (Chapter 2), detailed methods, results and interpretation for the component studies (Chapters 3–10), and a discussion of the overall results and implications of the component studies (Chapter 11).

Chlamydia and its clinical consequences

Chlamydia trachomatis is a bacterium whose sexually transmitted strains D–K cause genital tract infections in women (cervicitis and urethritis) and men (urethritis). These strains of *C. trachomatis* can also cause sexually transmitted rectal and pharyngeal infections, be transmitted during labour, causing pneumonia and eye infections in infants, and be spread by close contact to cause eye infections in adults. The *C. trachomatis* strains L1, L2 and L3 cause lymphogranuloma venereum. This tropical sexually transmitted infection is currently responsible for outbreaks of ulcerative proctitis mainly affecting homosexual men (many with HIV infection) in various European countries and the USA.[4–6] Uncomplicated lower genital tract chlamydia infections can be cured by a single dose or short course of antibiotics.[7] The term 'chlamydia' is used throughout this report to mean genital *C. trachomatis* infection caused by strains D–K.

Chlamydia is the most common bacterial sexually transmitted infection (STI) in the world, causing an estimated 89 million new cases of infection each year.[8] In England, Wales and Northern Ireland in 2004, 104,155 cases of chlamydia were diagnosed in genitourinary medicine clinics.[9] The number of diagnosed infections has been increasing steadily since 1995, partly owing to increased numbers of people being tested: nearly 700,000 genital infections and STIs were diagnosed in genitourinary clinics in 2003 compared with 442,000 in 1995.[10,11] Population-based studies in Europe and the USA suggest that the prevalence of chlamydia in men and women aged 15–24 years is 2–6%.[12–15] The peak age group for infection is 16–19 years in women and 20–24 years in men.[9] It is the upper genital tract consequences of untreated infection in women that are mainly responsible for the estimated $1.5 billion cost of chlamydia in 1994 in the USA.[16]

Many infections in both men and women remain undetected and untreated because they cause few or no specific symptoms. Untreated infection that ascends in the female genital tract can cause pelvic inflammatory disease.[17] Scarring in the fallopian tubes, which is strongly influenced by immunological factors, can then result in ectopic pregnancy, tubal factor infertility or chronic pelvic pain.[17] Ascending infection in men can lead to epididymitis, but the effects of this on future fertility are not clear.[18] There is not thought to be any lasting immunity following a chlamydia infection that has resolved spontaneously or been treated with antibiotics, so repeated infections can occur.[19]

There is much ongoing debate about the natural history of chlamydia and the frequency of reproductive tract complications following lower genital tract infection.[20–22] This is primarily because of methodological difficulties: long-term follow-up of untreated chlamydia infection would

be unethical, but if diagnosed infections are treated the natural history has been altered; studies conducted in hospital or clinic populations may be affected by selection bias;[21] objective diagnosis of pelvic inflammatory disease is difficult;[23] and chlamydia cannot be unequivocally established as the cause of any sequelae, particularly after the acute infection has resolved. Early studies in clinical populations suggested that about 30% of untreated cervical chlamydial infections resulted in pelvic inflammatory disease within a few weeks,[17,24] and that 20–25% of women with pelvic inflammatory disease from any cause went on to have an ectopic pregnancy or become infertile.[25] It is thought that about 50% of chlamydia infections resolve spontaneously within a year,[26–28] and up to 90% of diagnosed pelvic inflammatory disease might be managed in primary care.[29] Clinic-based studies therefore probably include women with severe disease,[21] and overestimate the risk of complications. More recently, estimates from population-based studies suggest that the overall incidence of hospital-diagnosed pelvic inflammatory disease is 2–7 per 1000 woman years.[20,21,30,31] Estimated rates including cases diagnosed in primary care are somewhat higher.[29,31,32]

Laboratory diagnosis of *Chlamydia trachomatis*

One of the main advances facilitating large-scale chlamydia screening programmes has been the advent of nucleic acid amplification technology, which can be used to detect very small amounts of chlamydial genetic material in clinical specimens.[33,34] Traditional methods for screening and diagnostic testing require a clinical examination by trained professionals to obtain specimens directly from the site of infection: endocervix or urethra in women and urethra in men. Some chlamydial genetic material is also shed into urine or vaginal and vulval secretions. The high sensitivity of nucleic acid amplification tests (NAATs) means that specimens can be taken non-invasively from these indirectly affected sites and fluids with rates of detection that are close to those of the urethral swab in men and endocervical swab in women.[35,36] This allows convenient specimen collection in a variety of settings outside healthcare settings.[37] NAATs used on non-invasively collected specimens have been widely evaluated in sexually transmitted disease (STD) clinics,[34] but not in community-based settings, where the prevalence of chlamydia is lower and where infected people are more likely to be asymptomatic with potentially lower chlamydia loads.[38] A further issue that could affect the feasibility of large-scale chlamydia screening is that manufacturers recommend storing specimens in the refrigerator.[39] Roche Diagnostics advise that first catch urine specimens are stable at room temperature for up to 24 hours, which allows for up to 24 hours' delay in transport from a clinic to a laboratory. Posting specimens often takes longer than this and could result in a reduction in test sensitivity.[40] Becton Dickinson state that 'dry' male urethral or female endocervical swabs are stable for up to 6 days at room temperature.

A number of NAAT platforms are now available. When the ClaSS project was being designed the Roche Cobas CT Test [polymerase chain reaction (PCR); Roche Diagnostics, Basle, Switzerland] and Abbott LCx ligase chain reaction test (Abbott Diagnostics, Chicago, IL, USA) were the most widely used. The researchers decided to evaluate the Roche PCR and a new test, the Probetec ET system (Becton Dickinson, Franklin Lakes, NJ, USA), which had the highest throughput of the available platforms. This test used the method of DNA strand displacement amplification (SDA), targeting the cryptic plasmid to detect chlamydial DNA in specimens.[41] The Abbott LCx test was withdrawn in 2003 because of high rates of reactive results that could not be confirmed.[42,43]

At the time of undertaking the ClaSS project there was evidence that one enzyme immunoassay (EIA), the IDEIA PCE EIA (Dako, Ely, UK), could perform as well as NAATs on specimens taken in a clinical setting.[44] The testing strategy for the assay, which included an amplification step to improve sensitivity,[45,46] involved repeat testing of specimens where the optical density was just below the cut-off point for a negative test result (the negative grey zone) with a NAAT.[40] The principle was that low levels of chlamydial DNA, which were below the level of detection of an EIA, would be detected by a NAAT. Studies directly comparing the PCE EIA test with a NAAT showed conflicting results in male urine samples in men with urethritis,[46,47] but good performance with vulvovaginal swabs.[44,46,48] Given the much lower costs and higher throughput of EIA, the PCE EIA with negative grey-zone testing for both male urine and female vulvovaginal specimens needed to be evaluated in a community-based setting with a lower prevalence of chlamydia.

Initial evaluations of NAATs to detect *C. trachomatis* used first catch urine specimens in men and

women.[34] A variety of self-taken vulval and vaginal specimen types can also be used to detect chlamydia in women. A clinic-based study in Bristol suggested that vulvovaginal swabs could be a more sensitive specimen type (215/238, 90%) for detecting *C. trachomatis* than first catch urine specimens (201/238, 84%) using the PCR (Roche Cobas PCR, Roche Diagnostics, Basle, Switzerland).[44]

One potential method of reducing the high cost of testing with NAATs is to pool the specimens for testing. This is especially effective when the condition being tested for has a relatively low prevalence and a highly sensitive assay is available.[49–52] Chlamydia screening may be particularly appropriate for pooling because there is not the same urgency to produce results in a screening programme as there is with routine diagnosis. Factors determining the success of pooling include: the sensitivity of the assay; the capacity of the assay to accommodate extra specimen to counteract dilution; the distribution of pathogen target levels in the specimens, that is, the number of specimens that contain such a low level of target that they will be just detected by individual assay but will be below the detection threshold after dilution; the frequency and concentration distribution of inhibitors of the assay in the specimens; and the prevalence of infection, which determines the optimum number of specimens to pool.

Screening for chlamydia

Screening programmes for infectious diseases differ from those for other conditions. For non-communicable diseases, for example breast cancer, the end-point is reducing mortality by early detection of the target disease. Screening for an infection also aims to prevent mortality or morbidity in individuals, but long-term control at the population level requires a sustained reduction in transmission of infection. Most descriptions of chlamydia screening programmes include both aims.[1,53]

There are two main approaches to screening programmes, which differ according to health service organisation, administrative support and infrastructure. Proactive, register-based screening involves inviting a group of individuals not seeking healthcare to be screened. This is also referred to as active, systematic, cyclical or call–recall screening. Opportunistic screening involves offering a screening test to individuals already attending health services for another reason. Either approach can be selective (only offered to people fulfilling specific criteria) or non-selective (offered to everyone). These four categories correspond with definitions used by Wilson and Jungner.[54] Non-selective proactive population screening is equivalent to mass screening; selective proactive population screening is equivalent to selective screening of high-risk groups in the population; opportunistic screening was originally described as case-finding, and can be selective or non-selective.

Existing chlamydia control measures

Sweden was the first country to introduce widespread testing in healthcare settings to detect asymptomatic chlamydia:[55] some counties began in the early 1980s.[56] Since 1988, it has been legally compulsory to provide free testing, treatment and contact tracing to any patient with suspected chlamydia, and to report diagnosed infections.[57] Opportunistic screening of asymptomatic people is targeted at sexually active women aged 15–29 years in family planning or abortion clinics, but also takes place in other settings. Men are screened when found through contact tracing or if symptomatic in genitourinary medicine and youth clinics. Surveillance data are collated centrally, but there is no national coordination of screening or official policy.[56,64] In the USA, opportunistic chlamydia screening of women in public family planning clinics began in region X (including Washington state) in 1988, and has been recommended nationally in a range of healthcare settings for young women, but not men, since 1993.[58] Screening is offered to women as part of state infertility prevention programmes and the National Job Training Program, and on entry to some prisons.[59] Surveillance data are collated centrally, but there is no national coordination of screening.

The National Chlamydia Screening Programme in England is an opportunistic programme. The goal of the programme is to control genital chlamydia through the early detection and treatment of asymptomatic infections and prevention of sequelae and onward transmission.[1] The target population is sexually active men and women under 25 years attending a variety of healthcare settings,[1] although the government white paper on public health, 'Choosing health', indicates that resources will be focused on young women attending family planning clinics.[2] The programme was piloted in women only in two areas, Portsmouth and the Wirral.[60,61] By the end of 2004, 25% of PCTs had begun screening, and

by the end of March 2007 screening should be taking place across England. Increasing male participation in screening is being encouraged by offering urine testing in non-clinical settings such as universities, shopping centres and military bases.[1] The programme is coordinated nationally, but organised locally.

Researchers in Denmark[31,62] and The Netherlands[13,63] have investigated the feasibility and effectiveness of population-based screening using population registers to invite eligible individuals to submit home-collected specimens. The uptake of a screening invitation and test kit was about 30% in women and 25% in men in Denmark,[15] and about 50% in women and 30% in men in The Netherlands.[13,63] The Dutch government has decided that there is insufficient evidence to justify a national screening programme.[65]

Criteria for establishing a screening programme

Although a National Chlamydia Screening Programme is being introduced in England, there is still debate as to whether[1,3] or not[66] chlamydia satisfies the criteria set out by Wilson and Jungner,[54] and adapted by the UK National Screening Committee (see Appendix 1).[67] There are important gaps in the evidence in the following four areas.

The epidemiology and natural history of the condition should be adequately understood and there should be a detectable disease marker and a latent period

Poor understanding of the natural history of chlamydia is still a major barrier to knowing whether chlamydia screening is likely to be effective or not. As mentioned above, lower genital tract chlamydia precedes pelvic inflammatory disease, but the latent period and incidence of complications are not well defined.

Clinic- and hospital-based studies might have overestimated the incidence of complications of chlamydia by selective inclusion of women with more severe disease.[20–22] These risks may, therefore, not be applicable to asymptomatic chlamydia infections diagnosed in the community, or to cases of pelvic inflammatory disease managed in primary care (which may account for 90% of all diagnosed pelvic inflammatory disease). Mathematical models that use risks estimated from a biased sample of the population to predict the effectiveness or cost-effectiveness of screening will then exaggerate the benefits of the intervention. The economic evaluation for this study used estimates of the incidence of chlamydial sequelae from population-based rather than clinical studies.

There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing morbidity

There are no randomised controlled trials (RCTs) examining the effects of opportunistic chlamydia screening in low-risk populations on the incidence of reproductive tract morbidity or on chlamydia transmission.[22,53] Experience in Sweden and the USA, and pilot studies in the UK[60] and The Netherlands,[68] show that this approach is feasible. Ecological associations between falling rates of chlamydia and its complications in Sweden[56,57,69,70] and the USA[71,72] during the 1990s have been widely cited as evidence of the effectiveness of opportunistic screening.[73–75] This interpretation ignores evidence that the fall in pelvic inflammatory disease in Sweden began before any chlamydia control activities were introduced.[57] In other European countries without chlamydia screening programmes, falling rates of gonorrhoea, syphilis[76] and pelvic inflammatory disease,[77] were attributed to safer sexual behaviour resulting from HIV/AIDS prevention campaigns from 1987 onwards.

Two RCTs have found that proactive selective screening for chlamydia can reduce the incidence of pelvic inflammatory disease in women by around 50%.[29,31] The first trial randomised women aged 18–34 years in Seattle, USA, to an invitation to be screened for chlamydia at a health clinic or usual care. Women were included if they fulfilled specified criteria for being at high risk of infection and were followed up after 1 year. The second trial involved Danish school pupils (women and men) in their final year.[62] The intervention was an invitation to post home-collected urine or vaginal specimens and test them using NAATs. The women were followed up after 1 year.[31] Methodological limitations in both studies have been documented: these might have resulted in an overestimate of the effectiveness of screening, and the choice of study populations and screening methods may limit the generalisability of the findings.[22,66,78–80]

There is no evidence from existing control activities that any form of screening has controlled chlamydia transmission, the second stated aim of chlamydia screening programmes. Chlamydia rates in Sweden have been increasing since 1997, in common with other European countries that

have no screening programmes.[55] Low coverage and frequency of opportunistic screening, and the limited involvement of men, have been suggested as reasons for the failure to control chlamydia transmission in Sweden.[22,81] In the USA, chlamydia rates in regions with infertility prevention programmes fell in four regions, rose in five and stayed the same in one.[59]

The benefit from the screening programme should outweigh the physical and psychological harm

Very little is known about the psychosocial effects of being screened for or diagnosed with chlamydia. A small qualitative study in the UK identified three main areas of concern after a positive diagnosis in women: the perceived stigma of STIs, worry about future reproductive health and anxiety about notifying sexual partners.[82] Evidence from breast screening suggested that the most likely adverse effect of chlamydia screening would be to raise levels of anxiety.[83,84] In other screening programmes anxiety has been associated with receiving an invitation,[85] participating in screening[86] and receiving a false-positive result.[87,88] Screening may also reduce people's self-perceived health status.[89] Those receiving negative screening test results may interpret this as 'a certificate of health' and be consequently less inclined to adopt healthy behaviours.[90] A major objective of this project was to investigate the reasons why people do or do not wish to participate in screening for an STI, and to determine the acceptability of home collection of specimens for postal chlamydia screening.

The opportunity cost of the screening programme should be economically balanced in relation to expenditure on medical care as a whole

There have been many economic evaluations of chlamydia screening. Most,[91] but not all,[92] have found chlamydia screening to be cost-effective. There are two major areas of concern that make further work on economic aspects of chlamydia screening necessary. First, economic evaluations should be based on an appropriate model of the disease process.[93] Decision analysis, a commonly used static approach, is inappropriate for modelling interventions to prevent chlamydia because it cannot incorporate the effects of untreated infection or reinfection on continued transmission. Secondly, regardless of the method used, all models make assumptions about the probability of events such as infection, progression and resolution. As previously stated, if these are incorrect then models may overestimate the benefits of screening.[94] This project aimed to examine the appropriateness of models used in economic evaluations and to conduct a full cost-effectiveness evaluation of population chlamydia screening using a dynamic model and realistic assumptions.

In summary, chlamydia is a common STI, which can have serious reproductive health consequences, particularly for women. Despite uncertainty about the natural history of chlamydia, the psychological effects of screening and the effectiveness of an opportunistic approach, screening has been widely advocated and is taking place in Sweden, the USA and England.

Chapter 2

Overview of the Chlamydia Screening Studies project

The research questions from the CMO's expert advisory group on *C. trachomatis*[3] and additional questions addressed by the ClaSS project are shown in *Box 1*. The ClaSS project, a series of linked studies, was designed to cover all these areas (*Figure 1*). An overview of the study has been published,[95] and the full project protocol, questionnaires, and sample size calculations are available on the ClaSS Project website at http://www.chlamydia.ac.uk. This chapter gives an overview of the whole project, describes core project activities, and explains protocol changes that were made to improve uptake of the intervention and the running of the study.

Research ethics committee approval

The South and West Multicentre Research Ethics Committee approved the study protocol in April 2000 (MREC/00/6/30). All local research ethics committees also gave approval.

ClaSS project research questions

1. How common is genital chlamydia in men and women in the general population?
2. What are the social, emotional and psychological effects of screening and partner notification for genital chlamydia?

Expert advisory group research questions

3. What is the best test and specimen to use for screening for genital chlamydial infection in men and women?
4. What are the most effective methods of accessing partners of infected patients for the diagnosis and treatment of genital chlamydial infection?
5. What are the most cost-effective criteria for targeted screening and which outcomes should be measured?
6. How can the cost-effectiveness of screening for genital chlamydial infection in non-genitourinary medicine clinic settings be maximised?

BOX 1 *Research questions addressed by the ClaSS project*

Study design

The core project component was a large, cross-sectional, population-based study that was used to measure the feasibility, acceptability, coverage and uptake of chlamydia screening and chlamydia prevalence (*Figure 1*). A proactive screening approach was investigated, using a personal invitation from GPs requesting people to post home-collected specimens to a local laboratory. In a pilot study for the project a home-collected specimen was requested from 200 randomly selected men and women aged 18–45 years. Of those invited, 32% did not live at their registered address. Of those who received a pack, 76% returned a specimen after two reminder letters, rising to 83% after a telephone call and home visit.[96] It was assumed that 60% of invited participants in the main study would accept the screening invitation.

The cross-sectional screening study provided the study participants, clinical specimens and empirical data for the other study components. From the core study, the researchers could estimate the population prevalence of chlamydia (research question 1, Chapter 2), include large numbers of men outside genitourinary clinics and, in laboratory-based studies, evaluate the performance of tests in non-invasive specimens in low-prevalence settings (research question 3, Chapter 7). A case–control study was nested within the prevalence survey to investigate risk factors that could be used to improve the targeting of screening, which is relevant to opportunistic as well as proactive screening programmes, particularly if it identifies groups at high risk of chlamydia who do not use health services frequently (research question 5, Chapter 5). A randomised, controlled partner notification trial was designed to evaluate a partner notification strategy in primary care (research question 4, Chapter 6). Primary data from all of these studies were used in an economic evaluation (research question 6, Chapters 6 and 7 related to partner notification and laboratory evaluations, and Chapters 8–10 for formal evaluation). Finally, studies were performed on the psychological,

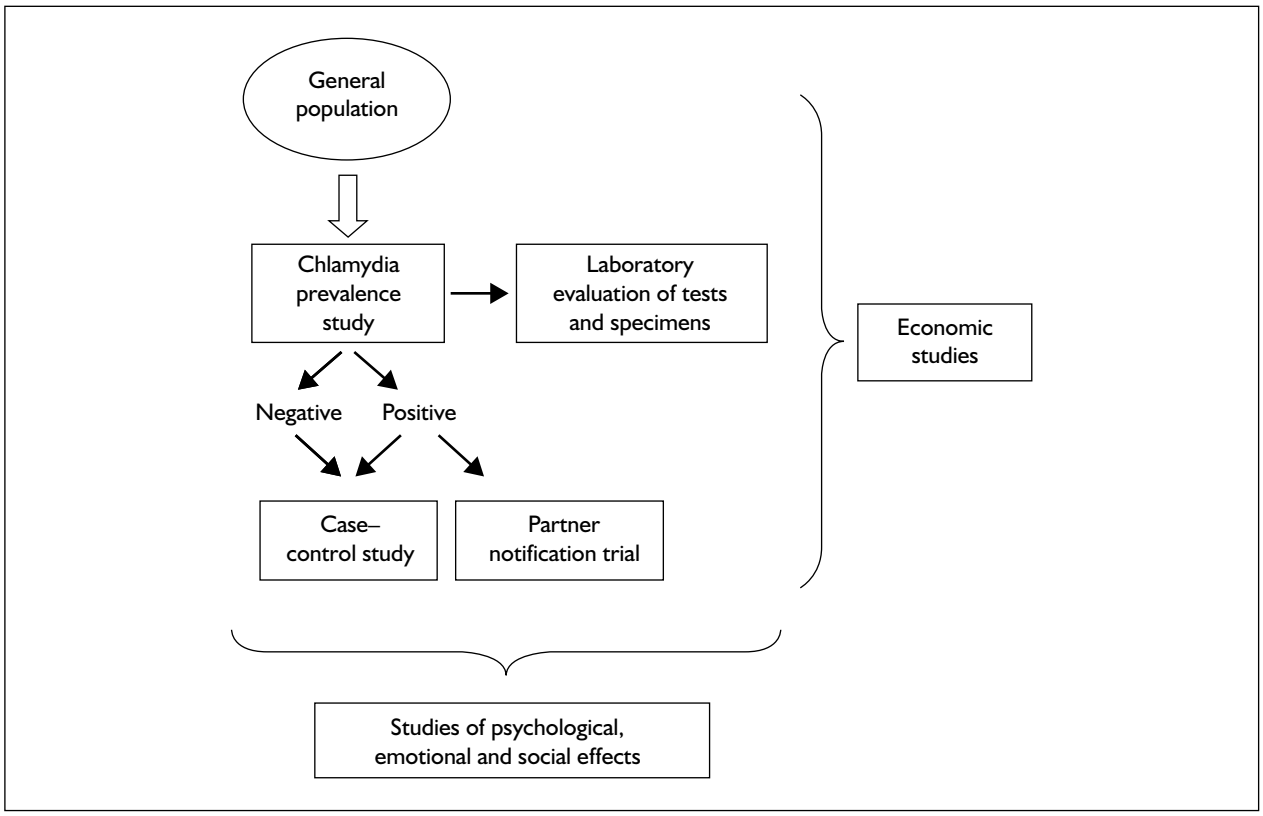

FIGURE 1 *Overview of chlamydia screening studies project components. Source: Low* et al. *(2004).*[95] *Reproduced with permission from the BMJ Publishing Group.*

emotional and social effects of the screening and partner notification processes at all stages of the project (research question 2, Chapters 4, 6). Detailed objectives, methods and results for each study component follow in the next eight chapters.

Study population

The ClaSS project was carried out in two sites: Bristol and surrounding areas, and the West Midlands and surrounding areas (*Figure 2*). These provided a large population covering urban, suburban and rural areas with differing levels of material deprivation and a diverse mix of ethnic groups (*Table 1*).

General practice lists were used as the population register from which to select the study sample. The project was advertised in the newsletters of primary care research networks in the study areas. Expressions of interest were received from more practices than required, so practices were sampled purposively to include approximately equal populations from each area, to ensure socio-economic and ethnic diversity, and to include rural as well as urban populations (*Figure 2*). All of the 27 general practices (11 in the Bristol area, 16 in the West Midlands) that were invited agreed to take part in the ClaSS project.

The aim was to study men and women aged 16–39 years. Men and women were selected from the lists of participating practices using a two-stage random sampling process. First, a fixed proportion of patients in each practice was selected. Then, only one subject per household was selected, so that the study sample did not include cohabiting sexual partners. An individual's sampling probability therefore depended on the list size and number of eligible people in a household.

After analysing screening uptake and chlamydia prevalence in the first four practices, it was found that the response rate was lower than expected from the pilot study, and that prevalence in those over 25 years of age was very low (*Table 2*).[95] In the remaining 23 practices, a decision was made to sample only individuals aged 16–25 years to increase the number of individuals with chlamydia who would be eligible for other components of the ClaSS project (Protocol amendments 2 and 3; http://www.chlamydia.ac.uk/pdf/prev/Prev%20Survey%20Protocol.pdf, section 14).

Study pack

A commercial company designed the ClaSS study pack (*Figure 3*) to fit through a standard letterbox

TABLE 1 *Comparison of ClaSS study population with population of England and Wales*

	ClaSS					
	Avon[a]		**West Midlands**[b]		**England and Wales**	
Population (thousands)[c]						
Total	1.000.6		5,319.9		52,793.7	
15–24 years	137.3		684.8		6,680.6	
25–39 years	217.8		1,096.7		11,369.1	
Deprivation score (rank)[d]						
Least deprived	9.76 (298)	S. Gloucs	16.44 (183)	Solihull	4.17 (354)	Hart, Hampshire
Most deprived	27.72 (67)	Bristol UA	37.57 (15)	Birmingham	49.78 (1)	Liverpool
Ethnic mix %[e]						
White	91.84		88.74		90.92	
Black	2.33		1.98		2.30	
South Asian	2.85		7.32		4.57	
Chinese/other	0.90		0.58		0.89	
Mixed	2.09		1.39		1.31	

[a] Avon includes Bath and North East Somerset, Bristol UA, North Somerset and South Gloucestershire.
[b] West Midlands includes Birmingham, Coventry, Dudley, Sandwell, Solihull, Walsall and Wolverhampton; two practices were in Hereford and Worcestershire.
[c] Office for National Statistics (ONS), Table D8549: Mid-year population by local authority.
[d] ONS, Index of Multiple Deprivations, 2004. Score increases with higher deprivation. Rank in brackets, 1 is most deprived, 354 least deprived.
[e] ONS, Table KS06: Ethnic group by local authority. Aggregated data for Avon authorities were not available, so figures for Bristol UA are given. Black includes black Caribbean, black African and black other; South Asian includes Indian, Pakistani, Bangladeshi and Asian other.

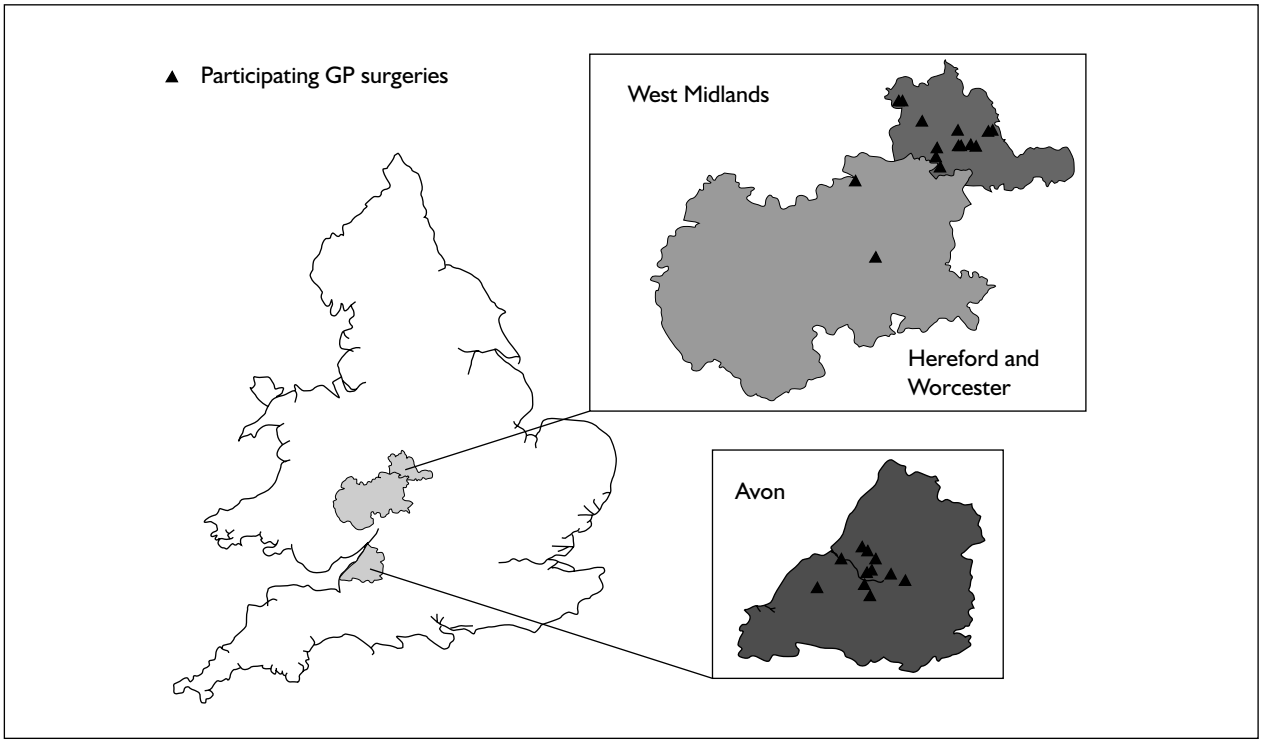

FIGURE 2 *ClaSS project sites and general practice locations*

TABLE 2 *Response to screening invitation in first four practices*

	Men		Women		Total
	16–25 years	26–39 years	16–25 years	26–39 years	All age
Response	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Responded	220 (28.5)	82 (29.7)	310 (38.5)	130 (42.2)	742 (34.3)
Declined	219 (28.4)	75 (27.2)	237 (29.4)	99 (32.1)	630 (29.2)
Did not respond	333 (43.1)	119 (43.1)	258 (32.0)	79 (25.6)	789 (36.5)
Total	772 (100)	276 (100)	805 (100)	308 (100)	2161 (100)

Total excludes 818 'ghost' patients.
Source: Low *et al.* (2004).[95] Reproduced with permission from the BMJ Publishing Group.

FIGURE 3 *Study pack and contents*

and to comply with European regulations on transporting biological samples (Health and Safety at Work etc. Act 1974, Certificate of Exception No. 2, June 2000). The researchers market tested and made changes to a prototype pack with 11 people in the age range of the study sample, who were selected at random from among those in the first four study practices who had not been selected for the main study (Protocol amendment 1; http://www.chlamydia.ac.uk/pdf/prev/Prev%20Survey%20Protocol.pdf, section 14).

The final pack contained: information about chlamydia and the study; consent forms; a form explicitly to decline participation in the study; a brief questionnaire covering demographic details and sexual activity in the past year; sampling kits with instructions on how to collect specimens; a prepaid addressed envelope for returning specimens, questionnaire and consent forms to the local Public Health Laboratory Service (now Health Protection Agency) laboratories in Bristol or Birmingham; and a postcard to request study materials in languages other than English. Project staff made up the packs for each practice, labelling specimen collection kits with barcoded labels and inserting individually barcoded consent forms and questionnaires.

Clinical specimens

Both men and women were asked to provide a urine specimen first thing in the morning (early-morning specimen) that included only the first part of the urine stream (first catch urine) in a 25-ml universal container. They recorded the date and time of collection, and women recorded the date of their last menstrual period. Laboratory staff recorded the time of arrival of specimens. Samples were only processed if they were accompanied by a signed consent form and completed prevalence questionnaire. Where no signed consent form was received, samples were frozen and staff in the project coordinating centre sent a reminder to request the consent form. Information about frozen samples was documented. Project staff also contacted participants to complete contact details on the questionnaire. All additions to the forms were signed and dated. If the information could not be obtained the sample was not tested. Laboratory staff telephoned the study coordinating office (*Figure 4*) with test results, entered the results manually onto the prevalence questionnaire, and sent these, together with the consent forms, to the coordinating office. Project staff in the study coordinating office sent letters to study participants to give them negative results, or to invite them to their GP to receive their results.

For the purposes of this study a swab was designed for women to collect vulvovaginal specimens, which would facilitate the laboratory evaluations of different diagnostic tests. Two dry, cotton-tipped swabs were mounted on separate plastic shafts into

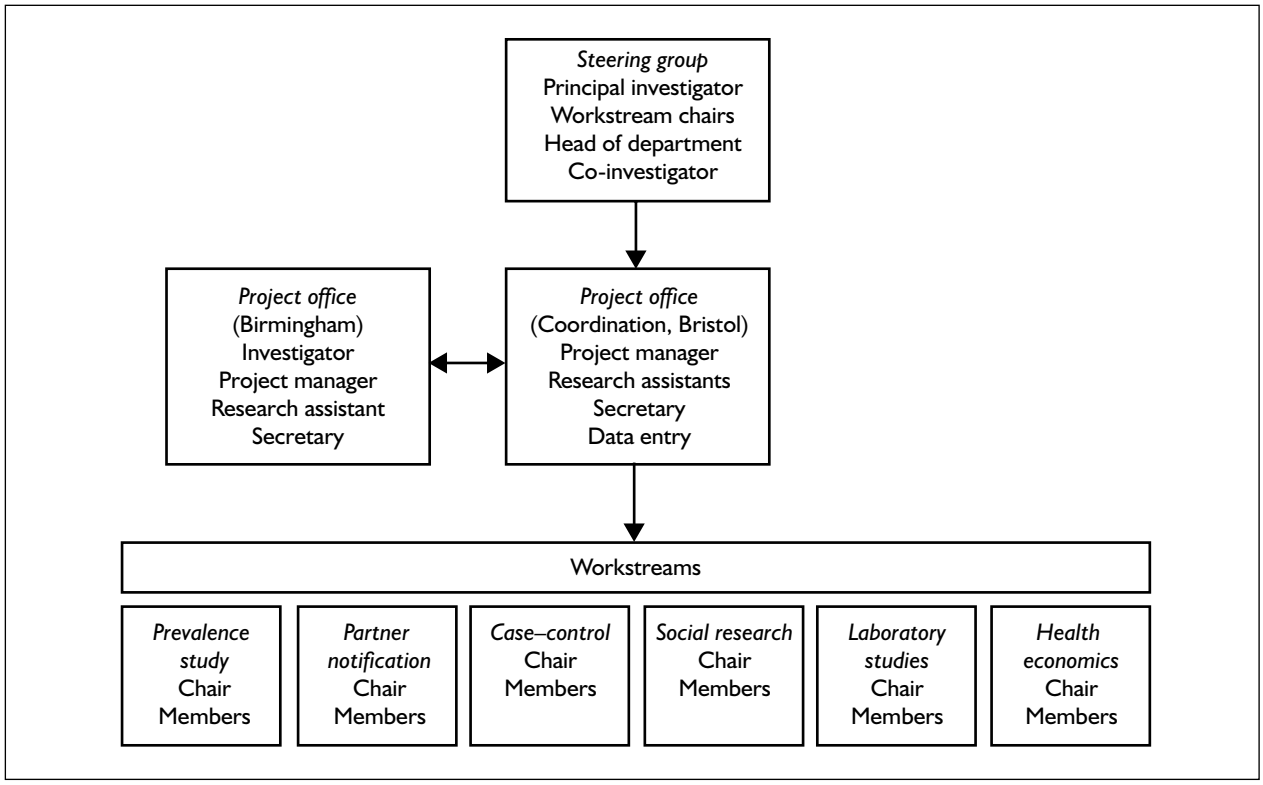

FIGURE 4 *Project management flowchart*

the cap of a single container (Technical Service Consultants, Heywood, Lancashire). The swab complied with Medical Device Agency (MDA SN9827) regulations. Each swab could be removed from the cap and used directly in a single assay, according to the manufacturer's instructions.

Delivery of study packs

The cross-sectional screening study was rolled out to practices in turn between February 2001 and July 2002. Practice registers were obtained and cleaned, and potential participants randomly sampled a maximum of 3 months before study packs were made up and sent out. It was planned to deliver all study packs by registered mail. Packs that could not be delivered were returned to the post office to await collection and, if not collected, were then returned to the study coordinating centre. When the response rate in the first four practices was lower than expected, the researcher found that the information provided by the Royal Mail did not allow them to determine whether the intended recipient did not receive the pack because they had changed address, or had simply decided not to collect the pack. For the remaining 23 practices, mail courier services were used to deliver packs and ascertain addresses directly. Couriers made up to five attempts to deliver packs, including at least one visit after 18.00 hours or at a weekend. Research staff ascertained whether non-responders whose packs had been delivered by mail were resident at the mailing address by making the same number of visits.

Testing methods to improve uptake

Several factors that might have contributed to reducing the anticipated uptake of the invitation to be screened were considered. Various methods were tested to improve uptake: sending an introductory letter in advance of the study pack; using a single, rather than the specially designed double-headed self-sampling swab for women; omitting potentially intrusive questions on sexual behaviour from the questionnaire; sending a reminder study pack rather than a letter; and offering a £10 gift voucher (with the alternative of a donation to charity). In addition, potential participants were 'flagged' at their practices; those attending the practice during the study period were invited to participate if they had not already agreed to do so.

Each intervention was tested in a single practice. Invited people in each practice were individually randomised using computer-generated random numbers and the response was recorded before unblinding. Odds ratios were then estimated for response to each intervention compared with the

TABLE 3 *Results of interventions to improve response rates to cross-sectional postal screening survey*

Intervention	Randomised	Responded	No response	Ghosts	OR (95% CI)[a]	p
Advance letter						0.970
Yes	285	69	162	54	1 (reference)	
No	287	77	174	36	0.99 (0.62 to 1.58)	
Swab type						0.040
Single	337	114	131	92	1 (reference)	
Double	338	99	143	96	0.63 (0.40 to 0.98)	
Sexual behaviour						0.499
Questions asked	252	51	123	78	1 (reference)	
No questions	250	52	111	87	0.83 (0.48 to 1.44)	
Reminder						0.046
Letter	320	28	218	74	1 (reference)	
Pack	320	50	198	72	1.90 (1.01 to 3.55)	
Gift voucher						0.565
Yes	419	73	219	127	1 (reference)	
No	419	69	227	123	0.89 (0.59 to 1.34)	

CI, confidence interval.
[a] Odds ratios (ORs) were calculated excluding 'ghost patients', who were not living at the delivery address and did not receive a study pack.

control conditions using inverse probability weights to account for sampling probabilities.

Table 3 shows that sending a reminder pack instead of a letter, and sending a single rather than a double-headed swab were associated with higher response rates. The differences were not large. For logistical and pragmatic reasons the following changes were made: an invitation letter was sent in advance of the study pack, the double swab was retained, reminder letters were still sent instead of packs for financial reasons, incentives were still offered (Protocol amendment 4, http://www.chlamydia.ac.uk/pdf/prev/Prev%20Survey%20Protocol.pdf, section 14).

Statistical analyses

Stata (Release 8.2; Stata Corporation, Austin, TX, USA) was used for all quantitative statistical analyses. Statistical methods are described in detail in the relevant chapters.

Project management

The study coordinating centre was in Bristol (*Figure 4*) and the study began on 1 August 2000. A project manager in Bristol and an assistant project manager in Birmingham supervised the day-to-day running of the project. The project managers, together with a research assistant in Bristol, communicated with the study practices and were available to provide information and support throughout the study period. Each study component (workstream) was managed by a chair and a team of three to five co-investigators. The epidemiological studies and laboratory workstreams had one chair from each study site. The health economics (Birmingham) and social research (Bristol) workstreams had one chair each, from the centre providing the expertise. Each workstream developed a detailed protocol, standard operating procedures and data collection forms (http://www.chlamydia.ac.uk/arms.htm). The workstreams met regularly to review fieldwork progress and deal with operational issues. The workstream chairs and principal investigator comprised a steering group to oversee the conduct of the project overall, and to make collective decisions about how the study was run, and about publication and dissemination of results. All data management, data entry and statistical analysis took place at the study coordinating centre in Bristol.

Training

Each participating general practice nominated one or more practice nurses to manage patients diagnosed with chlamydia, enrol participants for the partner notification trial and deal with respondents to the case–control study. All nominated practice nurses attended a one-and-a-half day training course in September 2000 in Bristol or Birmingham. The course was developed by ClaSS workstream members and Dr Philippa Matthews, lead GP for the Sexual Health in Practice project, Heart of Birmingham Teaching PCT. The course included training about:

chlamydia clinical manifestations, diagnosis and treatment; the ClaSS project design and documentation; and dispensing and observing single-dose azithromycin treatment. Role play with actors from the Interactive Skills Unit at the University of Birmingham was used to simulate a range of clinical scenarios to provide experience in how to give a positive chlamydia result, obtain consent for participation in the RCT, take a sexual history and conduct partner notification by patient referral (where the patients themselves are encouraged to inform sexual partners of the infection and to seek treatment). The study procedures took half a day and the clinical aspects one day.

Data management

A dedicated Microsoft Access relational database was developed to handle all data generated by the ClaSS project. The database was used:

- to upload and clean data from general practice patient lists (in particular, to ensure that recorded postcodes could be matched with official Post Office accepted addresses)
- to prepare the sampling frame for the study population, and sample at random individuals to be invited to take part in the study
- to allocate unique identifiers, which were converted to computerised barcodes for use on study specimens and forms
- to track individuals' progress through the study, log specific events such as receipt of forms, and select the appropriate groups requiring invitations, reminders and study documents at each stage
- to enter data
- to generate data sets for analysis.

All data handling, storage and access complied with the Data Protection Act 1998.

Chapter 3

Cross-sectional population-based survey of coverage and uptake of chlamydia testing and chlamydia prevalence

Objectives

The objectives of this part of the study were:

- to assess the coverage and uptake of postal chlamydia testing in the general population
- to determine the prevalence of chlamydia in a general population sample
- to estimate the potential coverage of opportunistic chlamydia screening offered in general practice
- to provide potential participants for the case–control study, partner notification trial and studies of the psychological and emotional impact of chlamydia screening
- to provide clinical specimens for laboratory evaluation studies.

Results from this study covering the uptake of chlamydia screening, chlamydia prevalence and general practice consultation patterns have been published previously.[97,98]

Methods

Invitation to participate in systematic screening

Participants were sent an invitation letter signed by their GP followed by a study pack. The invitation letter asked people to take part even if they thought it unlikely that they could be infected, to encourage people who were not sexually active to participate. Men and women who decided to take part were asked to sign a consent form, complete a one-page questionnaire, and collect a first void urine sample; women were also asked for a vulvovaginal swab. Participants posted their specimens and completed consent forms and questionnaire in a prepaid envelope to Health Protection Agency (former Public Health Laboratory Service) laboratories in either Bristol or Birmingham. People who did not wish to take part in the study could complete a 'non-participation' form and return this to the study coordinating centre in a prepaid envelope.

If there was no response to the initial study pack reminder letters were sent and up to three telephone calls made. A random 5% sample of households contacted by couriers was recontacted by research staff to check the data for accuracy. Individuals were classified as 'participants' (returned a postal specimen), 'refusers' (responded to indicate that they did not wish to participate), 'non-responders' (known to have received a pack, but did not respond) or 'ghosts' (confirmed as not resident at the address held by the practice or not contactable by any method).

Testing of samples, informing patients and treatment

NAATs were used for *C. trachomatis* diagnosis, following the manufacturers' instructions. Each laboratory used a different test: SDA (BD Probetec ET, Becton Dickinson, Franklin Lakes, NJ) in Birmingham and PCR (Cobas Amplicor CT, Roche Diagnostics, Basel) in Bristol. All positive results were confirmed by another NAAT or an EIA (for algorithm see *Table 25*, p. 61). Most participants with negative results were informed by letter. The remainder (a random sample of people with negative results who were asked to take part in the case–control study) and participants with positive results received a letter with an appointment to visit their practice. Practice nurses gave the results and single-dose azithromycin therapy according to a protocol. The practice nurses then invited participants to take part in an RCT of two strategies for partner notification, and either carried out the partner notification themselves or gave the patient the telephone number of a research health adviser and asked them to make an appointment to be seen at a local genitourinary medicine clinic (Chapter 6). Decisions were explored that assessed the acceptability of screening by in-depth interview (Chapter 4).

Consultation patterns in primary care

Details of doctor–patient or nurse–patient contacts were obtained for all selected patients at their general practice for the period around the screening survey. Data collection in each practice

took place after all packs had been delivered. Practice staff provided anonymised details of whether the patient was still registered with the practice and the date of their most recent attendance (which could have been before the study pack was sent out). Those collecting data were unaware of whether or not patients had participated in the study.

Statistical analysis

Coverage was defined as the proportion of the sample confirmed to have received a study pack, and uptake as the proportion of these returning a specimen. Logistic regression with inverse probability weights was used to account for sampling probability by household and age, and robust standard errors to correct for clustering at practice level to estimate coverage and uptake rates and chlamydia prevalence (with 95% CI), and to investigate factors associated with chlamydia infection at both the individual and practice level. Practice-level averages of deprivation score (Index of Multiple Deprivations, 2000)[99] and proportion of non-white residents (2001 Census) were calculated for each practice using the postcode of all individuals sampled from that practice. Meta-analysis of the estimated log odds of chlamydia in each practice was used, with inverse probability weights, to investigate heterogeneity in practice prevalence. Regression analyses were restricted to under-25-year-olds to facilitate direct comparisons with other studies[12–15] and with the target population of screening in England.[1,61]

Survival analysis was used to estimate the cumulative proportion of individuals who consulted their general practice. For each individual invited to participate in the screening study, time at risk of consulting was measured from the date when the study pack was sent out. Observations were censored at the date of the last attendance, or at the date of data collection, whichever was first. For individuals no longer registered with the practice who had no recorded attendance the date on which they had left was unknown, so these observations were censored at the midpoint between the pack being sent out and the date of data collection.

Kaplan–Meier methods were used to estimate the cumulative probability (with 95% CI) of patients aged 16–24 years consulting the practice at least once within 1 year of the study pack being sent out, and estimates were stratified according to age group, gender, chlamydia test result and whether they could be contacted by post. The cumulative probabilities of consulting were used, stratified by whether patients could be contacted by post or not to estimate the proportions of patients aged 16–24 years who would be covered by opportunistic and systematic screening strategies over a 1-year period.

Results

Study packs were sent between February 2001 and August 2002. Of 19,773 people selected, there were 9704 men and 10,069 women (*Figure 5*), comprising 15,319 16–24-year-olds and 4454 25–39-year-olds.

Coverage of postal invitation

Of all individuals invited to participate, 5391 out of 19,773 (27%) could not be contacted at their registered address, did not receive the study pack and were categorised as ghosts (*Figure 5*). Overall coverage in 16–24-year-olds, taking into account sampling probability, was 76%. Coverage was similar in men and women, but varied between practices from 50 to 86% (*Table 4*). At the practice level, reduced coverage was associated with a higher proportion of practice residents being from minority ethnic groups (*Table 5*).

Uptake of screening

Overall, 4740 out of 14,382 of those who received a study pack responded accepting screening and 4731 out of 14,382 (33%) provided a sample for testing (there were nine returned packages with a completed questionnaire but no specimen); 13% (1926/14,382) actively declined participation; and 54% (7718/14,382) did not respond (*Figure 5*). Uptake overall, taking sampling probability and clustering into account, was 34.5% (95% CI 31.2 to 38.0%) and in 16–24-year-olds 31.5% (95% CI 28.6 to 34.6%). Uptake was 29.5% (95% CI 28.0 to 31.0%) in men and 39.5% (95% CI 37.7 to 40.8%) in women ($p < 0.001$). Uptake increased with age from 30.2% (95% CI 27.4 to 33.2%) in 16–19 year-olds to 40.2% (95% CI 33.7 to 47.0%) in 35–39-year-olds ($p < 0.001$). At the practice level, uptake varied from 16 to 52% (*Table 4*); uptake of screening was lower in practices with higher deprivation scores and a higher proportion of patients from non-white ethnic groups. After controlling for deprivation there was no evidence of an association between uptake of the screening invitation and ethnicity (*Table 5*).

Most people who accepted screening did so after a single postal invitation (*Table 6*); however, both a postal reminder and face-to-face contact (either

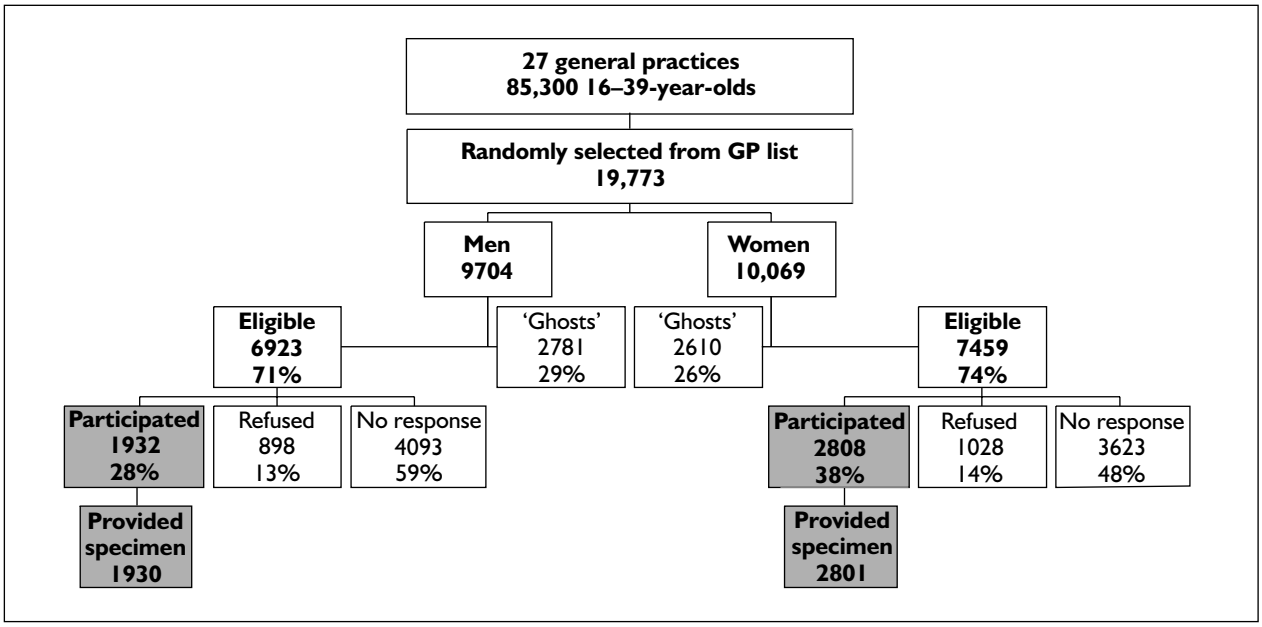

FIGURE 5 *Flowchart of participants in the cross-sectional screening survey. Source: Macleod J,* et al. *(2005).*[97] *Reproduced with permission from the BMJ Publishing Group.*

through a home visit or through 'flagging' in the surgery) each increased uptake by around 5% overall. Telephone reminders had little influence on uptake.

Chlamydia prevalence

There were 219 confirmed positive tests for *C. trachomatis*. Overall prevalence was 3.2% (95% CI 2.8 to 4.2%) and was similar in men and women (*Figure 6*).

In both genders prevalence was highest in those under 25 years of age. In men, the highest prevalence (6.9%, 95% CI 5.2 to 9.0%) was seen in 20–24-year-olds, while in women it was similar in 16–19 (6.2%, 95% CI 4.8 to 8.6%) and 20–24-year-olds (6.2%, 95% CI 4.9 to 8.4%). Prevalence was below 1% in men over 24 years and in women over 29 years.

There was some evidence to suggest that the likelihood of having chlamydia was associated with the ease of securing participation in screening (*Table 6*). This pattern was strongly apparent among women aged 16–24 years, where prevalence was 5.3% (95% CI 3.9 to 7.3%) in participants responding after a single mailed invitation, rising to 7.3% (95% CI 4.8 to 11.0%) in those responding after a mailed reminder and 8.7% (95% CI 6.8 to 11.1%,) in those only responding after face-to-face contact (p for trend = 0.007). Among men, and among women aged 25–39 years, however, there was little association. The prevalence in men responding after a single mailed invitation was 2.8% (95% CI 2.2% to 3.5%) and after face-to-face contact 3.9% (p for trend = 0.55). The corresponding figures in women aged 25–39 years were 1.3% (95% CI 0.5–3.0%) and 0.6% (95% CI 0.1 to 2.5%) (p for trend = 0.66).

Tables 7 and *8* show the prevalence of chlamydia stratified by age group, marital status and ethnic group in 16–24-year-old men and women, respectively. Among men, being aged 20–24 years and from a black ethnic group were factors associated with an increased risk of infection (*Table 7*). After controlling for individual- and practice-level factors, only older age remained strongly associated with chlamydia. In women, only being single was strongly associated with chlamydia in both univariable and multivariable models (*Table 8*).

Chlamydia prevalence in 16–24-year-olds varied among the 27 practices from zero to 12.4% (95% CI 7.2 to 20.6%) (*Figure 7*). There was weak evidence of heterogeneity between practice estimates of prevalence (p = 0.052). Meta-analysis suggested that 34% of this variation (I^2 statistic)[100] was not due to chance. There was no strong evidence of associations between chlamydia prevalence and practice-level factors in men or women (*Table 7* and *Table 8*). For men and women combined, however, there was weak evidence to suggest that the chlamydia was more common in

TABLE 4 *Chlamydia prevalence, uptake of screening, coverage, area deprivation and ethnic mix by practice, 16–24-year-olds only*

Practice number	n^a	n^b	Coverage (%)[c]	Uptake (%)[c]	Prevalence (%) (95% CI)[c]	Deprivation score[d]	Ethnic mix (%)[e]
1	345	38	83.4	16.4	0.0 (0.0 to 0.9)[f]	63.6	68.3
2	60	13	79.5	28.1	0.0 (0.0 to 4.9)[f]	42.7	25.5
3	746	130	73.2	23.3	1.7 (0.4 to 7.1)	32.3	3.7
4	573	117	81.4	25.1	2.6 (0.8 to 8.3)	36.0	4.5
5	381	53	69.7	19.9	3.1 (0.8 to 11.8)	63.4	65.1
6	477	117	85.2	28.5	3.3 (1.2 to 8.5)	15.2	1.2
7	752	237	63.1	52.0	3.4 (1.6 to 6.9)	10.6	8.8
8	330	80	86.3	28.6	3.8 (1.2 to 11.2)	36.4	9.7
9	338	116	86.2	39.8	3.8 (1.7 to 8.3)	10.1	1.4
10	1308	249	49.6	41.3	4.1 (1.8 to 9.0)	35.2	21.6
11	535	190	85.5	41.3	4.5 (2.2 to 8.8)	7.7	1.7
12	1009	266	64.2	39.0	4.8 (2.8 to 8.2)	28.1	10.6
13	226	45	76.9	25.5	4.9 (1.2 to 17.9)	44.2	9.9
14	852	165	77.2	24.1	5.0 (2.3 to 10.5)	38.1	7.3
15	402	129	84.8	37.4	5.2 (2.3 to 11.4)	32.3	3.7
16	553	195	79.9	43.3	5.3 (2.8 to 9.9)	27.3	3.8
17	209	56	83.3	32.2	5.5 (1.7 to 15.8)	30.3	14.2
18	552	137	86.6	27.9	6.5 (3.4 to 12.1)	38.8	5.8
19	1321	274	72.8	30.4	7.2 (4.2 to 12.2)	15.6	2.0
20	689	188	78.2	33.1	7.6 (4.5 to 12.6)	26.5	7.4
21	963	194	69.6	29.0	8.5 (5.3 to 13.3)	59.1	67.7
22	718	197	83.4	34.0	8.5 (4.7 to 14.7)	47.0	7.5
23	290	58	69.4	27.8	9.0 (3.7 to 20.0)	40.0	40.8
24	265	70	83.6	31.5	9.9 (4.8 to 19.5)	45.9	9.7
25	444	74	77.2	21.3	11.2 (5.1 to 23.1)	38.4	35.6
26	340	76	80.6	27.0	12.3 (6.5 to 22.1)	56.2	4.0
27	641	145	84.4	27.7	12.4 (7.2 to 20.6)	30.6	5.5
Combined	15319	3609	75.6	31.5	5.9 (5.0 to 7.0)	34.2	8.3

Source: Macleod *et al.* (2005).[97] Reproduced with permission from the BMJ Publishing Group.
[a] Total number of 16–24-year-olds in each practice, including 4074 ghost patients.
[b] Number responding in each practice.
[c] Weighted to take sampling probability into account.
[d] Index of Multiple Deprivations 2000 score. Average score for ward of residence of sampled 16–24-year-old patients in each practice, weighted for sampling probability. Score increases with higher deprivation.
[e] Proportion of practice population from non-white ethnic groups, 2001 Census. Average score for ward of residence of sampled 16–24-year-old patients in each practice, weighted for sampling probability.
[f] Exact 95% CI: this does not account for sampling probability.

TABLE 5 *Practice-level factors associated with coverage and uptake of postal screening*

Factor	Deprivation score		Proportion non-white	
	OR (95% CI) per 10-point increase	*p*	OR (95% CI) per 10% increase	*p*
Screening coverage				
Crude[a]	0.98 (0.88 to 1.10)	0.762	0.93 (0.87 to 0.99)	0.019
Adjusted[b]	1.13 (0.98 to 1.29)	0.083	0.87 (0.81 to 0.94)	0.001
Uptake of screening invitation				
Crude[a]	0.86 (0.80 to 0.93)	0.004	0.92 (0.87 to 0.97)	0.003
Adjusted[b]	0.88 (0.80 to 0.96)	0.004	0.98 (0.92 to 1.05)	0.708

Source: Macleod *et al.* (2005).[97] Reproduced with permission from the BMJ Publishing Group.
Models include 15,319 men and women aged 16–24 years in 27 general practices.
[a] Controlled for sampling probability and clustering by practice only.
[b] Additionally controlled for age and gender.

TABLE 6 *Uptake of screening according to effort needed to secure participation*

Groups by gender and age	Effort needed	No. of people who received this form of invitation to be screened	No. of people who responded after each form of invitation[a]	(%) uptake (95% CI)	Cumulative uptake (%) (95% CI)	No. of cases	Prevalence (95% CI)	*p*-Value for linear trend	Cumulative prevalence (95% CI)
All	Single postal invitation	14,382	3,239	25.0 (21.7 to 28.6)	25.0 (21.7 to 28.6)	137	3.0 (2.3 to 3.9)	0.014	3.0 (2.3 to 3.9)
	Two postal invitations	11,143	663	5.3 (3.9 to 7.1)	30.3 (26.5 to 34.3)	32	3.4 (2.1 to 5.4)		3.1 (2.3 to 4.0)
	Telephone call	10,460	53	0.5 (0.1 to 2.2)	30.8 (26.9 to 35.0)	2	2.0 (1.1 to 3.8)		3.0 (2.3 to 3.9)
	Home visit or flagging[b]	10,407	765	3.7 (2.0 to 6.8)	34.5 (31.2 to 38.0)	48	5.0 (3.4 to 7.2)		3.2 (2.5 to 4.2)
All 16–24	Single postal invitation	11,245	2436	22.2 (18.6 to 26.2)	22.2 (16.6 to 26.2)	133	5.4 (4.3 to 6.6)	0.054	5.4 (4.3 to 6.6)
	Two postal invitations	8,809	507	4.3 (3.0 to 6.2)	26.5 (22.6 to 30.8)	29	6.5 (4.7 to 6.9)		5.5 (4.6 to 6.7)
	Telephone call	8,302	39	0.5 (0.1 to 2.2)	27.0 (22.9 to 31.5)	2	4.4 (2.8 to 6.8)		5.5 (4.6 to 6.7)
	Home visit or flagging[b]	8,263	627	4.6 (2.0 to 10.0)	31.5 (28.6 to 34.6)	45	7.4 (5.5 to 9.9)		5.8 (4.9 to 6.9)
Men 16–24	Single postal invitation	5,454	1,017	18.9 (16.0 to 22.3)	18.9 (16.0 to 22.3)	46	5.4 (4.4 to 6.5)	0.768	5.4 (4.4 to 6.5)
	Two postal invitations	4,437	196	3.57 (2.6 to 4.9)	22.5 (19.3 to 26.1)	9	5.3 (2.8 t 9.8)		5.4 (4.3 to 6.6)
	Telephone call	2,241	21	0.49 (0.1 to 2.5)	23.0 (19.6 to 26.8)	0	0.0 (0.0 to 0.1)		5.2 (4.2 to 6.5)
	Home visit or flagging[b]	4,220	243	3.61 (1.5 to 8.3)	26.6 (24.0 to 29.4)	12	5.4 (3.3 to 8.8)		5.3 (4.4 to 6.3)
Women 16–24	Single postal invitation	5,791	1,419	25.3 (20.9 to 30.3)	26.3 (20.9 to 30.3)	76	5.3 (3.9 to 7.3)	0.033	5.3 (3.9 to 7.3)
	Two postal invitations	4,372	311	5.1 (3.4 to 7.7)	30.4 (25.7 to 35.6)	20	7.3 (4.8 to 11.0)		5.7 (4.3 to 7.5)
	Telephone call	4,061	18	0.4 (01 to 2.0)	30.9 (26.0 to 36.2)	2	9.5 (5.8 to 15.2)		5.7 (4.4 to 7.4)
	Home visit or flagging[b]	4,043	384	5.5 (2.5 to 11.9)	36.4 (33.1 to 39.8)	33	8.7 (6.8 to 11.1)		6.2 (4.9 to 7.8)

Source: Macleod *et al.* (2005).[97] Reproduced with permission from the BMJ Publishing Group.

[a] Includes nine people who returned a consent form but no specimen.

[b] A 'flag' was attached to patients' notes. Patients attending the practice during the study period were invited again to take part if they had not already participated, had declined to participate, or had been confirmed not resident at their address.

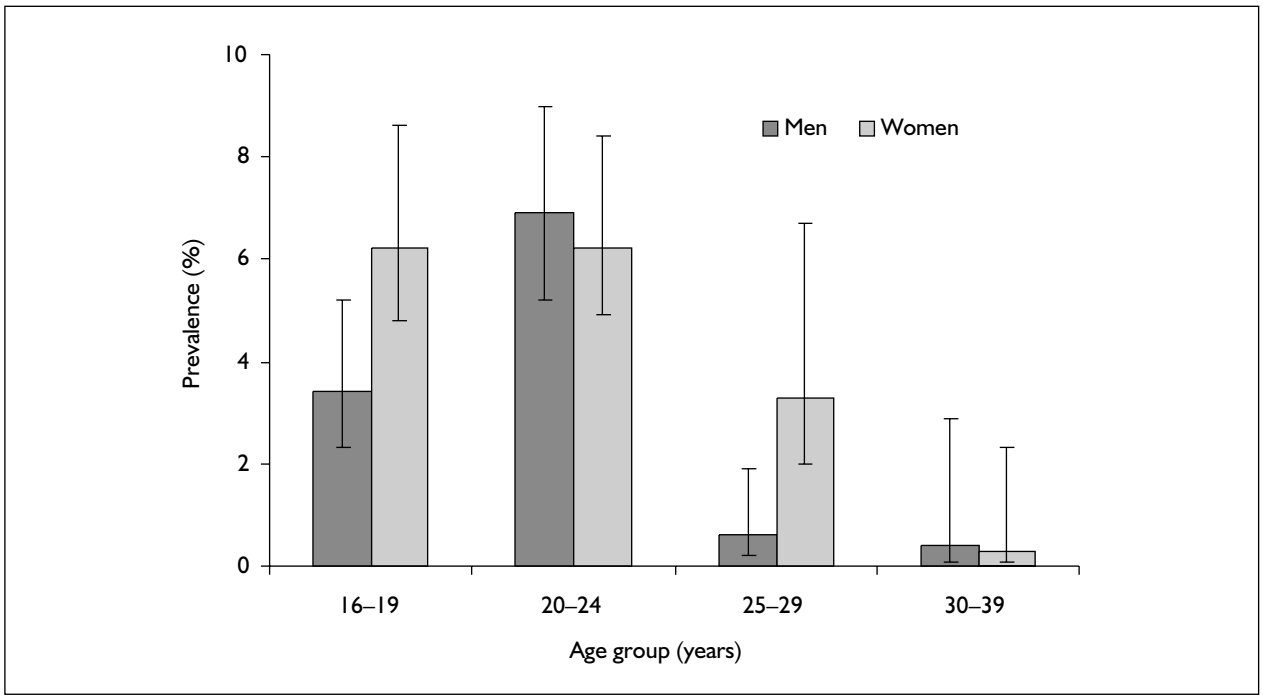

FIGURE 6 *Chlamydia prevalence by age and gender. Vertical bars are 95% CIs.*

practices with higher levels of deprivation (for a 10-point increase in deprivation score, adjusted OR 1.2; 95% CI 1.0 to 1.4, $p = 0.077$).

Sexual behaviour

Information on numbers of sexual partners was only collected from all subjects after showing that this did not affect response rate (*Table 3*). Around half of the study population were asked about the total number of partners and new partnerships in the past year, and 91% responded. Among 16–17-year-olds, 52% of men and 74% of women reported ever having had sex. Over 80% of 18–19-year-olds and over 90% of those 20 years or more were sexually active. Among people who reported ever having had sex, chlamydia prevalence was very similar to the estimates in the whole study population, except among men aged 16–19 years, where prevalence was 5.3% (95% CI 3.5 to 8.1%) among those reporting sexual experience compared with 3.4% (95% CI 2.3 to 5.2%) in all 16–19 year-old men. There were three positive results in women who reported never having had sex.

Table 9 shows that chlamydia was uncommon among individuals who reported no new sexual partner in the preceding 12 months. Prevalence increased with increasing numbers of partners, reaching a plateau of around 12% in those with a total of three or more partners, or two or more new partners in the past year. In a multivariable model taking into account both measures of recent sexual behaviour and other individual-level factors, chlamydia was associated with increasing numbers of new sexual partners, rather than the total number.

Consultation behaviour

For the analysis of consultation behaviour among the 15,319 patients aged 16–24 years data were excluded from 2084 (13.6%) patients from three practices that provided no data, and 262 (1.7%) records with implausible dates. Therefore, data were analysed from 12,973 (84.7%) patients aged 16–24 years in 24 practices. The distribution of patients by age and gender was similar for those with and without complete data. Among patients with complete data, 2705 (20.9%) were found to be ghosts. Of the remaining 10,268 patients, 3318 (32.3%) returned a specimen, 1364 (13.3%) declined to participate and 5586 (54.4%) did not respond in any way. *Table 10* shows the estimated cumulative probabilities of men and women aged 16–24 years consulting their general practice in the year after they were invited to participate in postal screening. Overall, an estimated 68.6% (95% CI 67.3 to 69.9%) of patients had consulted their practice by 12 months and 89.3% (95% CI 88.1 to 90.3%) by 17.5 months, the maximum follow-up period. The probability of consulting was higher in women (75%) than in men (60%, $p < 0.0001$), and in those who could be contacted at their registered address (73%) than in ghost patients (44%, $p < 0.0001$).

TABLE 7 *Associations between prevalence and individual and practice level covariates, men*

Men		*N*[a]	Positive	Prevalence, (%) (95% CI)[b]	OR (95% CI)		
					Crude[b]	Adjusted[c]	*p*[d]
All		1446	64	5.1 (4.0 to 6.3)			
Individual-level factors							
Age (years)	16–19	684	22	3.5 (2.3 to 5.2)	1 (reference)	1 (reference)	0.010
	20–24	762	42	6.7 (5.0 to 8.8)	2.0 (1.1 to 3.5)	2.1 (1.2 to 3.7)	
Marital status	Single	1315	58	5.1 (4.0 to 6.5)	1 (reference)	1 (reference)	0.706
	Married	119	5	5.2 (2.2 to 12.2)	1.0 (0.4 to 2.9)	0.8 (0.3 to 2.2)	
	Divorced	3	0	–	–	–	
Ethnic group	White	1252	55	5.3 (4.1, 6.5)	1 (reference)	1 (reference)	0.322
	Black	79	9	11.1 (5.9, 20.0)	2.3 (1.1 to 4.6)	1.6 (0.6 to 3.9)	
	Indian	70	0	–	–	–	–
	Chinese	5	0	–	–	–	–
	Other	40	0	–	–	–	–
Practice-level factors							
Deprivation score in practice population (per 10-point increase)				–	1.1 (1.0 to 1.2)	1.1 (0.9 to 1.4)	0.427
Proportion non-white in practice population (per 10% increase)				–	1.0 (0.9 to 1.2)	1.1 (0.9 to 1.3)	0.536
Uptake rate in practice (per 10% increase)				–	0.9 (0.7 to 1.1)	0.9 (0.6 to 1.2)	0.411

Source: Macleod *et al.* (2005).[97] Reproduced with permission from the BMJ Publishing Group.
[a] Model restricted to 1446 men aged 16–24 years with complete data for all variables.
[b] Adjusted for weighting and clustering.
[c] Adjusted for weighting, clustering and other variables in table.
[d] Wald test for heterogeneity between categories: refers to adjusted model.

TABLE 8 *Associations between prevalence and individual and practice level covariates, women*

Women		*n*[a]	Positive	Prevalence (%) (95% CI)[b]	OR (95% CI)		
					Crude[b]	Adjusted[c]	*p*[d]
All		2104	129	6.2 (5.2 to 7.8)			
Individual-level factors							
Age (years)	16–19	893	55	6.0 (4.6 to 8.4)	1 (reference)	1 (reference)	0.367
	20–24	1211	74	6.2 (4.9 to 8.4)	1.0 (0.7 to 1.6)	1.3 (0.8 to 2.0)	
Marital status	Single	1646	116	7.0 (5.9 to 9.2)	1 (reference)	1 (reference)	0.007
	Married	426	12	2.6 (1.5 to 4.8)	0.4 (0.2 to 0.8)	0.3 (0.1 to 4.8)	
	Divorced	11	0	–	–	–	
Ethnic group	White	1798	105	5.9 (4.9 to 7.7)	1 (reference)	1 (reference)	0.573
	Black	164	18	9.5 (6.1 to 21.0)	1.7 (0.7 to 4.3)	2.0 (0.8 to 5.1)	
	Indian	74	2	3.8 (1.0 to 21.4)	0.6 (0.1 to 4.0)	1.0 (0.1 to 9.8)	
	Chinese	11	2	17.9 (4.5 to 56.8)	3.5 (0.6 to 22.1)	3.5 (0.5 to 24.2)	
	Other	57	2	4.6 (1.2 to 17.3)	0.8 (0.2 to 3.4)	1.0 (0.2 to 4.8)	
Practice-level factors							
Deprivation score in practice population (per 10-point increase)				–	1.1 (0.9 to 1.3)	1.2 (0.9 to 1.6)	0.169
Proportion non-white in practice population (per 10% increase)				–	1.0 (0.8 to 1.2)	0.8 (0.6 to 1.1)	0.132
Uptake rate in practice (per 10% increase)				–	0.8 (0.6 to 1.1)	0.9 (0.6 to 1.2)	0.412

Source: Macleod *et al*. (2005).[97] Reproduced with permission from the BMJ Publishing Group.
[a] Model restricted to 2104 women aged 16–24 years with complete data for all variables.
[b] Adjusted for weighting and clustering.
[c] Adjusted for weighting, clustering and other variables in table.
[d] Wald test for heterogeneity between categories: refers to adjusted model.

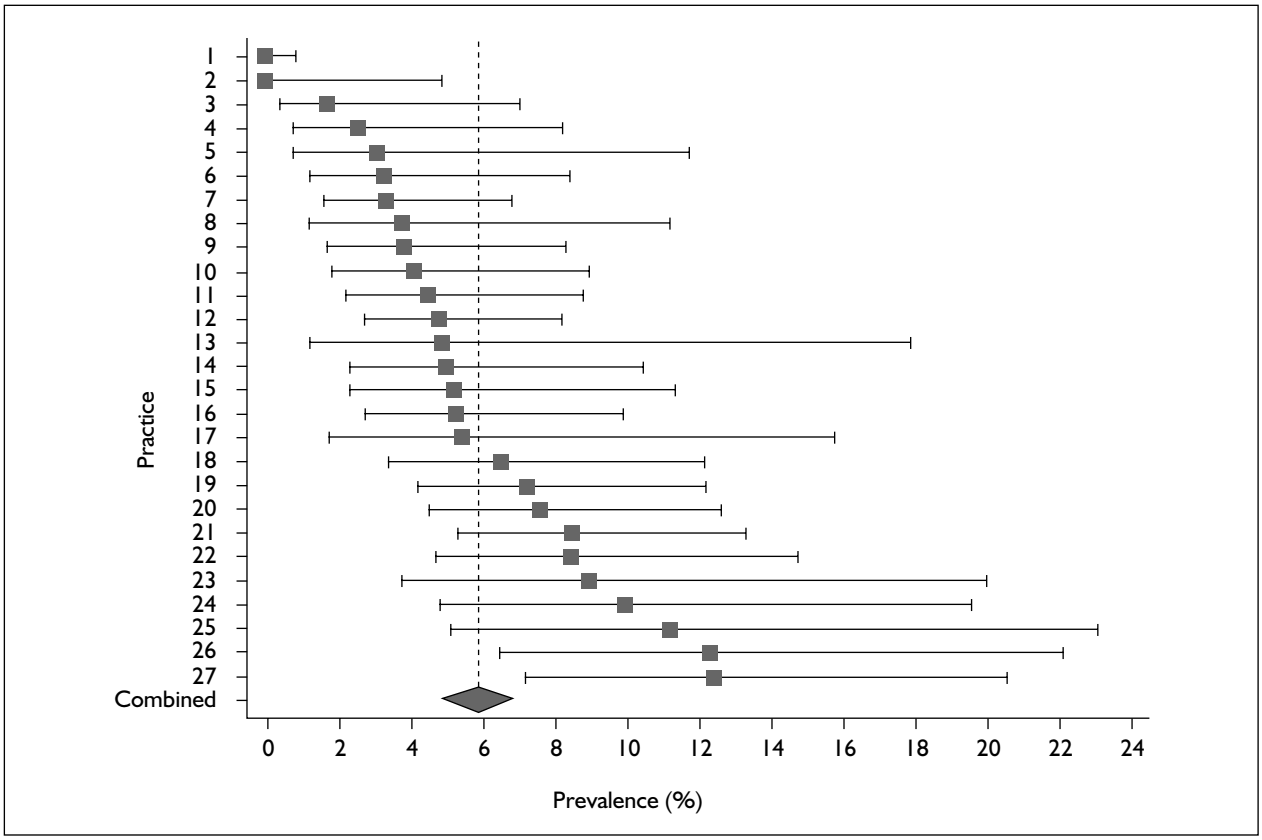

FIGURE 7 *Chlamydia prevalence according to practice, 16–24-year-old men and women*

When stratified by gender, the probability of men consulting was higher in 16–19 (64%) than in 20–24-year-olds (58%, $p = 0.004$), and among those participating in postal screening, in those with positive (72%) compared with negative chlamydia test results (69%, $p = 0.036$). Consultation patterns in women did not vary by age or chlamydia test result.

Figure 8 illustrates the estimated proportion of people who would potentially be contacted in 1 year of an opportunistic or a systematic chlamydia screening programme. Most people (57.7%) would be contacted by either strategy. However, 21.3% of people would not attend the practice but would receive an invitation at their home address, whereas 9.2% of people would not have received a postal invitation address but would attend their surgery. The remaining 11.8% of people would not be reached by either strategy. These figures do not take into account the proportions attending primary care who would actually be tested, or whether a specimen was actually returned.

Discussion

In this multicentre, population-based study, which simulated a single round of proactive systematic postal screening for chlamydia, 76% of 16–39-year-olds were successfully contacted and invited to provide a home-collected sample. The proportion successfully contacted tended to be lower in areas with a higher proportion of non-white residents. Uptake of this offer was 34.5% (95% CI 31.2 to 38.0%) overall, with lower response rates in more deprived areas. The prevalence of chlamydia in 16–24-year-olds was 5.1% (95% CI 4.0 to 6.3%) in men and 6.2% (95% CI 5.2 to 7.8%) in women. Having at least one new sexual partner in the past year appeared the most important determinant of infection. The comparison of opportunistic and systematic screening strategies demonstrated that the majority of both men and women aged 16–24 years attended their general practice at least once in a 1-year period. However, an estimated 21% of patients would not be reached by opportunistic screening in primary care, but would receive a postal invitation.

TABLE 9 *Association between prevalence and sexual behaviour, in men and women*

Variable	Group	No. of participants[a]	No. of cases	Prevalence[b]	OR (95% CI)		p^c	Adjusted OR (95% CI)[d]	p^d
					Crude	Adjusted[c]			
Total partners	0/1	941	38	4.1 (3.0 to 7.0)	1 (reference)	1 (reference)	0.018	1 (reference)	0.149
	2	226	15	8.8 (5.4 to 13.4)	2.3 (1.1 to 4.7)	2.0 (1.0 to 4.0)		1.0 (0.4 to 2.4)	
	3	139	15	11.7 (7.2 to 15.5)	3.1 (1.5 to 6.3)	2.9 (1.4 to 6.2)		1.6 (0.7 to 3.8)	
	≥ 4	200	27	12.5 (8.7 to 18.6)	3.3 (1.5 to 7.3)	3.0 (1.4 to 6.5)		1.9 (0.9 to 4.2)	
New partners[e]	0	697	23	2.9 (1.9 to 5.7)	1 (reference)	1 (reference)	<0.001	1 (reference)	<0.001
	1	417	24	7.4 (5.0 to 11.1)	2.7 (1.3 to 5.5)	2.7 (1.3 to 5.6)		2.6 (1.4 to 4.8)	
	2	166	21	13.9 (9.3 to 20.7)	5.5 (2.7 to 11.2)	5.1 (2.5 to 10.3)		4.2 (2.0 to 9.1)	
	≥ 3	226	27	11.0 (7.7 to 15.6)	4.2 (1.8 to 10.1)	4.1 (1.7 to 9.9)		2.4 (1.1 to 5.3)	

Source: Macleod *et al.* (2005).[97] Reproduced with permission from the BMJ Publishing Group.

[a] Logistic regression models include 1506 people aged 16–24 years who had ever had sex and who responded to questions about numbers of sexual partners.

[b] Prevalence weighted for selection probability and adjusted for clustering at practice level by using inverse probability weights and robust standard errors.

[c] From model additionally adjusted for age, marital status and ethnic group.

[d] From model additionally adjusted for age, marital status and ethnic group, and both sexual behaviour variables.

[e] Number of new sexual partners in the past year.

TABLE 10 *Cumulative probability of consulting general practice in one year, men and women aged 16–24 years*

Characteristic	Men			Women			Men and women		
	Consulted, total	% consulting by 1 year (95% CI)	*p*	Consulted, total	% consulting by 1 year (95% CI)	*p*	Consulted, total	% consulting by 1 year (95% CI)	*p*
All	2152	60.4 (58.3 to 62.5)		3435	75.3 (73.7 to 76.9)		5587	68.6 (67.3 to 69.9)	
Age group									0.196
16–19 years	975	64.0 (60.9 to 67.1)	0.004	1441	75.5 (73.1 to 77.9)	0.340	2416	70.3 (68.3 to 72.3)	
20–24 years	1177	57.5 (54.7 to 60.4)		1994	75.0 (72.8 to 77.2)		3171	67.2 (65.4 to 69.0)	
Participation status			<0.0001			<0.0001			<0.0001
Responded	597	69.1 (65.0 to 73.2)		1238	79.9 (77.4 to 82.3)		1835	75.9 (73.7 to 78.1)	
Refused	238	50.6 (45.2 to 56.3)		404	65.5 (60.8 to 70.1)		642	58.8 (55.2 to 62.5)	
Did not respond	1052	69.2 (66.1 to 72.3)		1401	81.9 (79.4 to 84.2)		2453	75.7 (73.7 to 77.7)	
Ghost	265	33.7 (29.3 to 38.5)		392	55.3 (49.9 to 60.9)		657	44.1 (40.5 to 47.8)	
Contactability[a]									<0.0001
Contactable	1887	65.9 (63.7 to 68.2)	<0.0001	3043	78.4 (76.7 to 80.0)	<0.0001	4930	72.9 (71.6 to 74.3)	
Not contactable	265	33.7 (29.3 to 38.5)		392	55.3 (49.9 to 60.9)		657	44.1 (40.5 to 47.8)	
Chlamydia result[b]			0.036			0.969			0.154
Positive	39	71.7 (56.7 to 85.1)		76	73.8 (62.9 to 83.7)		115	73.3 (64.5 to 81.4)	
Negative	557	69.1 (64.8 to 73.3)		1161	80.4 (77.8 to 82.8)		1718	76.2 (73.9 to 78.4)	

Source: Salisbury *et al.* (2006).[98]

[a] Patients who could be contacted included everyone except those classified as 'ghost' patients.

[b] Based on a subsample of 3318 respondents who provided a specimen.

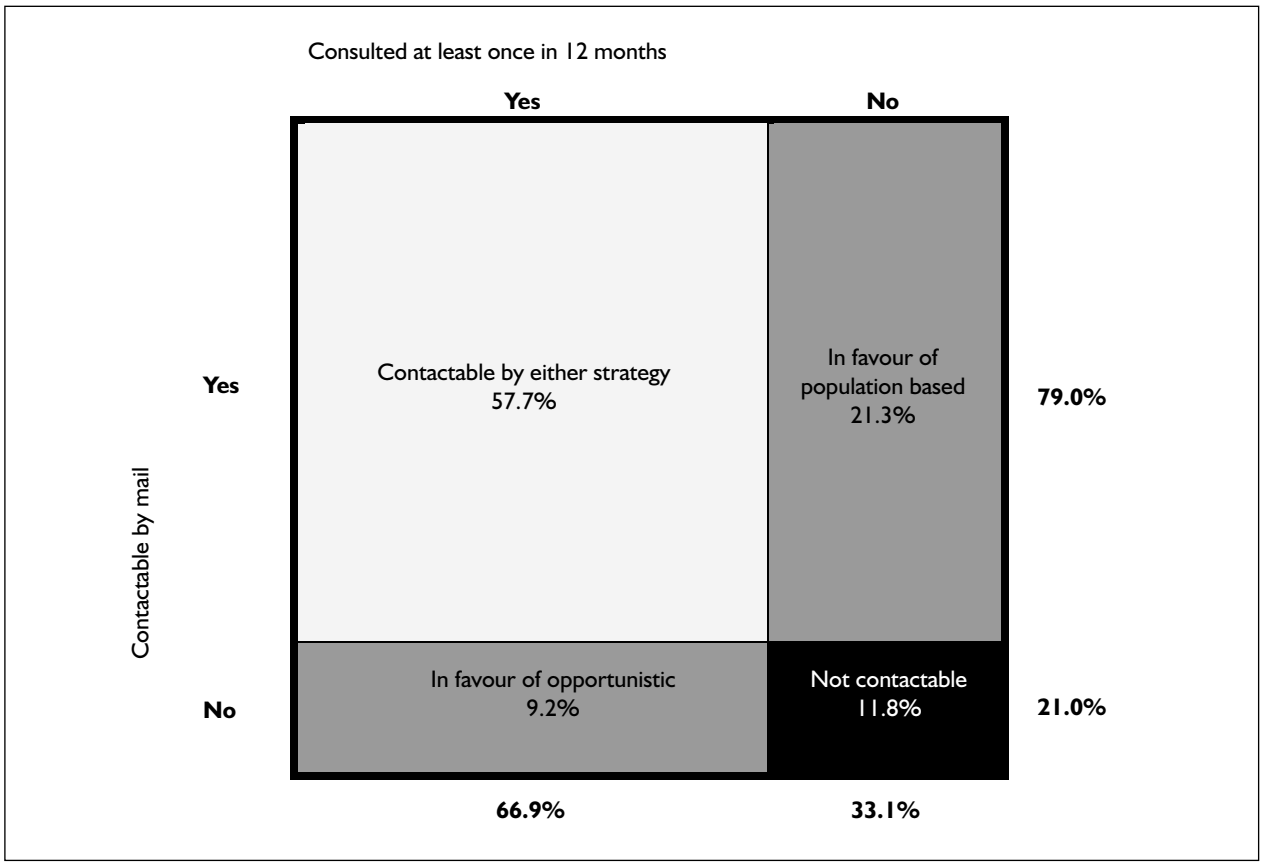

FIGURE 8 *Potential coverage achieved by opportunistic and population-based screening. Proportions attending sum to 100%. Figures derived from Kaplan–Meier estimates, stratified by contactability and consultation.*

Methodological issues

The strengths of this study are that it was large, multicentre, population-based, and included both men and women. The proactive screening strategy, which has been shown to be feasible in other European countries, used posted home-collected samples and molecular diagnostic methods. This study aimed both to replicate the process of systematic postal screening and to estimate chlamydia prevalence. Some of the methods, such as using registered mail or courier to deliver packs, would not necessarily be part of a screening programme, but were required for research purposes. Provision of financial incentives to potential participants is unlikely to form part of a screening programme; however, there was little evidence that this inflated uptake of screening in this study.

Coverage of systematic screening in this study was incomplete because of inaccuracies in the population register. This problem is well recognised and the proportion of ghost patients was typical for this age group.[96,101,102] Coverage of systematic screening can approach 100% in countries with reliable population registers.[13,15] This study highlights the need to improve the accuracy of registers maintained by general practices, which also constitute the central patient register used by the NHS cervical and breast cancer screening programmes. Young adults may not see the need to inform their practice of frequent changes of address, so practices should use all contacts as an opportunity to keep records up to date.

Chlamydia prevalence

The estimate of chlamydia prevalence in this study, of about 3% in 16–39-year-olds, was comparable with the 2% found among sexually active 18–44-year-olds surveyed in the National Survey of Sexual Attitudes and Lifestyles (Natsal 2000), a national general population study.[14] There were, however, age-specific differences. Male prevalence in Natsal 2000 was highest among 25–34-year-olds (3.0%, 95% CI 1.7 to 5.1%), but less than 1% in this age group in the present study. Prevalence among women in both studies was highest in under-25-year-olds; 2.7% (95% CI 1.2 to 5.8%) in women aged 18–24 years in Natsal 2000, but 7.1% (95% CI 5.9 to 9.2%) in the same age group in this study.

Biases due to response rate and selective participation in both studies could contribute to these differences. Qualitative research in the ClaSS project suggested that levels of participation were related to perceived risk, particularly among women (see Chapter 4).[103] This is supported by the finding that 56% of women aged 16–24 years in this study reported a new sexual partner in the previous year, compared with 39% of this age group in Natsal 2000 (Chapter 5). In Natsal 2000, 63% of the whole sample participated in the questionnaire survey and 71% of sexually active participants invited to provide a urine sample did so. This meant that fewer than 45% of the original population sample was tested. There were only about 80 positive specimens in Natsal 2000 (compared with 219 in ClaSS), so misclassification of a small number of test results could have affected prevalence estimates.

Sexual behaviour appeared the most important determinant of risk of infection in this study. People reporting one new sexual partner in the previous year had approximately double the risk of infection compared with those reporting no new partner, and this risk doubled again among those reporting two or more new partners. Studies using data from genitourinary medicine clinics have found being from a black minority ethnic group to be strongly associated with chlamydia.[104,105] The present study did not find a strong association with ethnicity, but only 6.6% of participants were from black ethnic groups so the precision of these estimates is limited. Clinic-based studies may overestimate ethnic disparities because of the health-seeking behaviours of their patient populations. Alternatively, ethnic differences might have been underestimated because the postal screening invitation was less likely to have reached people living in areas with large ethnic minority populations, and those in deprived areas were less likely to be screened.

Chlamydia prevalence varied among practices. Meta-analysis suggested that most of this variation was due to chance. In logistic regression models controlling for individual characteristics, no practice-level factors were strongly associated with chlamydia prevalence. The present study did not use multilevel modelling techniques to examine the effects of practice level factors on chlamydia prevalence because these do not allow for the individual-level weights that were part of the sampling strategy.

Primary care consultation patterns in young adults

The standard method of calculating and presenting consultation rates demonstrates relative differences by age and gender, but does not show who does or does not attend the practice.[106,107] It was estimated in 1991/92 that 78% of all patients attend their practice each year,[107] but proportions stratified by age and gender were not provided. Survival methods were applied to estimate primary care use in a way that is more useful to those planning interventions: the cumulative proportion of patients attending the practice in a 1-year period. This showed that the majority of both men and women aged 16–24 years attended their practice at least once during the 1-year study period.

Although about one-fifth of young men and women were not contactable at the address registered with their general practice, 44% of them continued to use that practice as their source of primary medical care.

Implications for chlamydia screening programmes

Uptake of home-based testing, which gives privacy to patients and involves minimal additional workload for primary care, was lower than expected.[96] The response rates in this study were broadly consistent with comparable studies elsewhere in Europe, although more reminders were sent to encourage participation in the ClaSS project.[13,15,63] Reasons for not accepting the invitation to be screened were explored in in-depth interviews, which are reported in Chapter 4. Comparison of these sexual behavioural data with Natsal 2000[108] suggests that individuals who were more sexually active were more likely to take up the offer of postal screening. A systematic, population-based approach to screening may therefore be cost-effective even with modest response rates, as suggested by a Danish economic evaluation.[109]

Chlamydia prevalence was similar in men and women. This finding is consistent with the results of other population-based studies,[12–15,63] and emphasises the importance of including men in screening programmes.[22] Most opportunistic programmes only include men through contact tracing. Even in Sweden, where this is mandatory, only around half of partners identified are treated, so transmission of chlamydia continues. In addition, coverage and screening frequency of the eligible female population in Sweden has declined over time.[20,57] These factors, taken together, may explain why sustained reductions in prevalence have not been seen.[22]

Postal chlamydia screening could contribute to widening health inequalities if access is not

universal, particularly if access to screening is lower among people at higher risk of infection. In this study, the uptake of a postal invitation to provide home-collected specimens for chlamydia testing was lower in areas with higher deprivation scores, and fewer test kits were delivered in areas with high proportions of residents from non-white minority ethnic groups. No marked differences in prevalence were found according to area-level deprivation and ethnic group, but this in itself might have been due to differential screening coverage. At the individual level, the association between uptake and infection risk was not straightforward. Women with the highest prevalence of infection only appeared to take part following repeated reminders. Similar associations between risk of the target condition and readiness to participate in screening have been seen in relation to other screening programmes.[110,111] However, there were higher levels of sexual experience and partner change in participants in the ClaSS project, compared with national data from Natsal 2000. These issues are explored in greater detail in Chapters 4 and 5. It is difficult to generalise the findings from an active screening approach to opportunistic screening. Practices participating in the pilot studies received financial incentives,[1,60,61] but primary care participation in the National Chlamydia Screening Programme in England will be optional and probably unremunerated.[112] Practices serving disadvantaged populations tend to have both greater workload and costs, neither of which is fully compensated by deprivation payments.[113,114] Such practices may be less likely to offer an expensive additional service such as chlamydia screening.

The analysis of consultation behaviour showed that postal invitations reached a proportion of individuals who had not visited their general practice in the past year.[98] Optimal coverage in an opportunistic screening programme may therefore be obtained by combining high levels of screening of men and women using primary healthcare with periodic invitations to those not reached by this approach to participate in postal screening. Evidence for the effectiveness of chlamydia screening in reducing population prevalence and reproductive morbidity in women could be strengthened if strategies such as this were evaluated in RCTs incorporated within the phased introduction of national screening programmes.[22,66,97]

Chapter 4

Psychological, emotional and social effects of chlamydia screening

Objectives

The objectives of this part of the study were:

- to assess the acceptability of the screening and partner notification procedures used
- to describe the effect of screening on the well-being of those screened
- to establish the reasons for taking up and for not taking up the invitation to be screened
- to explore the views and experiences of primary care staff providing treatment and partner notification.

Both qualitative and quantitative research methods were used. This chapter describes a quantitative questionnaire survey to examine the effects of the screening process on psychological well-being, and individual in-depth interviews with people who were screened, those who declined screening and health professionals to explore the experience of the screening process and the opinions of health professionals. The results of interviews that covered the acceptability and experiences of partner notification are reported in Chapter 6 with the RCT.

Effect of chlamydia screening on anxiety and self-esteem

A version of the description of this study has been published by *BMC Public Health* under an open-access licence.[115]

Methods

Short questionnaires were sent to a random sample of those offered screening. The Hospital Anxiety and Depression Scale (HAD) was used as the main outcome measure.[116] This comprises seven item subscales for anxiety and depression, each with a total score ranging from 0 to 21. Scores from 0 to 7 are classed as normal/non-case, 8 to 10 as mild/doubtful case, and 11 or more as psychological distress that is believed to be clinically significant. In addition, the Rosenburg Self Esteem Scale was used as a measure of the possible stigmatising effects of screening for an STI.[117] This comprises ten items with a total score range of 10–40.

Questionnaires were sent at three time-points: baseline (1 month before the screening invitation and testing kit were posted); on receipt of the screening invitation (the questionnaires were incorporated into the study pack), and after receipt of negative test results. The plan was to measure responses in a cohort of individuals randomly sampled from all those invited to be screened. Because of low response rates to the screening study overall, in the last 12 study practices independent cross-sectional samples of individuals were selected at each of the three time-points.

The first two general practices were excluded from this study in case the publicity surrounding the launch of the ClaSS project influenced the baseline measurements. Data from the final questionnaire were not collected from participants who had entered into the case–control study, as their experiences would not have been typical of people participating in a population-based chlamydia screening programme.

Sample size

Data from a study of breast screening suggested that a standard deviation (SD) of 2.4 could be anticipated for paired differences in mean anxiety scores between baseline and receipt of an invitation (Dr Kav Vedhara, University of Bristol: personal communication, 2000). For a mean difference in anxiety scores of 1, a sample size of 355 would result in a 95% CI of 0.75 to 1.25. To have responses from a cohort of 400 people at all three time-points, allowing for non-response and attrition, a random sample of 1000 was initially drawn by applying a sampling fraction to each practice. For the final 12 general practices where a cross-sectional approach was used, it was calculated that to detect a difference of 0.4 SDs in anxiety scores at 90% power, 132 patients were needed in three independent samples. The response rate in the first 13 practices was used to inform the sampling fraction used in the remaining 12 practices.

TABLE 11 *Numbers in the study and reply and response rate, for each period, by sampling design*

	Before invitation		At invitation		After negative result	
	Sent, *n*	Returned, *n* (%)	Sent, *n*	Returned, *n* (%)	Sent, *n*	Returned, *n* (%)
Questionnaire reply rates[a]						
Cohort	687	297 (43)	680	177 (26)	172	126 (73)
Cross-sectional	624	250 (40)	763	241 (32)	146	101 (69)
All	1311	547 (42)	1443	418 (29)	318	227 (71)
Analysis response rates[b]						
Cohort	186	113 (61)	186	168 (90)	172	126 (73)
Cross-sectional	175	105 (60)	244	229 (94)	146	101 (69)
All	361	218 (60)	430	397 (92)	318	227 (71)

[a] Denominator: all individuals to whom questionnaires were posted. Numerator: all those who replied regardless of their chlamydia test result and regardless of their inclusion in the case–control study.
[b] Denominator: all individuals with a negative test result and not included in the case–control study. Numerator: of these individuals, those who responded.

TABLE 12 *Respondents according to gender and age for each period*

Sex	Age group (years)	Before invitation	At invitation	After receipt of negative result	Total
		n (%)	*n* (%)	*n* (%)	*n* (%)
Male	16–25	64 (29)	146 (37)	76 (34)	286 (34)
	26–39	13 (6)	21 (5)	18 (8)	52 (6)
	All	77 (35)	167 (42)	94 (41)	338 (40)
Female	16–25	123 (56)	209 (53)	113 (50)	445 (53)
	26–39	18 (8)	21 (5)	20 (9)	59 (7)
	All	141 (65)	230 (58)	133 (59)	504 (60)
Total		218 (100)	397 (100)	227 (100)	842 (100)

Statistical analysis

The primary analysis included individuals from both the cohort and the cross-sectional samples. Mean scores for anxiety, depression and self-esteem were compared at the three time-points using generalised estimating equations to allow for within-individual variation in the cohort. In addition, practice was incorporated as a fixed effect and practice-specific sampling fractions were accounted for by using appropriate weights in the regression analyses.

Results

Overall, 687 people from 13 practices were invited to participate in the cohort sample and, in total, 1533 people from 12 practices were invited to participate in the three cross-sectional study samples. Questionnaire reply rates to the cohort and cross-sectional approaches were very similar (*Table 11*). Forty-two per cent of individuals responded to the baseline questionnaire. After excluding individuals selected to be in the case–control study and those with positive results, response rates at each time-point were 60% or more.

Sixty per cent of the sample was female (*Table 12*). Only 13% of the sample was aged 26–39 years, reflecting the oversampling of individuals aged 16–25 years in the cross-sectional study as a whole (see Chapter 3).

The descriptive statistics for the three psychological measures according to age and gender are shown in *Table 13*. These were very similar whether from cross-sectional or cohort data. For example, the mean anxiety, depression and self-esteem scores for women aged 16–25 years in the cohort were 8.14, 3.63 and 7.46, respectively. The corresponding mean scores in the cross-sectional data were 7.87, 3.45 and 7.56. In the study population as a whole, scores

TABLE 13 *Anxiety, depression and self-esteem scores according to gender and age*

Gender	Age group (years)	Anxiety Mean (SD)	Depression Mean (SD)	Self-esteem Mean (SD)
Male	16–25	6.51 (3.6)	3.01 (2.8)	8.57 (2.0)
	26–39	6.33 (3.4)	4.20 (3.6)	8.35 (2.4)
Female	16–25	8.13 (3.9)	3.63 (3.2)	7.45 (2.7)
	26–39	8.28 (3.6)	4.42 (3.2)	8.47 (2.3)
All	All	7.49 (3.8)	3.51 (3.1)	7.96 (2.5)

TABLE 14 *Differences between mean anxiety, depression and self-esteem scores over the three time-points*

Time-point	Difference between means (95% CI)[a]	*p*-Values		
		Difference between time-points	Interaction with age band	Interaction with gender
Anxiety		0.0049	0.99	0.012
Before invitation	0			
At invitation	–0.66 (–1.23 to –0.09)			
Negative result received	–0.99 (–1.60 to –0.38)			
Depression		0.25	0.41	0.041
Before invitation	0			
At invitation	–0.47 (–1.09 to 0.15)			
Negative result received	–0.26 (–0.91 to 0.39)			
Self-esteem		0.26	0.27	0.98
Before invitation	0			
At invitation	0.12 (–0.26 to 0.50)			
Negative result received	–0.13 (–0.57 to 0.31)			

[a] From model with no interaction terms. Adjusted for age band, gender, practice and clustering effects, and weighted to account for sampling probability.

for all three measures were lower than conventional thresholds for clinical intervention in the majority of individuals, although there was considerable variation and some individuals did have levels that would cause concern. In general, anxiety levels were higher among women, but there were no differences across age groups. Depression scores were higher in the older age group and in women. Self-esteem was lower in the younger age groups, but only among women.

Table 14 shows the results of statistical models investigating changes in the three psychological measures over time, with full adjustment for the sampling design as well as the potential confounding effects of age and gender. There was a clear decrease in anxiety levels across time (overall $p = 0.0049$), and strong evidence that this pattern was different for men and women (p for interaction = 0.012). The decline in men's anxiety levels occurred when they submitted their test sample, whereas for women anxiety levels only declined on receipt of a negative test result. For neither gender was there any suggestion of an increase in anxiety as a result of receiving the invitation, at least among those responding to questionnaires. There were no clear patterns across the three time-points for measures of depression and self-esteem.

Qualitative studies of the effects of chlamydia screening on emotional well-being

Methods

In-depth interviews were conducted with individuals in the following groups: people who did not take up the invitation to be screened; those who were screened and received positive or negative test results; people who tested positive

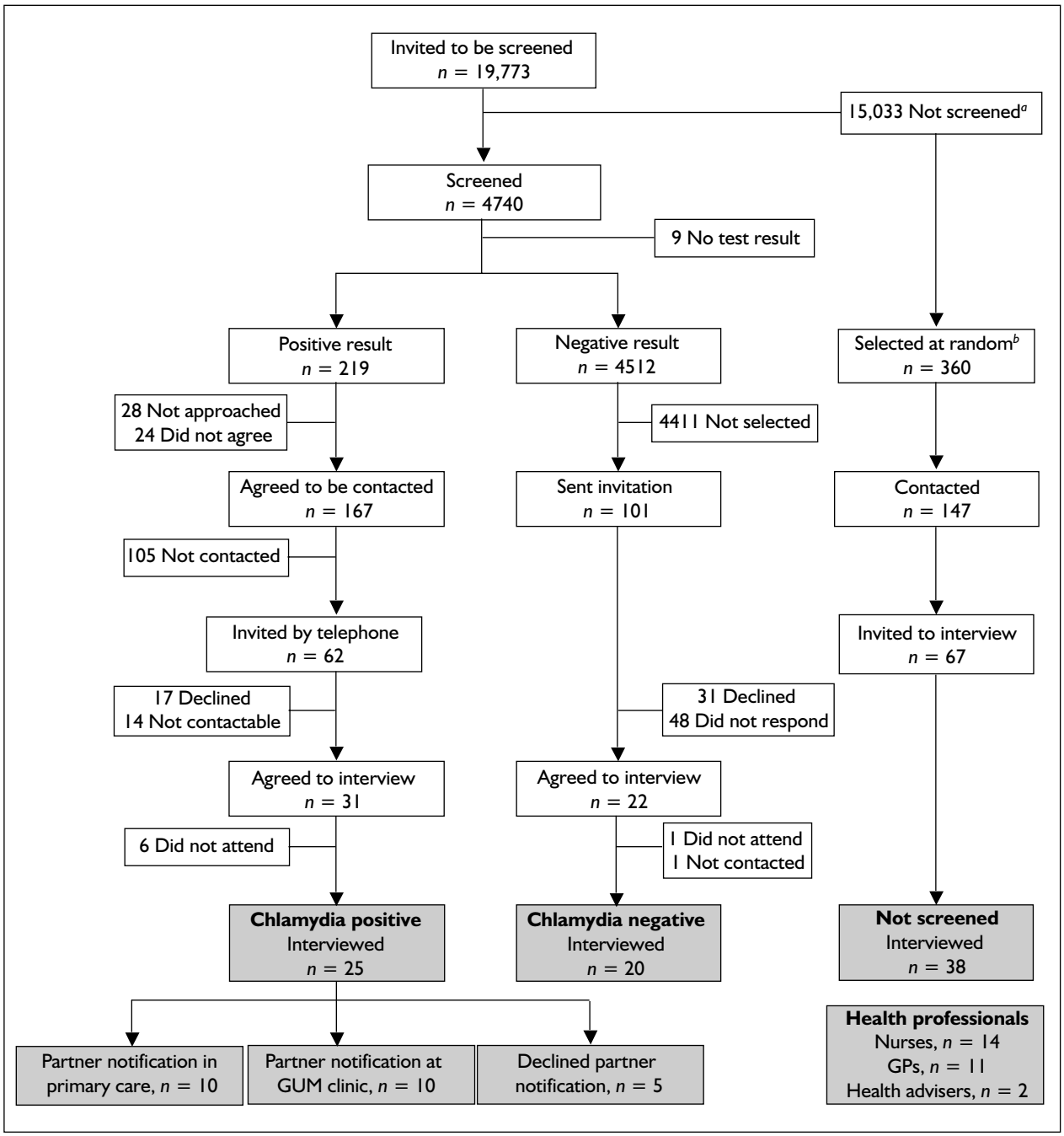

FIGURE 9 *Flow chart of qualitative research studies.[a] Includes 1926 who declined screening, 1532 who were not contactable, 3859 ghosts and 7716 who did not respond. [b] Selected from non-responders in six practices. GUM, genitourinary medicine.*

and had partner notification done; and primary care staff who provided the treatment and partner notification (*Figure 9*). The two research health advisers were also interviewed. The findings related to partner notification are reported in Chapter 6.

People who were screened for chlamydia were invited to an in-depth interview in one of two ways, depending on their test result. A random sample of those with a negative test result was sent an invitation letter from their GP, whereas practice nurses asked people with a positive test result after giving them their results and treatment. Interviewees were then selected purposively from those willing to be contacted to ensure a mix of gender, age and geographical location. In six practices people who had declined an invitation to be screened were invited by telephone. They were invited when non-responders to the survey were being followed up by telephone and sampled purposively to include a balance of men and

women from different age groups and geographical locations.

Interviews were conducted with people who had been screened either in their own homes, or at the University of Bristol or Birmingham, within a few weeks of giving results, with health professionals at general practice or university premises, and by telephone with people who were not screened. In all cases a checklist of topics was used to ensure that primary themes were covered in each interview. As the interviews progressed and other themes emerged, these were added to the list of topics and explored in subsequent interviews. Face-to-face interviews lasted between 45 and 60 minutes on average. Telephone interviews were somewhat shorter, lasting between 20 and 30 minutes.

Four project team members conducted the interviews (NM, GDW and RC interviewed people in all categories, and AG conducted interviews with GPs only) and recorded them on audiotape with the informant's permission. The interviewers made extensive written notes when the interviewee did not give their permission, or in the case of recording failure. Tapes were transcribed verbatim, then checked, and any identifiable material was anonymised. Transcripts were coded and indexed thematically, using the computer software package Atlas.ti (V4.2, Scientific Software Development, Berlin) to organise the data. Data collection and analysis ran in parallel. The coding index was added to or refined, and coded material regrouped, as new themes and categories emerged from subsequent interviews. In further analysis the constant comparison method of grounded theory was used to scrutinise textual data for differences and similarities within themes, keeping in mind the context in which themes were mentioned in each interview.[118] Descriptive accounts were then compiled, which were pooled to write the final account. The team met regularly to agree on the thematic categories used to index the interview transcripts and to check the plausibility of the data interpretation.

Results

Interviews were conducted with 45 women and men who took part in the screening studies, 38 people who did not respond to the invitation to be screened, and 25 health professionals involved in the ClaSS project.

Acceptability of chlamydia screening procedures

Results are presented from the 45 people who received an invitation to be screened and mailed a home-collected specimen for chlamydia testing. There were 26 women (17 with chlamydia, nine without chlamydia) and 19 men (eight with chlamydia, 11 without chlamydia). A version of these results has been published.[252]

Home testing kit

It became immediately apparent that although the kits (see *Figure 3*, p. 10) were dispatched to an individual, they were received into a household. Most people were not offended by being sent the testing kit:

> NM: So how did you feel then about this, this test pack being sent to your home?
>
> N08: Oh I didn't have a problem with that: no that didn't bother me at all.
>
> NM: No. That was alright?
>
> N08: No that didn't bother me at all. It's got to come somewhere. I'd rather have it here than at work [laughs]. No, no it was OK. I didn't have a problem with it, not at all.
>
> *Male, aged 32, tested negative*

> NM: Um how did you feel then about having this, this test pack turn up at your home asking you to provide a sample at home?
>
> N07: I had no problems with that at all: I just had to try and remember to do it first thing in the morning.
>
> *Male, aged 40, tested negative*

Receiving the testing pack was a source of mild embarrassment and discomfort for some and occasionally people experienced being sent such a kit stigmatising.

> RC: How did you feel about the pack being sent to your home as opposed to say you being called to go to the surgery?
>
> P25: Maybe I was a little bit embarrassed about it coming to the house cos I do, I do live with like a sort of a mixed group.
>
> *Female, aged 24, tested positive*

> NM: What was your initial response to that [receiving the screening pack]?
>
> N12: I think the initial response [to receiving the study pack] was bloody cheek [laughs] to be honest. I thought well it's a sexually transmitted disease and I've been married twenty years, why, why would I be chosen for this? … I think it was just sort of shock. I think if I'd have been sort of a younger woman maybe, I've been married twenty years, I've got three children, I'm respectable [laughs] … I wouldn't have thought I could have been approached for something like that.
>
> *Female, aged 39, tested negative*

In addition, a small minority of non-responders who were contacted by telephone, but declined to be interviewed, indicated that they had been affronted having been sent, unsolicited, a testing kit for an STI. Some practice nurses recalled people coming to the GP surgery with the kits or telephoning in, upset that they had been sent such a thing.

RC: Just thinking about the population that you have here, do you think they are quite happy to come forward or do you think it's only a selected group of people who'd come forward for the screening, given your knowledge of what your practice population is like in general?

PN5: Well I think in general they are quite happy to trot down and in fact we've had a lot. Some are very unhappy, or perhaps not them, their parents.

RC: Really? So you've had some folk coming back about it [the testing kit]?

PN5: Yeah, don't want to know about it. Couple of parents have been quite angry with it as it happened. And I think a couple of youngsters have been quite embarrassed about the whole thing.

RC: And have they rung up the practice about that?

PN5: Yeah, yes they have and I know one of the nurses who was rung ran foul of one of the fathers. Although he [the son who was sent the pack] sent his swabs off.

RC: So they'd sent the samples back?

PN5: Yeah and uhhh to make an appointment she's [nurse colleague] had to run the gauntlet with father. So that's been very difficult.

RC: So that's one of your colleagues, who's got a result and has been trying to get the young person to come in and see her and that's been difficult?

PN5: Yes 'cause he's obviously told his family about it.

Later in the interview the interviewer asked:

RC: And have you had other incidences where people have got in touch with the practice and expressed their unhappiness?

PN5: Yes, yes. I haven't come across any personally but there have been and I've had the feedback. But they certainly don't want to have been bothered by this [testing kit] and also if they haven't had one package they've had another one, they've sent it back but they've still got another one and, you know, they've flung it across the desk sort of thing.

In a separate interview a practice nurse recalled a telephone call to the surgery:

PN2: No. We had one irate lady on the phone with um, what happened to her. She had a note put through her door by the postman to say that there was a parcel for her because it was recorded delivery I believe. And, when she, it was for her daughter, and when she rang up [laughs] the post office said to her oh it's alright, it's that sex thing [laughs]. So mother wasn't amused.

RC: Right. So she got on the phone to you?

PN2: Yes. Yes. She was on the phone to us.

Those who responded to the invitation to be screened approved of the home-testing kit. They welcomed the privacy and convenience it afforded and most experienced no problems providing a urine sample.

GDW: And how did you feel in general about being asked to sort of do these procedures yourself at home?

P17: It was quite nice actually because, you know, to be able to do it in your own time at your own convenience, because they're not the most genteel things to have to go to a surgery to do

Female, aged 26, tested positive

NM: Um. Did you mind actually providing a urine sample and sending it off?

N04: No, no it was fine. I think, I think when we was kids I've given a urine sample for so that kind of took me back to being kids and it was fine. Not, not a hassle at all and kind of packed it off.

Male, aged 24, tested negative

A few people were worried that a urine specimen might leak in the post.

NM: Would you have preferred perhaps to have gone to the GP surgery to do it or?

N07: Well no I mean it's really it's, it's just as easy doing it at home than it is in the GPs. I mean all you're doing is you know is filling a bottle, and then put the lid on. The only thing that crossed my mind I, you know, if it, what if it does break in transit. That was the only thing that did cross my mind. Maybe you could do the sample at home and then drop it into the doctor. But no I, I had no, no problems about doing the sample at home.

Male, aged 40, tested negative

Some women were put off by having to provide a vulvovaginal swab.

NR31: They just gave me, they just gave me this little instrument [vulvo-vaginal swab] and said, "Off you go". Well that's quite hard to explain especially for a 17-year-old girl.

Female, aged 17, non-responder

NM: How did you feel about the idea of providing a swab sample?
NR22: Um no I wasn't too keen about it … I should have gone, gone there [to the GP surgery] to have it done.

Female, aged 18, non-responder

In some cases, women associated the vulvovaginal swab with having a cervical smear for cervical cancer screening.

> NR34: And I've had chlamydia before if I remember. After the rape I went to X hospital in [name of city] and they tested me for chlamydia and I had, I don't know they found some abnormal cells or something like that they had to remove.
>
> *Female, aged 32, non-responder*

> NR36: Would I be asked to do it again if you haven't got these, you know, got suspicious cells?
>
> *Female, aged 25, non-responder*

Impact of the screening process on emotional well-being

Informants highlighted how anxiety can be brought on at any stage of the screening process. Simply receiving the invitation to be screened made some people anxious because it raised the, hitherto unconsidered, possibility of having an STI. Waiting for the test results was also reported as an anxious time for some, but others reported that they had simply sent the test samples off and had given it no thought until they received a response.

Testing negative

For those receiving negative results any anxiety was soon relieved. In line with the results of the quantitative study, this group did not seem to experience any adverse effects as a result of participating in the screening programme.

> NM: The fact that they were asking you to, to do a, a test for chlamydia. You were OK about that?
>
> N19: Yeah because, like I say, I mean before I never sort of really thought anything about it. But it did make me think, you know, what if I have got it [chlamydia] and I don't know that I've got it? Cos there's not really any signs is there, not really. I thought, well, you know, I could, I could have had it for like two or three years and not known that I had it. So it was quite like, you know, after I done it and was waiting for the result to come back, and then like when it was negative, I was like, phew thank God for that. But until that point you sort of think well, you know, I could have it and not know.
>
> *Female, aged 23, tested negative*

> N03: So I think the 'what if' [I had chlamydia], yeah, it was niggling in the back of my mind until it come back and then when it [the test result] comes back you open it, you read it and you think right, ok then, thank God for that.
>
> *Male, aged 20, tested negative*

> N14: I think it was a few weeks before it came back. I wasn't anxiously waiting for it. I wasn't thinking oh gosh it hasn't come yet.
>
> NM: Right
>
> N14: I didn't, I wasn't overly anxious about it.
>
> *Female, aged 37, tested negative*

> NM: So after you'd done the urine, sent it off, put it in the post box, wondered if it was actually gonna be sent be delivered from that post box, what was going through your head in that time?
>
> N08: I'd forgot all about it.
>
> NM: Before you got the results back?
>
> N08: I forgot all about it then. I honestly forgot all about it. It wasn't until the letter come back I sort of realised again. But I did I just forgot. Once it was over and done with, I forgot all about it. I didn't realise it, we'd get a letter back anyway.
>
> NM: Right. What did you think or?
>
> N08: I just thought if there was something wrong you'd get one and when it, like I got this letter, I mean I didn't know what it was until I opened it and when it told me what it was anyway there was no problem but I, I didn't bother about it at all then. Once I'd done the thing it was all over and done with.
>
> *Male, aged 32, tested negative*

Testing positive

Most informants who received a positive diagnosis of chlamydia were shocked and the news was a source of considerable distress for some. Specific concerns were the possibility that they might have other STIs, and the need to inform current and recent sexual partners of their test result. Participants also recognised the benefits and were, on the whole, glad to have been tested.

> RC: So what were you feeling when she [the practice nurse] actually was telling you? What was going through your mind, can you remember?
>
> P14: That what? That I was positive?
>
> RC: Yes when she told you that you were positive.
>
> P14: I was shocked. It didn't worry me cos I know you cannot have, it can stop you getting pregnant and stuff. That didn't worry me but it's just unbelievable really. To think I was so sure when I went in there I was gonna be negative. And I was so glad I did it. I just kept saying … I said to her 'I'm glad I done it then so'.
>
> RC: So once she [the practice nurse] told you the result what happened next in that consultation?
>
> P14: She just said 'How do you feel about it?' and I said 'I'm shocked' and she said 'Right take these tablet things.' So I took those. Then she said 'Right, I'll give you another packet. You've got to do another one [test] in six weeks' or something 'to make sure that it has gone'. That was about it really. Bit of a nasty shock.
>
> RC: Were you upset?
>
> P14: No cos I knew that I was gonna get sorted out so … so … [sounded upset … voice cracking slightly].
>
> *Female, aged 24, tested positive*

Women often experienced a positive chlamydia test result as stigmatising. Many women felt polluted or contaminated and feared that others, learning of their diagnosis, would label them as unclean or sexually promiscuous.

P09: In a way, first of all I felt really dirty. I didn't think it would be me as it made me feel dirty.

NM: Why do you think you felt dirty?

P09: Well it makes you think you're like a tart innit and when you say disease you think oh my god.

Female, aged 23, tested positive

P10: I just [laughs] I just really didn't want to speak to anyone else about it. Didn't really want anyone to know cos I felt bad enough as it was. So I didn't want anyone else knowing … You know [laughs] hardly slept with many people at all and I've got something, you know, I've got chlamydia. So I think, that was, that upset me thinking that. Thinking well, you know, if you can get it being careful, then God knows what else you can get, or what else can happen.

Female, aged 21, positive

A third of women with a positive chlamydia result mentioned unanswered concerns about future fertility.

P13: It's just, it's just one of those things. Just been unlucky at least I know about it now and done something about it and hopefully won't have any long-term implications and …

NM: Does that concern you?

P13: Um yeah, I mean obviously, I mean cos the that leaflet really only raises infertility as a problem that's related to it. And that does concern me because long term I do want to have children. So I s'pose the only, the only issue I've still got outstanding from the study is, is, is there any way of telling whether or not, if it is an issue or not. You know, obviously I did ask that to that nurse, but she sort of [laughs] didn't really help much so … I do see that because I have been tested and it has been caught now that's reduced the, the, the likelihood of that happening. But, you know, I don't know. I, I'd like to know whether it is an issue or not. I'm quite scared about the outcome of that obviously, but I think it would be something I'd like to know. And I think it's something that, that, you know, is probably a concern for a lot of people who are who do get a positive result and maybe they should, you know, that leaflet doesn't really answer the questions that, that I have about that. And I don't know whether anything more could be produced but I think that it's probably something better discussed with a, with a health professional rather than just reading about it so.

Female, aged 25, tested positive

The men interviewed generally did not report having an emotional reaction to the diagnosis and did not appear to feel stigmatised by it. Their attitudes seemed to be more one of regarding chlamydia as a minor sexual hazard. Men were, however, aware that there were more serious STIs to which they could have been exposed and this was voiced as a concern.

P02: But I got it and I expected it so it wasn't, it wasn't a problem like and then I was thinking to myself, I was chatting to the nurse about it, and I said I've got this so she, she made the appointment for me down the GU clinic. I asked her that time, I said 'look if you could make a phone call to ask for a appointment on whatever day it was now' I, I said 'like could you ring them up and ask for me to be tested for everything.' She said 'like what?' I said 'well everything like: hepatitis, HIV, syphilis, gonorrhoea, chlamydia again, everything, the works'. I had everything done like. You had that thing stuck up you: yeah but I was happy with that.

Male aged 22, tested positive

NM: OK and what does it mean to you like personally knowing that you've had chlamydia?

P01: Like I say it don't really bother me.

NM: No?

P01: It's like no, it's knowing that I've had it, er I don't know, it's like same, the way I look at it, it's sort of similar to thrush. I know that it's quite common. I know that it's a high risk you're gonna get it, cos I think it's just going up and up, the chances of getting so, it doesn't really bother me. As far as I see it's sort of like thrush as long as I know I haven't had anything like you know well anything serious sort of thing.

NM: In what way serious? What would you class as serious?

P01: Right you know well yeah like gonorrhea [laughs] things like that you know. This doesn't really bother me.

Male, aged 24, tested positive

Patient satisfaction with practice nurse consultations

Interviews with those who had a positive test result indicated a high level of satisfaction with the care provided by the practice nurses. There were only occasional suggestions that the nurses had not been totally comfortable with their role, or that they had not fully answered participants' questions. As noted in the previous section, a number of women who received a positive diagnosis felt that their questions about future fertility had not been dealt with adequately.

P11: I, I, I'm sure I had to have my results at a certain part of the interview, sort of thing, that I was with her [the practice nurse]. And I, I was crying. I was really

upset and she was really nice. Really, really nice and like she was sort of saying, I suppose she was reassuring me more in saying things like 'lots of people get it' and different things like that. And she was just really reassuring me about it, sort of that I wasn't the only one, and there are obviously more, and she was just, oh she was brilliant, absolutely fantastic.

Female, aged 24, tested positive

NM: OK. How do you feel um overall then about that consultation with the nurse, like how it went generally and the advice she gave you and stuff like that?

P05: Oh yeah I thought it was totally cool: really good. It was quite nice the fact that I was a bit shocked that basically I found out that I got it. She was quite nice in sort of her reaction really. She sort of made me feel a bit better about it.

Male, aged 26, tested positive

P22: I'd just say probably it's an STD um and I'd know the symptoms, 'cos I had them and if it goes untreated you can sort of, get, sort of, your tubes can be damaged or something can't they? That's what I'm worried about now. Cos I think if I've had it on and off for that long. Like who knows what damage it's done.

NM: Have you spoken to anyone about that?

P22: No

NM: No?

P22: I did say to the nurse, and she sort of said 'Oh well, you know, well'. She didn't really say anything. She just sort of said 'Oh right' sort of thing. I think she wanted to get on and it was all written down. She was lovely, don't get me wrong, but I think she was like, not a hundred per cent comfortable doing it. So God knows what she would have been like if I was like on edge and like completely shocked so.

NM: And is this something that is still in your mind or has it subsided a bit?

P22: No it's still there. It's still there.

Female, aged 24, tested positive

Reasons for responding or not responding to an invitation to be screened

The results of these interviews, with 38 people who decided not to be screened, have been presented at an international conference and are being written up for publication.[103] A number of distinct elements were identified that characterised the accounts of those who decided to respond to the invitation to be screened and those who decided against participation. Foremost was whether they saw chlamydia screening as being relevant to them. On receipt of the invitation, many of those interviewed seemed to have undertaken a form of personal risk–benefit assessment.

Deciding to be screened

For those who collected specimens at home and returned them to the laboratory, the decision-making process involved consideration of their personal risk of having chlamydia and the potential benefit of being tested.

NM: What prompted you then to ask to be tested?

P11: Somebody I knew had had it and been treated and they'd come back and sort of said it can cause infertility. I suppose I knew, but when it's sort of somebody you know's caught it, you think cor that is a bit close to home. … When somebody I knew sort of got it I thought God what if I've got it?

Female, aged 24, tested positive

In some cases this assessment appeared to involve an acknowledgement of the population or theoretical risk of being infected, even if they felt that their own lifestyle made it unlikely that they would have chlamydia. It therefore made sense to be tested.

NM: And what then prompted you to actually go ahead and be tested?

P12: I think it's the fact that I'm sort of like sexually active. I think you do worry about things like that. Cos no matter how careful you are, there are chances.

Female, aged 19, tested positive

Family and friends had some influence on individuals' decision-making. In the case of those who responded, they generally played a role in encouraging participation. This was particularly apparent where the informant was a younger adult living in the family home. Parents seemed to have tried to persuade their son or daughter to be tested.

NM: Yeah [laughs]. Um what did you do then with the test pack when you got it?

N09: Did it [laughs].

NM: Did it, yeah?

N09: Yeah just did it [laughs].

NM: That quickly?

N09: Well I waited a few days, with my Mum and Dad pestering me to do it once I said I would.

NM: Oh really [laughs]?

N09: Eventually got round to it and I think my Grandma took it down to the GP clinic. It was, it didn't take that long, no. Did it pretty soon, yeah.

Male, aged 17, tested negative

However, this was not always the case and it depended on the cultural background of the family and whether it was considered acceptable for young people to be sexually active outside marriage.

Deciding not to be screened

For non-responders the personal risk–benefit assessment resulted in a feeling that chlamydia was not personally relevant to them, that they were at low personal risk of having contacted chlamydia, or that there was little personal benefit to them of being tested.

> NR05: It doesn't affect guys apparently I read. I sort of lost interest after that.
>
> *Male, aged 19*

Some informants, particularly young men, seemed to be unable to assess the relevance of the invitation to themselves.

> NM: OK. And what did you do with the test pack when you got it?
>
> NR22: Um I don't know. I was a bit puzzled by it at first really but.
>
> NM: Really?
>
> NR22: Yeah.
>
> NM: In what way?
>
> NR22: Um, er [long pause] I don't, oh I don't know. Um just a bit, I didn't really know what to do. [pause] I think, [pause] I don't know. A bit surprised really. Like, I don't know. I'm not really too sure.
>
> NM: What was going through your head?
>
> NR22: Um, er, I don't know, I just, just thinking oh my God, what's this kind of thing, I think really. Um I didn't mind at all. I was just, you know, um [laughs].
>
> *Female, aged 18*

Taking responsibility

A further distinction between those who did and did not respond was that those who responded were prepared to take on responsibility for their health and those of their partners. Some who responded also articulated a sense of a responsibility towards society and to the research project as their rationale for participation.

Responsibility for your own health

> N11: I don't know because it's like peer pressure in a way. If, all my mates didn't do it, I'd probably say argh 'I won't do it, as well.' Because I'm like a freak if I do it and they don't. But I probably would still of done it, probably, because it's like for my own sake rather than anyone else's.
>
> *Male, aged 17, tested negative*

Responsibility for a partner's health

> N11: Well he (respondent's friend) didn't know whether he should do it or not, same as me, because we didn't really have an intimate sexual relationship except like ages ago … We've only slept with a few women at that and we didn't really know what they had or anything. But we thought just to be sure. Because I really done it for my girlfriend rather than me, because it makes you infertile, so yeah I mainly done it for her as well.
>
> *Male, aged 17, tested negative*

Responsibility to society and research

> NM: So can I ask why you actually decided to participate and provide a sample?
>
> N14: I've got young children that are obviously going to be growing up into adults and if it can be something that can help and prevent and increase people's awareness of things then I feel that's a good thing … .
>
> *Female, aged 37, tested negative*
>
> N04: [Reason agreed to participate] Research in a, in a nutshell, being part of research, which I'm quite happy to be part of.
>
> *Male, aged 24, tested negative*

Non-responders' accounts, in contrast, suggested unwillingness or a lack of readiness to take on any responsibility or, in some cases, a sense that their not taking part was of no consequence.

Did not want to or not ready to take on responsibility

> NR05: I would have actually answered the pack and whatever but I never actually got round to completing it. I thought it was perhaps more for educating for girls.
>
> NM: Why do you think that?
>
> NR05: Well because it doesn't, if it has no effect on men … If it has no effect on myself [laughs] … I wouldn't feel that bothered about it. I wouldn't go out of the way to test myself for it if it had no effect on me.
>
> *Male, aged 19*
>
> NR28: I'm in a bit of a catch 22 situation. I would provide a sample but I'm concerned that if I do have it [chlamydia] what: 1. My reaction would be; and 2. Having to tell all my exes.
>
> *Female, aged 23*

Did not feel their taking part in the research project mattered

> NM: How do you feel now about your decision not to have gone ahead with the test?
>
> NR02: Um no, I'm not too like, I don't mind if I don't do it cos other people have already done it so I can't imagine it made a huge difference me not doing it.
>
> *Male, aged 18*

Health professional's experience of population screening for chlamydia

The researchers asked 14 practice nurses and 11 GPs about their experience of taking part in the ClaSS project, and of dealing more generally with chlamydia and with chlamydia screening. Practice

nurses were generally enthusiastic about their involvement in the ClaSS project. They were, however, a self-selected group because they had all volunteered to take on this role. They acknowledged the help and advice given by the research health advisers as being invaluable.

> PN14: I have to say that they were, [name of health adviser] was very supportive and you felt that you could just ring him up and ask [name of health adviser] anything and he would come and see you. So I felt that there, that you weren't on your own. There was always someone out there that you could ring for help.
>
> GDW: And is there anything else you want to say about how you think the research is going or how it's been for you?
>
> PN13: I think it was a good ideal [sic] to have [name of health adviser] around cos he was very supportive and very helpful and even if he wasn't actually available when you phoned he would ring back within an hour.
>
> PN13: I had to ring him for advice on one or two occasions and he's been very good at coming up with it. He was really, really good. Very supportive. And I actually, you know, someone who you can really rely on, sort of be there, if you like. Just as well [laughs] and he's obviously very knowledgeable isn't he, he knows his job, he knows all the answers.
>
> PN10: But certainly [name of health adviser] I've got to say extremely supportive. Any queries I'd had, if it was an answer message he'd ring me back. So that is very, very good. So if I had any worries or even worrying that because there was times I was perhaps going on holiday it was literally left to myself. What are we going to do? You know, it was just quite nice to fall back on him. It was a bit of reassurance, 'No that'll be fine and I'll see them at another time.' So that was, it was very good having him so.
>
> RC: To have that back-up?
>
> PN10: Back up yeah. Because I didn't feel I had any back up from anybody in the practice at all.

Practice nurses revealed that they had been initially apprehensive about taking on the new role, but all those that we interviewed found they adjusted to it fairly quickly. They welcomed the opportunity it had provided to extend their knowledge and experience of sexual health work. Most reported that being involved in the project had improved their sexual health nursing practice by making it more likely that they would explore sexual health issues in a routine consultation, and because they felt much more confident about taking a sexual history.

> PN8: And that's given me the impetus really, through doing the chlamydia study, that opportunities where, you know, as I say, travel health, I probably wouldn't have discussed it in as much depth as I do now, in that, you know, when they come for their vaccinations we not only talk about travel vaccinations but also other health issues and that does include sexual health.
>
> RC: So you mentioned that the training day had been, for you, a good experience. What particular things did you find helpful in the training day?
>
> PN7: I think the sexual history training and I think being sort of told by someone, to say, it's actually OK to ask somebody straight out if their partner is male or female. I think it's, I don't know, whether it's just giving you permission or just sort of being reassured that actually yes it is OK. I'm very, very, very, much more honest now and I will ask straight questions. I don't beat around the bush where perhaps I used to ask six questions where I could have just asked one.

GPs were generally happy about the way in which the study had progressed and had not found that it impinged greatly upon them. They were, however, concerned about the resources available to them to take on sexual health work in primary care. Some also indicated that they would prefer to have someone from outside the practice come in to take on this work, rather than have existing staff do it.

> AG: Recent government initiatives have argued that primary care should play an increased role in the provision of sexual health services – how do you feel about these initiatives in the context of this practice and your own experience of sexual health work?
>
> GP1: Oh I think we should provide an increased role no question – I think we should provide an increased role in nearly everything. We'll need some money because it takes a long time. If we're really going to do contact tracing we'd probably have to employ someone separate.
>
> GP5: Recent government initiatives have also suggested that we will be running an improved service for coronary heart disease, mental health, diabetes, medicines management, every – you know, lots of initiatives under the sun. And the answer to all of them is, 'Yes that sounds like good practice and a good thing for our patients to do, but when are we going to do it and what staff are we going to use to do it?' So the issues are the same. … And yes primary care probably can do, and we probably already do do for a small number of people. But the issue is a big one in terms of time and resources.

Discussion

The results of these quantitative and qualitative studies about the effects of chlamydia screening on the individual suggest that asking men and women aged 16–39 years to collect specimens at

home and mail them to a laboratory for testing was generally well accepted. Sending out unsolicited specimen collection kits for an STI was mildly embarrassing to some recipients, but seemed to cause real offence to only a small minority of people. Receiving an invitation for screening and waiting for results caused mild anxiety in some people. Quantitative measures showed that, at the group level, postal chlamydia screening did not raise levels of anxiety or depression, or decrease self-esteem among those with negative tests.

Methodological issues

The strengths of the studies were that both quantitative and qualitative methods were used to examine the psychological and emotional impact of chlamydia screening, and that all stages of the screening process were examined. The qualitative studies involved in-depth interviews with a large number of informants who were invited to take part in the ClaSS project, including people who had decided not to take part in the screening study. The main weakness of the quantitative study was that the method of sampling had to be changed part of the way through the study because of the low overall response rate to the screening study. The authors do not think that this affects the conclusions drawn from this study because reported levels of anxiety, depression and self-esteem were very similar with both sampling methods. It is possible to take into account the use of the two sampling designs in the statistical analysis. It is possible that the ClaSS project screening study had deleterious effects not captured by the measures that were used.

Comparison with other studies

No adverse psychological effects of an active approach to chlamydia screening were detected among those who took part in screening and had a negative test result. Indeed, in both women and men, anxiety levels decreased from their baseline levels. The mean levels of anxiety and depression measured at any of the stages were below any treatment threshold. These results are consistent with those of screening studies for breast and cervical cancer.[119–122] Similarly, Götz and colleagues. found that among men and women aged 15–29 years in The Netherlands who responded to an invitation to be screened for chlamydia by posting home-collected urine specimens, 42% felt relieved at receiving a negative result and only a small minority of those receiving a negative result remained anxious.[123] These studies suggest that sending unsolicited chlamydia specimen collection kits as part of a screening programme does not harm the vast majority of those screened who do not have the infection.

Gender and chlamydia screening

Chlamydia testing and screening usually focuses on women because most activities take place opportunistically in healthcare settings used mainly by women. Only recent large studies of active screening using home-collected specimens have included men.[12–15,62,123,124] Findings from both qualitative interviews and quantitative questionnaires in the ClaSS project suggest that men and women reacted differently to being invited to take part in chlamydia screening, being tested and receiving a positive diagnosis. Response rates were lower among men than women in this study and in other studies.[12–15,62] In-depth interviews with those who did not send in samples for testing suggest that many of them did not see the test as relevant to them or that they were very unsure about what the invitation and the test meant, and therefore were unable to assess its relevance. Among people who took part in screening and tested negative, anxiety in men fell once they had submitted a urine sample for testing, whereas for women anxiety fell when they received a negative result. Men and women also responded differently to news of a positive chlamydia test result: women found the diagnosis upsetting and anxiety provoking, while men generally took it in their stride and did not seem to be unduly concerned by it. Some men did recognise the possibility of exposure to other, as they saw it, more serious, STIs. Reactions to testing positive for chlamydia in women,[82] and gender differences,[125] have been previously reported in healthcare settings. Many women experienced the diagnosis as distressing, particularly because of the felt stigma incurred. To reduce such distress further efforts are required to destigmatise chlamydia. It is important to note that none of those interviewed regretted their decision to participate in the screening and most were glad that the infection had been detected and treated.

Implications for chlamydia screening

People who had taken up the invitation to be screened for chlamydia generally welcomed the convenience and privacy of home-collected specimens. Some women, however, reported that they had not taken part because of the request to provide a vulvovaginal swab. This is consistent with the findings of an RCT where response rates to an invitation to be tested for chlamydia were lower (32% versus 47%, $p < 0.05$) when the testing kit included a request to provide a vulval swab.[126]

This is important for future recommendations about chlamydia screening using non-invasive specimens in women. Laboratory studies suggest that vulvovaginal specimens might achieve slightly higher detection rates than female urine specimens (see *Table 35*, p. 68). This gain in sensitivity may be offset by a reduction in screening uptake in postal screening programmes. It is not clear whether women being offered chlamydia testing in healthcare settings have the same concerns.

News of a positive chlamydia diagnosis is unlikely ever to be welcomed. In general, however, informants reported very positive interactions with practice nurses and this consultation did not contribute to the sense of stigma that many of the women felt. The area in which questions seemed not to have been comprehensively addressed was that of future fertility in women.[82,127] This reflects the existing epidemiological uncertainty.[20,21] Further work is therefore needed to establish the prognosis of chlamydia and also to determine the best process for providing and discussing positive test results.

The evidence from the qualitative interviews clearly shows that practice nurses who had taken part in a short training course were able to take sexual histories, give positive chlamydia results, dispense treatment using patient group directives and do partner notification (Chapter 6) confidently and effectively. GPs were, however, very clear that additional resources would be required to fund an increase in sexual health work generated by chlamydia screening.

Chapter 5

Case–control study

Objectives

The objectives of this part of the study were:

- to identify demographic and behavioural factors associated with chlamydia in a general community sample of men and women in a community prevalence survey
- to define risk profiles that could potentially be used to assign risk status in screening programmes.

Methods

A questionnaire was designed for self-completion by pen and paper using questions from Natsal 2000[108] and additional questions about genital symptoms in the month before the survey. The complete questionnaire can be viewed at http://www.chlamydia.ac.uk/pdf/casecont/

Cases

All individuals with positive chlamydia test results were eligible to be cases (*Figure 10*). The questionnaires were sent to their home address at the same time as sending an appointment to receive their test result at their general practice.

Controls

For each chlamydia case two negative controls were selected (*Figure 10*). The controls were the next two respondents to the screening survey who were of the same gender and were in the same broad age band (16–25 or 26–39 years).

Both cases and controls were asked to complete the questionnaire and to bring it to the surgery. The practice nurse asked whether any help in completing the form was needed, before collecting the questionnaire and giving the chlamydia test result.

Statistical analysis

Results from men and women were analysed separately, and conditional logistic regression was used to estimate odds ratios for associations between chlamydia infection and demographic, behavioural and sexual behavioural factors in univariable and multivariable models. The multivariable model included factors that were associated with chlamydia in univariable analysis or that were deemed a priori to be important.

Results

In total, 219 people with positive chlamydia results were selected as cases. *Figure 10* shows the flow of patients who participated in the study. Individuals aged 25 and over were excluded because, after restricting sampling in the cross-sectional survey to 16–24 year olds there were too few older adults for comprehensive analysis. The response rates were, in cases 75% (148/197) and in controls 66% (246/374). Women were more likely to respond (75%) than men (63%).

Table 15 summarises the main descriptive characteristics of the study population. The majority of cases and controls were in full-time education or employment. There were very few respondents from minority ethnic groups. A high proportion of respondents reported having ever used illicit drugs.

There were very few responses from people who had ever had same-sex partnerships (*Table 16*). Most controls had only had one lifetime partner and no new partners in the past 12 months. About half of cases had ever had eight or more partners and two or more new partners in the past year. One-quarter to one-third of both cases and controls had had a concurrent relationship in the past 5 years.

Symptoms potentially related to chlamydia were frequently reported by women, both cases and controls (*Table 17*). Among men urethral discharge and dysuria (pain passing urine) were reported by about one-quarter of cases and one-tenth of controls. A higher proportion of women than men reported ever having had an STI or visited a GUM clinic.

Tables 18 and *19* show the results of univariable and multivariable associations between selected risk factors and chlamydia in women and men, respectively. In women and men, there were strong

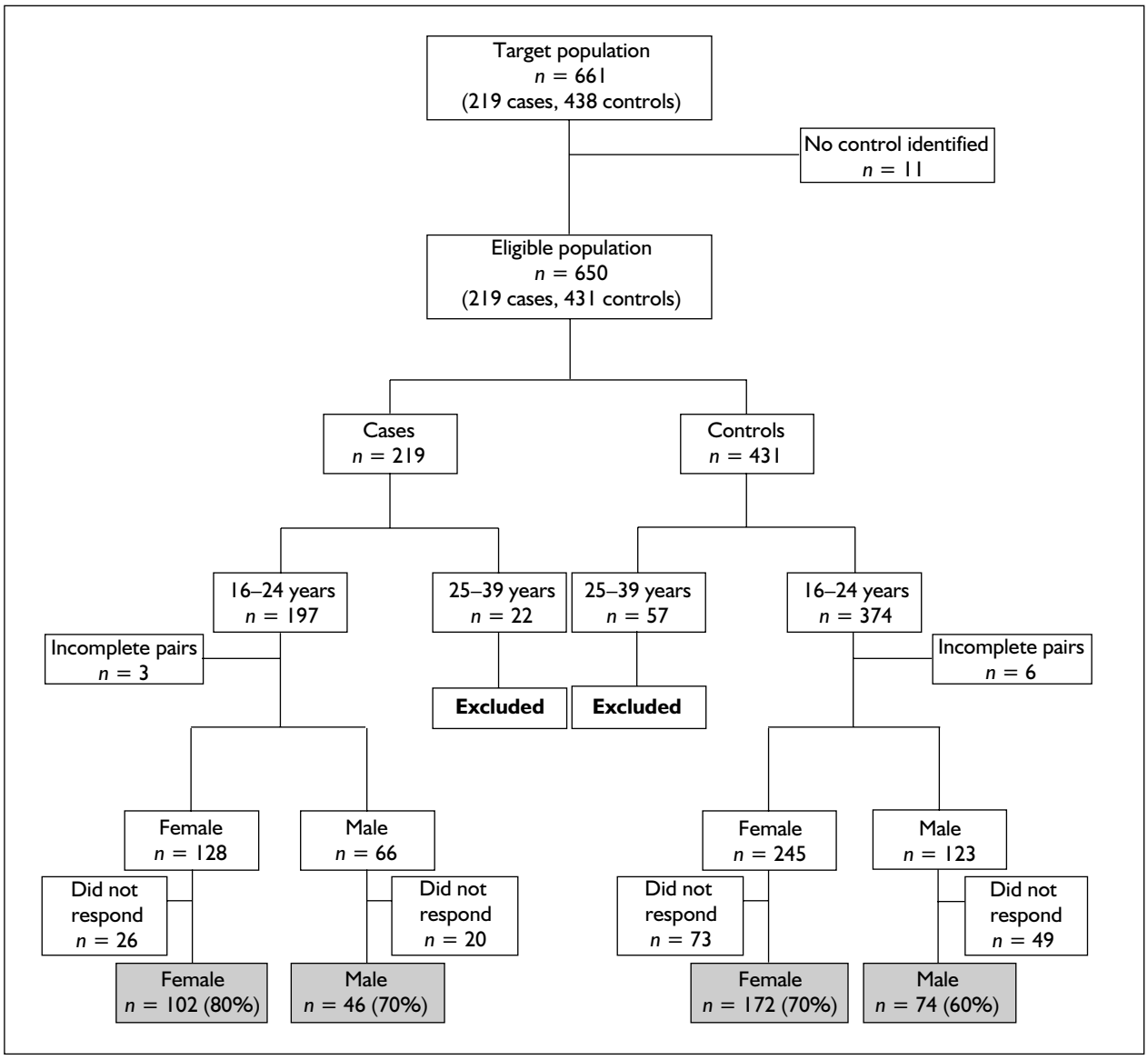

FIGURE 10 *Flowchart of people through the case–control study*

univariable associations between chlamydia and an increasing number of opposite-sex lifetime partners and partners in the past year. In men but not women, not having used a condom during last sex, smoking and ever having used cannabis were strongly associated with chlamydia. Genital symptoms of vaginal discharge and urinary frequency were associated with chlamydia in women. In men, the odds of chlamydia were increased in those with urethral discharge and dysuria, but confidence intervals included unity. Being married was associated with a lower risk of chlamydia in women but not men. Ethnic group was not strongly associated with chlamydia, although odds ratios were higher in women from black and Asian minority ethnic groups compared with white women.

In multivariable models, among women no factors remained strongly associated with chlamydia (*Table 18*). There was a trend for increasing numbers of lifetime partners ($p = 0.074$) to be associated with chlamydia and for married women to be at lower risk (OR 0.37, 95% CI 0.13 to 1.08, $p = 0.069$). The odds of infection also remained higher in women from minority ethnic groups (black Caribbean and other compared with white 5.62, 95% CI 0.70 to 44.83, Asian and other compared with white 4.83; 95% CI 0.77 to 30.36, $p = 0.13$). There was a weak association with urinary frequency in the past month (2.03, 95% CI 0.80 to 5.19, $p = 0.14$), but not for vaginal discharge or any other symptoms. In men, after controlling for potential confounders, no factors were strongly associated with chlamydia (*Table 19*).

TABLE 15 *Demographic and social characteristics*

Characteristics	Men				Women			
	Cases *n* = 46	(%)	Controls *n* = 74	(%)	Cases *n* = 102	(%)	Controls *n* = 172	(%)
Demographic								
Age group (years)								
16–19	15	(33)	39	(53)	47	(46)	72	(42)
20–24	31	(67)	35	(47)	55	(54)	100	(58)
Marital status								
Single	39	(85)	69	(93)	92	(90)	132	(77)
Married/living as married	4	(9)	4	(6)	9	(9)	34	(20)
Ethnic group								
White	38	(83)	62	(84)	89	(87)	154	(90)
Black Caribbean/Black other	6	(13)	4	(5)	8	(8)	6	(3)
Asian/Chinese/other	–	–	8	(11)	5	(5)	10	(6)
Missing	2	(4)	–	–	–	–	2	(1)
Educational experience								
≤ 16 years	19	(41)	16	(22)	20	(19)	38	(22)
≥ 17 years	17	(37)	22	(30)	51	(50)	71	(41)
Still in school	10	(22)	36	(48)	29	(28)	63	(37)
Employment status								
Full-time education	10	(22)	36	(49)	29	(28)	63	(37)
Paid employment	30	(65)	34	(46)	49	(48)	79	(46)
Unemployed/other	5	(11)	3	(4)	20	(20)	24	(14)
Social behaviours								
Cannabis/hash ever	36	(78)	31	(42)	46	(45)	67	(39)
Speed/amphetamine/ecstasy ever	21	(46)	15	(20)	19	(19)	34	(20)
Cocaine/opiates ever	17	(37)	14	(19)	11	(11)	21	(12)
Alcohol	43	(93)	62	(84)	88	(86)	153	(89)
Smoking	28	(61)	19	(26)	48	(47)	67	(39)

Missing responses are not shown where they were less than 5% of total.

The odds of infection were, however, higher in men who reported pain passing urine in the previous month (20.3, 95% CI 0.21 to 1978.85, $p = 0.20$).

Discussion

This population-based case–control study among women and men aged 16–24 years found no strong statistical evidence for factors associated with chlamydia that would help to target screening. The odds of infection were increased among women with increasing numbers of sexual partners and from minority ethnic groups. In men, the odds of infection were higher in those with higher numbers of sexual partners and those who had pain passing urine in the past month.

Methodological issues

The strengths of this study were that it was a population-based survey including both men and women with chlamydia diagnosed in the community. Participants completed their questionnaires before finding out the results of their chlamydia test, so response bias was minimised. The survey was adapted from Natsal 2000.[108] Therefore, it used questions that have been piloted and used extensively, and the results can be compared directly with a nationally representative sample. The numbers of lifetime heterosexual partners in this study was somewhat higher than observed in Natsal 2000 in women, but not in men (*Table 20*). Women in this study also reported more concurrent sexual partnerships and more new sexual partners than women of the same age in Natsal 2000. It is therefore possible that prevalence rates estimated from the ClaSS

TABLE 16 *Sexual behavioural characteristics of the study population*

Characteristics	Men				Women			
	Cases *n* = 46	(%)	Controls *n* = 74	(%)	Cases *n* = 102	(%)	Controls *n* = 172	(%)
Lifetime opposite-sex partners								
0/1	3	(7)	33	(45)	7	(7)	57	(33)
2/3	5	(11)	15	(20)	11	(11)	35	(20)
4/5	9	(19)	11	(15)	24	(24)	20	(12)
6/7	3	(7)	4	(5)	23	(22)	21	(12)
8/9	8	(17)	2	(3)	11	(11)	7	(4)
≥ 10	16	(35)	7	(9)	26	(25)	30	(18)
New opposite-sex partners last 12 months								
0	11	(24)	46	(62)	34	(33)	104	(60)
1	9	(20)	8	(11)	25	(24)	36	(21)
2	9	(20)	6	(8)	17	(17)	16	(9)
3	11	(24)	5	(7)	8	(8)	6	(4)
≥ 4	4	(8)	5	(7)	16	(16)	4	(2)
Homosexual	0	(0)	4	(5)	1	(1)	4	(2)
Lifetime same-sex partners								
<4	0	(0)	1	(25)	0	(0)	4	(100)
≥ 5	0	(0)	3	(75)	1	(100)	0	(0)
Concurrency								
Yes	5	(11)	4	(5)	11	(11)	12	(7)
No	12	(26)	14	(19)	34	(33)	40	(23)
Missing	29	(63)	56	(76)	57	(56)	120	(68)
No condom during last sex								
Yes	13	(28)	49	(66)	25	(25)	65	(38)
No	31	(68)	24	(33)	75	(73)	105	(61)

Missing responses are not shown where they were less than 5% of all responses. Concurrency is missing for many participants because this could only be estimated in those who provided details of two previous sexual partners.

project in women aged 16–24 years were overestimated. The weaknesses were related to the lower than expected numbers of cases. This was due to the low uptake of the screening invitation, which meant that there were fewer people with chlamydia available. In addition, risk factors in adults 25 years and older could not be investigated because the researchers stopped inviting people in this age group to be screened.

Comparison with other studies

Many risk factors for chlamydia have been identified in clinic-based studies in a large number of countries.[128–131] Young age, being from a black minority ethnic group, not using condoms, having new sexual partners or a partner with an STI, douching in women and intermenstrual bleeding have all been reported to be associated with chlamydia in some, but not all studies. Young age has, however, been found to be the only consistently identified risk factor.[132] In the present study of young adults, sexual behaviour was the only factor consistently associated with chlamydia.

Implications for chlamydia screening

In primary care settings, where the prevalence of chlamydia is lower than in GUM clinics, universal screening would entail offering tests to large numbers of uninfected women to detect a small proportion with chlamydia. In general practice-based studies in England and Belgium, and a population-based study in The Netherlands, criteria for identifying women at high risk of chlamydia have been investigated and criteria identified that would allow a smaller number of women to be offered screening to identify the majority of infections.[133–135] The present study did not identify any factors that would enable screening to be targeted more efficiently. It did find a number of infected individuals who reported recent genital symptoms, but these were presumably not severe enough to prompt a visit to the GP or GUM clinic. Further studies of health-seeking behaviour and risk factors for men in primary care settings are required.

TABLE 17 *Clinical characteristics of the study population*

Characteristics	Men				Women			
	Cases *n* = 46	(%)	Controls *n* = 74	(%)	Cases *n* = 102	(%)	Controls *n* = 172	(%)
Antibiotic use in last month	13	(28)	31	(42)	52	(51)	82	(47)
Symptoms, women								
Miscarriage	–		–		7	(7)	9	(5)
Termination of pregnancy	–		–		13	(13)	19	(11)
Trying for pregnancy >6 months	–		–		4	(4)	3	(2)
Vaginal discharge	–		–		24	(24)	26	(15)
Intermenstrual bleeding	–		–		12	(12)	20	(12)
Postcoital bleeding	–		–		11	(11)	11	(6)
Lower abdominal pain	–		–		30	(29)	48	(28)
Urinary frequency	–		–		27	(26)	25	(15)
Symptoms, men								
Urethral discharge	4	(9)	3	(4)	–		–	
Pain passing urine	9	(20)	7	(9)	–		–	
Penile irritation	10	(22)	5	(7)	–		–	
Testicular pain	1	(2)	5	(7)	–		–	
Circumcised	4	(9)	10	(14)	–		–	
Selected symptoms								
Discharge/dysuria	12	(26)	8	(11)	–		–	
Vaginal discharge/bleeding after sex	–		–		32	(31)	33	(19)
Ever had chlamydia	3	(7)	2	(3)	17	(17)	13	(8)
Ever had any STI	6	(13)	3	(4)	24	(24)	21	(12)
Ever been to GUM clinic	4	(9)	7	(9)	19	(19)	21	(12)

Missing responses are not reported where they were less than 5% of total.

TABLE 18 *Univariable and multivariable conditional logistic regression models, women*

Characteristics	Crude OR (95%CI)	*p*	Adjusted OR (95%CI)	*p*
Marital status				
Single	1	0.03	1	0.069
Married/living as married	0.40 (0.17 to 0.92)		0.37 (0.13 to 1.08)	
Ethnic group				
White	1	0.11	1	0.13
Black Caribbean/black other	6.11 (0.95 to 39.08)		5.62 (0.70 to 44.83)	
Asian/Chinese/other	3.24 (0.71 to 14.73)		4.83 (0.77 to 30.36)	
Employment status				
Full-time education	1	0.40	1	0.35
Paid employment	0.98 (0.49 to 1.97)		0.81 (0.34 to 1.91)	
Unemployed/other	1.70 (0.68 to 4.25)		1.67 (0.55 to 5.12)	
Lifetime opposite-sex partners				
0/1	1	<0.001	1	0.074
2/3	2.26 (0.76 to 6.72)		1.26 (0.38 to 4.17)	
4/5	9.26 (3.05 to 28.1)		5.39 (1.56 to 18.5)	
6/7	7.54 (2.47 to 22.9)		2.97 (0.74 to 12.0)	
8/9	8.97 (2.35 to 34.2)		4.87 (0.98 to 24.2)	
≥ 10	9.02 (2.95 to 27.5)		2.85 (0.66 to 12.2)	
New opposite-sex partners last 12 months				
0	1	<0.001	1	0.23
1	2.01 (0.98 to 4.10)		1.47 (0.64 to 3.40)	
2	4.39 (1.71 to 11.3)		2.54 (0.76 to 8.45)	
3	5.75 (1.67 to 19.8)		3.44 (0.82 to 14.5)	
≥ 4	11.7 (2.83 to 48.3)		5.31 (0.98 to 28.7)	
Condom at last sex				
Yes/never had sex	1	0.14	1	0.32
No	1.63 (0.86 to 3.09)		1.51 (0.68 to 3.36)	
Vaginal discharge				
No	1	0.038	1	0.85
Yes	2.12 (1.04 to 4.30)		1.09 (0.42 to 2.86)	
Urinary frequency				
No	1	0.002	1	0.14
Yes	3.21 (1.54 to 6.69)		2.03 (0.80 to 5.19)	
Postcoital bleeding				
No	1	0.61	1	0.80
Yes	1.28 (0.49 to 3.34)		1.17 (0.36 to 3.75)	
Intermenstrual bleeding				
No	1	0.33	1	0.65
Yes	1.50 (0.67 to 3.36)		1.27 (0.46 to 3.52)	
Smoking				
No	1	0.11	1	0.75
Yes	1.60 (0.90 to 2.83)		1.13 (0.53 to 2.42)	
Cannabis/hash				
No	1	0.19	1	0.86
Yes	1.48 (0.82 to 2.66)		0.93 (0.42 to 2.06)	

Adjusted odds ratios are adjusted for all variables in the table and age.

TABLE 19 *Univariable and multivariable conditional logistic regression models, men*

Characteristics	Crude OR (95%CI)	*p*	Adjusted OR (95%CI)	*p*
Marital status				
Single	1	0.50	1	0.03
Married/living as married	2.14 (0.23 to 19.65)		86.3 (1.68 to 4432.49)	
Ethnic group				
White	1	0.99	1	0.90
Black Caribbean/black other	1.25 (0.15 to 9.52)		3.14(0.02 to 399.48)	
Asian/Chinese/other	–		–	
Employment status				
Full-time education	1	0.57	1	0.68
Paid employment	1.77 (0.57 to 5.49)		1.68 (0.20 to 14.19)	
Unemployed/other	1.88 (0.24 to 14.8)		0.39 (0.01 to 15.73)	
Lifetime opposite-sex partners				
0/1	1	0.012	1	0.47
2/3	7.42 (0.61 to 90.80)		2.70 (0.11 to 69.54)	
4/5	19.8 (1.86 to 210.6)		11.6 (0.29 to 460.9)	
6/7	64.3 (2.57 to 1612)		9.01 (0.11 to 737.5)	
8/9	45.5 (3.02 to 683.1)		65 (0.73 to 5870.16)	
≥ 10	31.3 (3.18 to 308.0)		19.8 (0.41 to 970.64)	
New opposite-sex partners last 12 months				
0	1	0.005	1	0.40
1	5.66 (1.13 to 28.28)		7.59 0.40 to 144.3)	
2	12.0 (2.37 to 60.63)		4.06 (0.27 to 60.31)	
3	10.8 (2.40 to 48.38)		14.9 (0.79 to 282.4)	
≥ 4	7.63 (1.18 to 49.18)		1.02 (0.03 to 38.70)	
Condom at last sex				
Yes/never had sex	1	0.001	1	0.46
No	7.21 (2.19 to 23.71)		1.96 (0.33 to 11.61)	
Urethral discharge				
No	1	0.45	1	0.78
Yes	2.06 (0.32 to 13.42)		1.66 (0.04, 63.99)	
Pain passing urine				
No	1	0.26	1	0.20
Yes	2.26 (0.55 to9.19)		20.3 (0.21 to 1978.85)	
Penile irritation				
No	1	0.53	1	0.37
Yes	1.64 (0.35 to 7.60)		0.19 (0.00 to 7.62)	
Smoking				
No	1	0.004	1	0.12
Yes	4.57 (1.64 to 12.75)		5.66 (0.65 to 49.54)	
Cannabis/hash				
No	1	0.001	1	0.99
Yes	6.23 (2.03 to 19.17)		1.02 (0.10 to 10.23)	

TABLE 20 *Comparison between sexual behaviour of participants in the ClaSS case–control study with Natsal 2000*[108]

	ClaSS, 16–24-year-olds		Natsal, 16–24-year-olds	
	Men	**Women**	**Men**	**Women**
Lifetime heterosexual partners				
Mean (SD)	6.5 (10.0)	6.2 (6.9)	6.9 (13.1)	5.0 (7.6)
Median (99th percentile)	3 (50)	4 (33)	3 (63)	3 (30)
Unweighted, weighted no. of observations	51, 55.6	154, 167.4	1211, 1492	1433, 1439
Concurrency				
Concurrent partnership, % (95% CI)	22.9% (4.3 to 41.4%)	23.7% (12.7 to 34.5%)	20.8% (17.8 to 24.3)	15.2% (12.7 to 18.1%)
Unweighted, weighted no. of observations	18, 19.7	52, 58.12	820, 1143	1053, 1114
New partners in past year				
≥ 1 new heterosexual partners, % (95% CI)	48.8% (35.4 to 62.1%)	55.7% (48.1 to 63.4%)	51.9% (48.7 to 55.1%)	38.7% (35.8 to 41.8%)
New partners in past year, mean (SD) by marital status				
Single, mean (SD)	1.4 (1.8)	1.0 (1.4)	1.6 (3.4)	0.9 (1.4)
Unweighted, weighted no. of observations	84, 49.0	198, 119.8	1063, 1284	1058, 1021
Married/living as married, mean (SD)	NA	0.2 (0.4)	0.8 (1.2)	0.3 (3.0)
Unweighted, weighted no. of observations	4, 4.4	43, 35.2	27, 38	93, 100
All mean (SD)	1.3 (1.8)	0.8 (1.3)	1.5 (3.2)	0.8 (1.7)
Unweighted, weighted no. of observations	49, 53.6	149, 162.2	1190, 1466	1398, 1395

NA, not applicable.

Chapter 6

Randomised controlled trial of partner notification strategies

Objectives

The objectives were two-fold:

- to determine the feasibility, acceptability, and effectiveness of a simple practice nurse-led partner notification strategy compared with referral to a GUM clinic for people with community-diagnosed chlamydia
- to determine the financial costs and human resources involved in practice nurse-led partner notification.

The quantitative and economic findings from this study have been published and the trial is included in a clinical trials register (http://www.clinicaltrials.gov, NCT00112255).[136]

Methods

Individuals were eligible for this trial if they had chlamydia diagnosed as part of the ClaSS project cross-sectional screening survey and received the result at their general practice. To address the lower than expected number of people with chlamydia identified in the screening survey, in the last 8 months of the study, GPs in study practices were asked to refer patients diagnosed with chlamydia but not already participating in the ClaSS project to the practice nurse for assessment.

The practice nurse administered antibiotic treatment, explained the trial, and asked for written consent. Those who agreed were randomised individually using computer-generated random numbers in permuted blocks, stratified by practice. The allocation sequence was generated by a person not involved in the trial. Allocation was concealed until assignment by a central computerised telephone system. Practice nurses rang the randomisation system and recorded the allocation in the clinical report form.

Interventions

All study practice nurses received training about sexual history taking, management of chlamydia and partner notification, including role-play with actors who simulated clinical scenarios. This took up 1 day of the training course described in Chapter 2. A research health adviser visited each practice at the start of the trial to refresh nurses with details of the trial procedures and partner notification processes. The health adviser was then available during the trial by telephone or practice visits.

Index cases randomised to the general practice arm had partner notification undertaken immediately by a practice nurse. This included: a sexual history recording all sexual contacts in the 6 months before chlamydia diagnosis patient referral (the infected person informs contact themselves) using contact cards for each partner, advice about avoiding sexual intercourse until the sexual partner had completed treatment, and information about being screened for other sexually transmitted infections. Contact cards included details of the study GUM clinics (Milne Centre in Bristol, Whittall Street Clinic in Birmingham) and requested the doctor or clinic treating the partner to return the card to the study centre.

Participants randomised to GUM clinic referral were given details of a research health adviser at each clinic. If the index case did not telephone the clinic within a week, the health adviser made up to two attempts to contact them. Health advisers conducted partner notification using standardised protocols for patient referral, provider referral (informing partners on behalf of the patient immediately) or contract referral (contacting partners if the patient had not done so after an agreed period) and issued contact cards. They also offered patients a consultation for screening for other STIs.

People who did not want to be randomised were offered the choice of having partner notification done by the practice nurse, or being referred to a GUM clinic. Those who declined both were given details of the GUM clinic.

Outcomes

The prespecified primary outcome was treatment of sexual contacts, expressed as the proportion of

index cases with at least one sexual partner treated and the number of partners treated per case 6 weeks after randomisation. A partner was defined as having been treated if at telephone follow-up the index case said that the partner had been treated, a contact card was returned to the coordinating centre, or the partner was confirmed to have attended a local GUM clinic after the index case received the intervention. This primary outcome was modified from the original protocol, in which the researchers intended to use only contact cards as providing evidence of partner treatment. It became clear early on that few contact cards were being returned. A protocol amendment records this (protocol amendment 5).

Secondary outcomes included the number of partners per index case elicited in the sexual history; sexual intercourse before finishing treatment, and chlamydia positivity rate in a urine or vulval swab specimen 6 weeks after randomisation.

A further outcome, which was not specified in the protocol, was also analysed. Research that has become available very recently (some of which is unpublished) suggests that not having had all sexual partners treated[137] and not knowing whether a sexual partner was treated,[138] are strongly associated with repeated infection in women with chlamydia detected through screening. The study therefore compared the proportions of index cases with all partners treated in each arm.

Blinding of participants, practice nurses and health advisers at the time of the intervention was not feasible, but assessment of outcomes was blinded.

Statistical analysis

It was hypothesised that partner notification conducted by a specialist health adviser would be more effective than the practice nurse-led strategy.[95] The sample size calculation assumed that 60% of index cases referred to the GUM clinic[139] and 40% in primary care would have had at least one partner treated. With 80% power and a significance level of 5%, this would require 107 participants in each arm.

The primary analysis was carried out according to intention to carry out partner notification. The analysis included all index cases randomised and all sexual partners elicited, either during the partner notification interview, or at telephone follow-up with index cases who had not attended the GUM clinic (*Figure 11*, groups a, b and c). It was assumed that the sexual partners of index cases lost to follow-up had not been treated. In a further analysis only index cases who actually received partner notification were included (*Figure 11*, groups a and b). The absolute and relative risks were estimated of an index case having at least one partner treated with partner notification by a practice nurse compared with referral to a GUM clinic. The mean (SD) number of partners treated per case in the two groups was also calculated and the difference between means estimated using regression models with robust standard errors to calculate 95% CIs.

Resource use

The costs of each partner notification strategy in obtaining the observed outcome are presented from the perspective of the health service as a cost–consequence analysis.[140] Costs were originally obtained in sterling at 2003 prices and subsequently updated to 2005 prices. Hourly rates of pay (including employer contributions) and training costs were obtained from the ClaSS project. Practice nurses recorded the total duration of the consultation, which included the time taken to give results and treatment, explain the study, obtain consent and conduct randomisation followed by either partner notification or referral. Published data on the duration of GUM clinic consultations were used for partner notification.[141]

The time spent by health advisers providing support for partner notification and telephone follow-up was estimated. Research health advisers recorded the number and duration of telephone calls for following up partner notification outcomes. No data were recorded on the length of initial practice visits or of telephone calls between practice nurses and health advisers during the trial. These were estimated to be 2 hours per practice, and 0.1 hours per index case randomised. These figures were applied to a population similar to that served by Avon PCTs (one million people, five primary care trusts with 150 general practices, and 1800 chlamydia cases diagnosed in general practice in 2004) (Slater W, South West Public Health Observatory: personal communication, 2005).

Qualitative study

Practice nurses asked all individuals who received a positive chlamydia result whether they would be willing to speak to a qualitative researcher. Purposive sampling was then done, to include people who had taken part in the trial and had partner notification done by the practice nurse, or

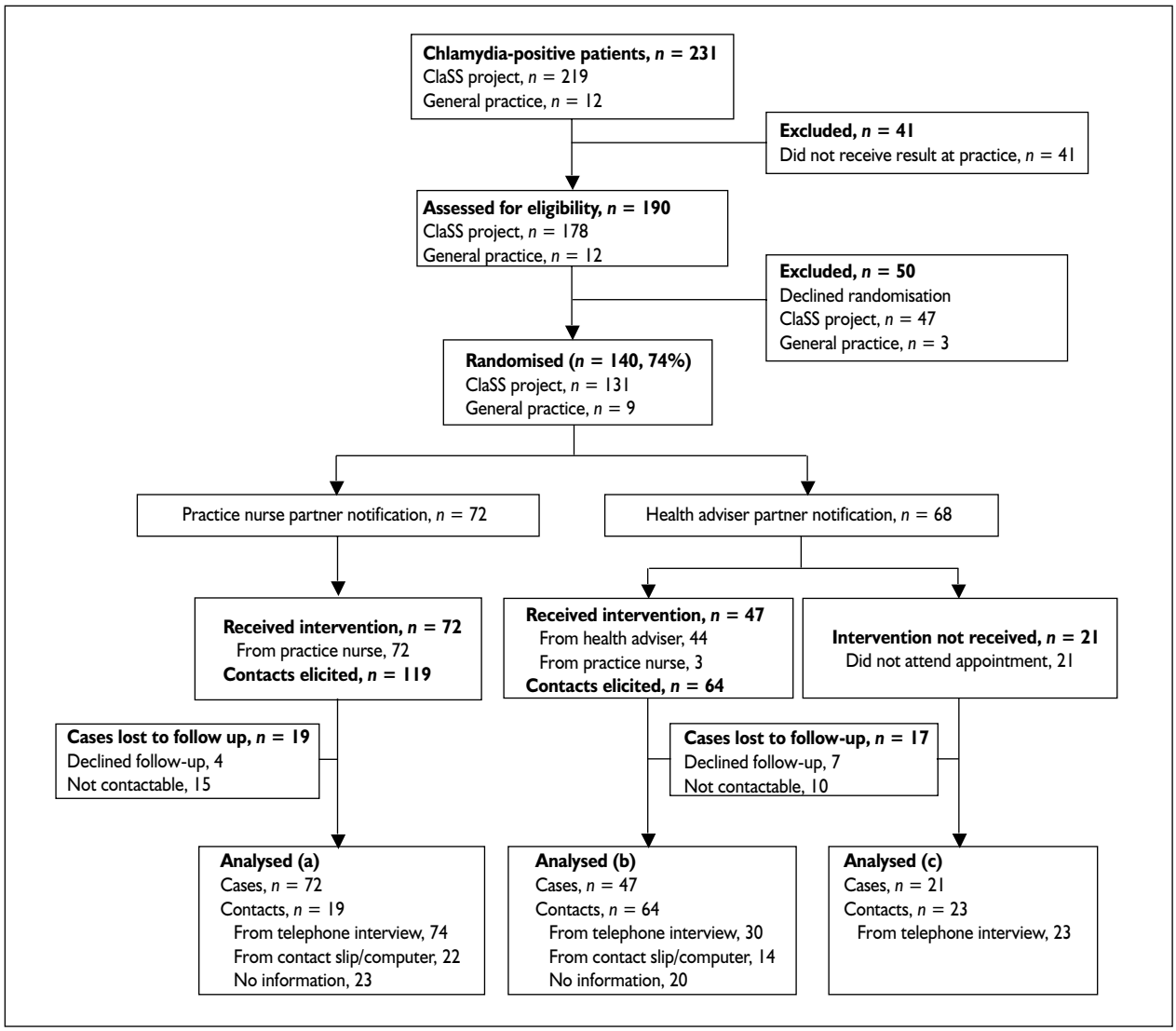

FIGURE 11 *Flowchart of participants' progress through the trial. Source: Low et al. (2006).*[136] *Reproduced with permission from the BMJ Publishing Group.*

had been referred to the GUM clinic, and people who had declined to be randomised. Interviews covering primary themes about partner notification and participating in a randomised trial were conducted and analysed using the same methods as described in the section 'Qualitative study on the effects of chlamydia screening on emotional well-being' (p. 31).

Results

Participants were enrolled from March 2001 to October 2002. Overall, 74% (140/190) of eligible participants were randomised (*Figure 11*). Thirty-six nurses in 25 of 27 ClaSS project practices enrolled at least one participant (median 4, range 1–13). The two groups were well balanced at baseline (*Table 21*). All 72 participants randomised to the practice nurse had a partner notification interview on the same day. Of those referred to the GUM clinic, 31% (21/68) did not attend. The remainder had a partner notification interview a mean of 13.2 days (SD 18.0) after randomisation. Outcome data were obtained on 74% (104/140) of index cases and 79% (163/206) of all contacts (*Figure 11*). Only 23 contact slips were returned.

Practice nurse sexual histories elicited details of 1.7 (SD 1.2) contacts per case compared with 1.4 (SD 1.0) contacts per case elicited from 47 index cases who were randomised to the GUM clinic and received a partner notification interview (difference 0.3, 95% CI –0.01 to 0.6, $p = 0.055$) (*Table 22*). Overall, 45% (92/206) of contacts of 140 index cases were considered treated (*Table 22*):

TABLE 21 *Characteristics of trial participants*

Characteristic	Partner notification by			
	Practice nurse *n* = 72	(%)[a]	GUM *n* = 68	(%)[a]
Gender				
Female	49	(68.1)	43	(63.2)
Male	23	(31.9)	25	(36.8)
Age group				
16–25 years	69	(95.8)	64	(94.1)
26–39 years	1	(1.4)	1	(1.5)
Missing	2	(2.8)	3	(4.4)
Ethnic group				
White	57	(79.2)	57	(83.8)
Black Caribbean	5	(6.9)	2	(2.9)
Black other	1	(1.4)	3	(4.4)
Indian/Pakistani /Bangladeshi	1	(1.4)	0	(0.0)
Chinese/other	1	(1.4)	2	(2.9)
Missing	7	(9.7)	4	(5.9)
Deprivation in ward of residence[b]				
Low	28	(38.9)	26	(38.2)
Medium	24	(33.3)	24	(35.3)
High	19	(26.4)	17	(25.0)
Missing	1	(1.4)	1	(1.5)

Source: Low *et al.* (2006).[136] Reproduced with permission from the BMJ Publishing Group.
[a] Proportions in parentheses unless otherwise specified;
[b] Tertiles of Department of the Environment, Transport and the Regions Index of Multiple Deprivations, 2000 score.

65.3% (47/72) of index cases seen by a practice nurse and 52.9% (36/68) of those referred to the GUM clinic had at least one sexual partner treated (relative risk 1.2, 95% CI 0.9 to 1.6, absolute difference 12.4%, 95% CI –3.7 to 28.6%). This is equivalent to 0.74 contacts treated per case randomised to partner notification by a practice nurse compared with 0.57 contacts treated per case randomised to referral to the GUM clinic. In analysis restricted to index cases who received a partner notification interview, there was no evidence of a difference between the arms (risk difference 7.9%, 95% CI –8.4 to 24.0%). In the GUM clinic referral arm, similar proportions of contacts were treated from index cases who attended the clinic (46.9%, 30/64) and those who did not (39.1%, 9/23). Half of index cases seen by a practice nurse (51.4%, 37/72) had all their partners treated, compared with 30.9% (21/68) of those referred to the GUM clinic (risk difference 20.5%, 95% CI 4.1 to 36.9%, $p = 0.014$).

Of 73 people (52%) who returned a specimen 6 weeks after treatment, only one (in the general practice arm) had a positive chlamydia result. This probably represented reinfection because the index case had reported two partners in the past 6 months, neither of whom had been treated. There were too few data to determine rates of sexual intercourse during treatment.

Among 50 patients who declined to be randomised, 29 elected to have partner notification done by the practice nurse. Sexual histories show that individuals choosing to receive partner notification from the practice nurse (1.14 partners per index case, SD 0.46) reported slightly fewer sexual partners in the past 6 months than patients randomised to this arm of the trial (1.65 partners per index case, SD 1.20, difference between means 0.51, 95% CI 0.00 to 1.02, $p = 0.079$).

Resource use

Partner notification and treatment undertaken by a practice nurse at the general practice was the dominant option: the cost per index case was £34.48 and 65.3% had at least one partner treated. In comparison, referral to the GUM clinic cost £34.55 per index case and 52.9% had at least one partner treated (*Table 23*). For index cases managed at the general practice, nurses took an average of 41.9 minutes (95% CI 37.0 to 46.7) to give the chlamydia test result and treatment, enrol the patient and conduct a partner notification

TABLE 22 *Outcome of partner notification by practice nurses or following referral to GUM clinic*

	Practice nurse	GUM clinic referral	Difference (95% CI)	*p*
All index cases randomised (intention-to-treat)	72	68		
Total number of contacts elicited[a]	119	87		
Contacts elicited per case randomised, mean (SD)	1.7 (1.2)	1.3 (1.0)	0.4 (0.02 to 0.7)	0.023
Number of contacts treated, *n* (%)	53 (44.5)	39 (44.8)		
Cases with at least one contact treated, *n* (%)	47 (65.3)	36 (52.9)	12.4 (–3.7 to 28.6)	0.135
Contacts treated per case randomised, mean (SD)	0.74 (0.6)	0.57 (0.6)	0.16 (–0.4 to 0.4)	0.115
Cases with all partners treated, *n* (%)	37 (51.4)	20 (29.4)	22.0 (6.1 to 37.8)	0.008
Index cases interviewed (on treatment)	72	47		
Number of contacts elicited at interview only[b]	119	64		
Contacts elicited per case interviewed, mean (SD)	1.7 (1.2)	1.4 (1.0)	0.3 (–0.1 to 0.7)	0.141
Number of contacts treated, *n* (%)	53 (44.5)	30 (46.9)		
Cases with at least one contact treated, *n* (%)	47 (65.3)	27 (57.4)	7.9 (–10.0 to 25.8)	0.385
Contacts treated per case interviewed, mean (SD)	0.74 (0.6)	0.64 (0.6)	0.1 (–0.1 to 0.3)	0.406
Cases with all partners treated, *n* (%)	37 (51.4)	17 (36.2)	15.2 (–2.7 to 33.2)	0.103

Source: Low *et al.* (2006).[136] Reproduced with permission from the BMJ Publishing Group.

[a] Numerator includes contacts elicited at partner notification interview plus 23 partners of ten participants randomised to the GUM clinic who did not attend the appointment.

[b] Denominator for 47 participants randomised to the GUM clinic includes only cases who received a partner notification interview.

interview. For those referred to the GUM medicine clinic the average consultation with the practice nurse was 38.8 minutes (95% CI 34.8 to 42.8). This included the time taken to give the chlamydia test result and treatment, enrol the patient and explain the process of referral to the GUM clinic. Index cases who attended the GUM clinic then had a second consultation, with a health adviser, estimated at 12 minutes (*Table 23*).[141] The 1-day training course at each study site cost an average of £1192.25. In addition, locum and travelling costs were estimated at £154.40 per nurse.

Research health advisers spent an average of 4.41 (SD 2.40) minutes on telephone follow-up with index cases who could be contacted and 3.73 (SD 1.30) minutes on unanswered telephone calls to non-contactable cases. Assuming that, as in this trial, about 75% of index cases could be contacted at follow-up, it was estimated that practice nurse-led partner notification would require 606 hours of health adviser time for practice visits, telephone support and follow-up for a population the size of Avon.

Qualitative findings

Twenty-five people were interviewed, of whom ten had received partner notification from the practice nurse, ten had been referred to the GUM clinic and five had not been randomised.

Irrespective of the arm to which they were randomised, most interviewees said that if they had been given the choice they would have preferred to have had partner notification undertaken at the surgery because of the ease of access, as these surgeries were a 'known quantity', and because of the perceived stigma attached to GUM clinics.

> NM: Um well, well basically first of all you. If you had to um, um choose a health professional who to talk to about um you know sort of the best way of notifying partners who would you prefer?
>
> P13: I'd probably go to the practice simply because for me now it's down the bottom of the road. Also, I don't know, I suppose there's that slight stigma about going to the clinic you know. I personally don't have a problem with it but, but my main decision is basically it being easier to go to the practice. But I do feel that I would also, maybe feel although I, I think that the person at the clinic may be more informed about it generally, I would probably just feel more comfortable just going, going to see the practice nurse at our clinic.
>
> *Female, aged 25, tested positive*

> NM: If you'd had the choice then and, you know, you weren't randomised and the nurse sort of said who would you prefer to talk to about partner notification?
>
> P21: I think that would have been a bit, yeah, yeah.
>
> NM: What, what would you have opted for?

TABLE 23 *The costs of partner notification*

	Randomised to practice nurse			Randomised to GUM clinic		
	n	**Unit cost (£)[a]**	**Total (£)[a]**	***n***	**Unit cost (£)[a]**	**Total (£)[a]**
Index case treatment	72	12.71	915.12	68	12.71	864.28
Partner notification advice, mean (95% CI)						782.00
At general practice	72	12.41 (10.98.to 13.85)[b]	893.52	68	11.50 (10.32 to 12.69)[c]	
At GUM clinic	–	–	–	47	4.41	207.27
Partner treatment	53	12.71	673.63	39	12.71	495.69
Mean cost per index case (95% CI)	72	–	34.48 (33.04 to 35.91)	68	–	34.55 (33.35 to 35.72)

Source: Low *et al.* (2006).[136] Reproduced with permission from the BMJ Publishing Group.
[a] All prices are UK pounds sterling inflated to 2005 prices. Cost of nurse £17.79 per hour, health adviser £20.96 per hour, azithromycin assumed to have been used for all index cases and sexual partners.
[b] Practice nurse partner notification costs include time for giving treatment, explaining study, gaining consent and undertaking partner notification.
[c] GUM clinic partner notification costs include time for practice nurse consultation for treatment, explaining study, gaining consent and explaining referral process to the GUM clinic for all 68 index cases.
[d] GUM clinic partner notification costs also include time for health adviser consultation for 47 index cases who attended the GUM clinic.

P21: Probably the nurse, cos obviously I'd seen her the first time and she and I live round there so it'd probably have been easier for me, sort of thing.

Female, aged 20, tested positive

In spite of respondents' preferences for primary care-based partner notification, there were few differences between interviewee accounts of those seen by a practice nurse and those seen by a health adviser, in terms of their experience of the contact tracing interview. All reported being asked about previous sexual partners, being given contact slips to give to their partners, and being informed that if they did not wish to contact partners themselves, this could be done anonymously. Most interviewees reported only having one partner, usually their current sexual partner, to contact. Many reported being fearful about notifying partners, but nearly all felt that this was the correct thing to do and did it face to face. In practice, most found that their partners reacted better than expected.

NM: So did, what did you think then about the nurse saying, 'Well I could contact your partners if you want or, you know, we could send these, these slips out?' What did you think about that way of doing it?

P01: I just wanted to do it meself. I rather just do it meself because like, like you say, like they, like I think what she was saying was, like, you know, what you're on about like, they can send it off, they'll do it, you know. Down the clinic, down town: and I thought I'd rather do it meself.

NM: Any reason?

P01: I don't know, you just know you've done it yourself then don't you? You know. And I rather, I don't know, I rather they'd hear it from me than just some card come through the door with you've got [laughs] you got the clap or whatever. They ain't gonna be happy are they? So I think, oh no, so I did it yeah.

Male, aged 24, tested positive

NM: How did you feel about actually telling your husband then, when you came back from that consultation, that you were positive? What was going through your head?

P20: I thought he would think the worst of me. And I knew that he would obviously be, he knew that he would be questioned by me as well, so it was quite difficult, but, like I said, he reacted a lot better than I thought he would. He was, he was fine about it. He was quite matter of a fact about it so it was easier.

NM: Did it cause any sort of problems in the relationship?

P20: No

NM: No?

P20: Luckily no.

Female, aged 28, tested positive

Even when partners had reacted negatively to being told about the infection, none of those interviewed reported that the partner notification process had had an adverse impact on their current sexual relationships.

P16: Frankly. His reaction wasn't exactly… not the most of understanding young men so.

NM: What was his reaction?

P16: [laughs] Oh hit the roof, accusing, then he was kind of like then, he sort of, you know, like, 'I'm restraining myself from doing something silly' and I'm sort of sat there looking at him going well 'I just had a random test. That's it. It's a random test. I don't know how, when or where so go and get yourself seen to.' And he was like, 'Well this is all your fault rah, rah, rah.' He's been cussing my name since so I assume, I'm assuming that either I had it before him, from someone before him but I, I don't know.

Female, aged 24, tested positive

Although some of those who attended the GUM clinic clearly found this an unhappy experience, others did not find it as unpleasant as they had expected to, and some could see advantages in that they could also be tested for other STIs to which they might have been exposed.

NM: How did you feel then about being randomised to go down to the clinic? Would you have preferred to have stayed with the nurse or did you prefer what happened?

P02: I'd of … I would prefer to stay with the nurse really. But then again I was glad that I did go down because I, I, it made me have the test. I thought, I'm down there. Why don't I have all the tests done? It was easier. So in a way for me I was glad that I did get randomised. I was glad about that.

Male aged 22, tested positive

Discussion

It was hypothesised that the outcomes of partner notification following referral to a specialist health adviser would be better than those of general practice nurses for individuals with chlamydia diagnosed in the community. Intention-to-treat analysis, however, showed some evidence of better outcomes for a practice-based partner notification strategy and excluded a clinically relevant difference in favour of specialist referral. This was because about one-third of those referred for specialist partner notification did not attend the GUM clinic. The costs of the two strategies were similar. Contact slips were not useful for ascertaining contact treatment. Single-dose azithromycin appears to have eradicated chlamydia among those who had follow-up tests 6 weeks after treatment. In qualitative research, practice nurse-led partner notification was acceptable and was the preferred choice of most people with a positive chlamydia test.

Strengths and weaknesses

The strengths of this study were that it was a multicentre randomised trial and included both men and women with newly diagnosed chlamydia who were enrolled from a large, population-based screening survey. Bias was minimised by concealing allocation to study groups, blinding the ascertainment of outcomes and analysing data according to the intention to carry out partner notification. The outcome of the study was not explained by any imbalance in sexual behaviour between the two arms, since the number of partners in the previous 12 months was, if anything, slightly higher in the referral arm (3.5 versus 2.6). The resources used by each strategy in obtaining the observed outcomes were compared and in-depth interviews were conducted with both trial participants and those who declined randomisation.

Some features of the research might have influenced the outcomes. Giving antibiotic treatment at the practice might have exaggerated the differences between groups if fewer people randomised to the GUM clinic then attended. Conversely, nurses explained the importance of sexual contacts being treated to all participants. This is standard clinical practice, but in a trial setting the differences between groups would diminish if some index cases randomised to the GUM clinic acted on this advice and defaulted from their appointment. The finding that, in the GUM clinic referral arm, the proportion of contacts treated was similar whether the index case attended the clinic or not is in keeping with this. For some participants the study clinic was not their nearest clinic; this might have contributed to the 30% default rate, although this was lower than in some primary care studies.[142] The number of trial participants was lower than anticipated because of low overall uptake of home-based chlamydia screening.[95] However, confidence intervals for the primary outcome excluded a clinically relevant effect in favour of specialist referral.

Comparison with other studies

This is the first randomised trial to have evaluated primary care-based partner notification in a developed country.[143] Contact tracing in UK GUM clinics is estimated to result in the treatment of 0.61 partners per case seen.[139] In the English National Chlamydia Screening Programme 44% of all contacts identified were treated.[1] Practice nurse-led partner notification compared favourably with these figures (0.74 partners per case, 45% of all partners treated). The combined cost of treatment and partner management in this

study was also similar to estimates from the national programme.[144] Another new partner notification strategy has been evaluated recently.[145] Expedited partner treatment reduces the time until sexual partners receive treatment because index cases deliver single-dose azithromycin and sexual health information directly to partners without a clinical consultation, or the partner collects treatment from a pharmacy. In the USA, 61% of index cases receiving expedited partner therapy reported that all of their partners were very likely to have been treated.[145] Similar strategies are being considered in the UK, although contact with the partner, at least by telephone, would be likely to be required for legal reasons.

Meaning of the study

Practice nurses with appropriate training and support can provide immediate partner notification for community-diagnosed chlamydia that is at least as effective as standard practice and costs the same. This strategy could improve population chlamydia control if delays in partner treatment caused by the referral process and long clinic waiting times[146] are reduced sufficiently.

The estimated costs of partner notification per index case were higher than they would be in clinical practice because trial procedures increased consultation times. These procedures were, however, the same for both study arms. The similarity in practice nurse consultation times between the trial arms suggests that the time taken to explain the referral process to a GUM clinic to someone with chlamydia could be spent on taking a sexual history and conducting partner notification at the practice.

From the preference arm of the trial there is weak evidence that people who did not want to be randomised had fewer partners than those that were randomised. The qualitative data suggest that people with only one recent sexual partner wanted to tell the partner themselves and did not want this to be delayed by the possibility of having a further consultation. People with greater numbers of sexual partners might have more complicated sexual histories and might prefer to be seen at a specialist clinic.

Implications for policy and practice

Practice nurse-led partner notification could be incorporated into the English National Chlamydia Screening Programme, which currently suggests referral to a GUM clinic.[112] This would relieve pressure from overburdened GUM clinics,[146] which are unlikely to be able to handle the substantial increases in chlamydia cases generated by a successful national screening programme. PCTs can use the results of this study directly to plan chlamydia screening because the entire model of care complied with the core requirements of the national programme:[112] the central project office received all chlamydia results, and a health adviser ensured that all patients in a group of practices received treatment, supported practice nurses conducting partner notification and followed up the outcomes. This model could be extended to other primary care settings, such as community contraception and NHS walk-in clinics. The initial training costs would be discounted over time and one health adviser could support a number of PCTs.

New interventions to improve health should be shown to be effective before their introduction into routine practice. Free chlamydia screening is being introduced in pharmacies in England to increase screening opportunities,[147] although there is no evidence of its effectiveness.[148] In contrast, the present study provides high-quality evidence that investing in training and support for practice nurse-led partner notification in primary care would be an effective use of government resources committed to improving sexual health.

Chapter 7
Laboratory studies

Objectives

The objectives of this part of the research were:

- to compare the performance of an enhanced EIA with NAATs for detecting *C. trachomatis* using urine specimens from men in the general population
- to determine whether, in women, a vulvovaginal swab is superior to a first catch urine specimen for detecting *C. trachomatis* when tested using NAATs
- to compare the performance of an enhanced EIA with NAATs for detecting *C. trachomatis* using vulvovaginal swab specimens from women in the general population
- to examine whether the pooling of specimens can reduce costs for detecting *C. trachomatis* using NAATs
- to assess the effect of storage for longer than 24 hours at ambient temperature on sample stability for first catch urine and vulvovaginal swabs on the performance of a NAAT.

Methods

The tests carried out by each laboratory are shown in *Table 24*. Throughout the text, the Cobas Amplicor CT Test is referred to as Cobas PCR, the Becton Dickinson ProbeTec ET as BD SDA, and the IDEIA PCE EIA as PCE EIA.

The general methods for testing and confirming specimens to compare specimen types and diagnostic tests are described below. Methods specific to the studies assessing specimen stability and pooling specimens are presented in the relevant sections. The results of all evaluations are discussed at the end of the chapter. Detailed protocols for handling, processing and evaluating the diagnostic tests can be found at http://www.chlamydia.ac.uk/evaldiag.htm (Laboratory Protocol, sections 6 and 10). In the project protocol, an additional objective was to undertake quality control by exchanging specimens from each laboratory and to repeat the testing of all positive specimens and a random sample of negative specimens using the alternative test platform. There was not enough time to complete this part of the study and no results are presented.

Testing of specimens

At both sites a biomedical scientist (grade 2) provided day-to-day supervision of the project and ensured adherence to the protocol. Testing was carried out on a daily basis and included as part of the routine work of the laboratory. Time and motion studies were carried out for each assay and the information included in the costing model developed by the economics workstream. These are described below.

Each test was carried out according to the manufacturer's instructions. Both laboratories have Clinical Pathology Accreditation to perform diagnostic work. Both laboratories had available both nucleic acid amplification platforms. Each used its primary test as the screening test and the alternative method to test inhibitory or indeterminate specimens, and confirm reactive results. In Bristol a real-time PCR system was also available to resolve discrepant specimens. This system was used for all confirmatory testing following problems with the SDA system. At the Birmingham laboratory, PCR was carried out on urine specimens where the volume was insufficient for SDA.

Diagnostic strategies

PCE EIA with negative grey-zone testing

The cut-off value for the PCE EIA was calculated by adding 0.05 absorbance units to the mean value of the negative control values. A sample was regarded as being in the negative grey zone if it fell within 0.025 absorbance units (50%) below that of the calculated cut-off.[40,149] All specimens that were reactive by PCE EIA required confirmatory testing by NAAT to be described as positive. PCE EIA test results were considered negative if the absorbance value was below the negative grey zone or was within the negative grey zone and negative by NAAT.

Cobas PCR testing strategy

A reactive Cobas PCR result was considered positive if it was confirmed by either a reactive PCE EIA or positive real-time PCR result (described below). The results of the Cobas PCR

TABLE 24 *Laboratory test and specimen evaluations*

Evaluation	Bristol		Birmingham		Comments
	Cobas PCR	PCE EIA	BD SDA	PCE EIA	
Men					
Urine specimens	×	×	×		Comparison of SDA with EIA not possible because urine volume insufficient for both tests
Women					
Vulvo-vaginal swabs	×	×	×	×	
Urine specimens	×		×		

Cobas PCR, polymerase chain reaction (Cobas Amplicor CT Test; Roche Diagnostics, Basel, Switzerland); BD SDA, DNA strand displacement analysis (ProbeTec ET; Becton Dickinson, Franklin Lakes, NJ, USA); PCE EIA, enzyme immunoassay (IDEIA PCE EIA, Dako, Ely, UK).

test were taken as negative if the PCE EIA was negative, without the need for a confirmatory real-time PCR test. Cobas PCR specimens that were initially inhibitory were retested by a second NAAT.

BD SDA testing strategy

A reactive BD SDA result was considered positive if it was confirmed by either a reactive PCE EIA or positive Cobas PCR result. The results of the BD SDA test were taken as negative if the PCE EIA was negative, without the need for a confirmatory testing. BD SDA specimens that were initially inhibitory were treated as recommended by the manufacturer and retested with the BD SDA test. Those that remained inhibitory were retested by a second NAAT (Cobas PCR or real-time PCR).

Real-time PCR

The in-house confirmation NAAT was a real-time PCR test using the LightCycler (Idaho Instruments, ID, USA). Use of this test as a confirmatory assay has been described previously.[150] Both real-time assays used in this assay have a detection limit of approximately 10 genome copies.[150] Nucleic acid was prepared from urine pellets from 1 ml of first pass urine using one of two silica binding techniques.[151] Early in the study, the Qiamp Viral RNA extraction kit was used (Qiagen, Crawley, UK).[152] The columns were eluted with 100 µl dH_2O. For later discrepant analyses, binding to MagPrep magnetic silica particles (Merck BDH, Poole, UK) was used. Specimens were dissolved in guanidinium isothiocyanate-containing L6 buffer[151] and 10 µl of beads was added. After incubation with shaking at room temperature for 15 minutes, the beads were washed three times after being immobilised with a magnet using 20 mM Tris Cl, pH 7.4, 1 mM EDTA and 100 mM NaCl mixed with an equal volume 100% ethanol. The beads were then dried at room temperature and eluted in 50 µl 10 mM Tris, pH 8.0, for 10 minutes at 80°C. Column or bead eluates (4 µl) were assayed in 10-µl reactions in the LightCycler. The confirmatory PCR was carried out using primers directed at the major outer membrane protein gene:

MOMPfp2: 5′ CCAGAAAAAGATAGCGAGCACAAA 3’
MOMPrp1: 5′ AGCAGAACTCAAAGCGGCAAAT 3′

The plasmid-based PCR adapted from Loeffelholz and colleagues uses the same primers as the Roche Cobas PCR assay.[153] This assay was only used to resolve inhibitory samples with Roche Cobas PCR. For both assays 50 cycles of PCR were performed on the LightCycler in the presence of SYBR Green I intercalating dye. Only those specimens that gave a clear peak in the melting point analysis of PCR product, with a melting point within ± 0.2°C of the positive control, were considered positive.

Final test results

A final result was issued according to the algorithm constructed for the study *(Table 25*). For women, specimen results from both vulva and urethra were available. True infection status was defined on the principle of the infected person rather than specimen. For example, if *C. trachomatis* was detected in the female urine specimen only (and this was confirmed by a second test) the woman was deemed chlamydia positive. The performance of the vulvovaginal swab was then assessed with the infection status based on the positive result from the urine specimen.

TABLE 25 *Algorithm for determining results of tests for* C. trachomatis

PCE EIA result	NAAT result	Comments[a]	Final report
+	+		True +ve
NGZ	+		True +ve
–	+	If confirmatory NAAT on second aliquot is +ve	True +ve
+	–	If confirmatory NAAT on second aliquot is +ve	True +ve
NGZ	–	If confirmatory NAAT on second aliquot is +ve	True +ve
–	+	If confirmatory NAAT on second aliquot is –ve	True –ve
+	–[b]	If confirmatory NAAT on second aliquot is –ve	True –ve
NGZ	–[b]	If confirmatory NAAT on second aliquot is –ve	True –ve
–	–[b]		True –ve

NAAT, nucleic acid amplification test (Cobas PCR or BD SDA); NGZ, negative grey zone; PCE EIA, IDEIA amplified enzyme immunoassay (Dako, Ely, UK).

[a] Original urine tested by confirmatory NAAT if volume allowed (1 ml required for real-time PCR). Otherwise, the residual urine was used.

[b] Internal control used to detect inhibitory specimens. Inhibitory specimens were retested using a second NAAT (see section 'Methods', p. 59).

TABLE 26 *Number of specimens tested per machine per day*

	PCE EIA	Cobas PCR	BD SDA
Maximum number of specimens per batch	272	22	46
Maximum number of runs per day	2	2	2
Maximum number of specimens tested per day	544	44	92

Specimen storage

Specimens were stored at +4°C until the result of the test was known. Where the result was equivocal or in the grey zone, samples were retested. On completion of testing, specimens were frozen at –20° C. Negative samples were discarded after 1 month, but positive and discordant samples were kept at –70° C.

Time and motion study

Labour

The length of time taken to complete each labour-dependent step was measured. After piloting data collection forms in each laboratory, laboratory staff collected data on a specified number of days, which included times when the number of samples was high and lighter times at the beginning, middle and end of the study (to eliminate learning effects).

The labour dependent tasks for each method were analysed in two categories: general activities undertaken for all testing techniques, such as unpacking returned packs and reporting results; and test-specific activities. The cost of posting the specimen to the laboratory was included in the general activities.

Resource use and cost data

Costs for each type of test and procedure were estimated in consultation with manufacturers and hospital finance departments. Hourly rates were calculated based on annual salaries divided by the total number of hours of expected work per annum, taking annual leave and bank holidays into account. All salaries were taken from the 2002/03 pay budgets and included employers' contributions for national insurance and superannuation and 40% employer overheads. All costs have been inflated to 2005 prices.

Laboratory staff listed the consumables used in an average test procedure and the costs estimated by applying costs obtained from the purchasing department. The costs of some consumable goods, such as control specimens, are applied to a batch of specimens. When calculating the unit cost of consumable goods, the total consumable costs per batch were calculated and then this was divided by the maximum number of specimens that can be tested in a batch. *Table 26* shows the number of specimens that can be tested in one batch for each

testing method. Annual equipment costs were estimated by the annuitisation of the initial capital outlay over the useful life of the asset to calculate the equivalent annual cost. The average cost of equipment per test was estimated by dividing the annual cost by the number of tests performed. Optimal capacity was assumed for all equipment. The costs of overheads and capital costs such as buildings and computers were not included.

To find the maximum annual number of specimens that could be tested, the maximum number of specimens tested per day (e.g. 544 for EIA) was multiplied by the total days per year excluding bank holidays. Costs were obtained from hospital purchasing departments and manufacturers. Maintenance costs were estimated from the maintenance contracts for each machine and then added to the annual cost.

Results

Time and motion forms were completed on 7 separate days for BD SDA, 8 separate days for Cobas PCR, 5 separate days for PCE EIA testing both urine and swabs, and 6 days for PCE EIA testing swabs only. Information relating to general activities was collected on 11 different occasions across the two laboratories. The total number of samples included in the analysis was 208 (129 urines and 79 swabs).

Costs per specimen

Table 27 shows the time taken to perform each labour-dependent task. For each test and specimen type, the time taken to complete general activities and test-specific tasks is reported separately. The time spent on test-specific activities to prepare swabs using Cobas PCR (4.35 minutes, 95% CI 2.00 to 13.00) was slightly shorter than for urine specimens (6.56 minutes, 95% CI 4.53 to 16.00). Swab and urine specimens processed for BD SDA took about the same time. Overall, specimens tested using PCE EIA involved slightly less hands-on time than either NAAT.

The average equipment costs for testing equipment for PCE EIA were much less than for BD SDA or Cobas PCR, at only 2 p per specimen tested compared with 23 p for BD SDA. Equipment costs were the same for both urine and swab specimens. The average costs per urine specimen tested and cost per swab tested (including consumable and equipment costs) are presented in *Table 28*. Testing using PCE EIA had the lowest average costs per specimen tested. Testing a urine or swab specimen using a NAAT cost about £7 per specimen.

Costs of pooling specimens

The average consumables and equipment costs were lower for pooled specimen testing (*Tables 29* and *30*) than for individual specimen testing for both NAATs (*Table 28*). Consumables and equipment costs were lowest for specimens tested in pools of four using BD SDA: £0.53 for urine specimens, £0.42 for swabs, compared with individual testing (£5.09 for both urine and swabs). For Cobas PCR, there was a smaller difference between the costs of consumables and equipment for specimens tested in pools of four (£3.49 for urine and £3.66 for swabs) and individual testing (£4.47 for urine, £4.64 for swabs). The average cost of laboratory technician's time spent testing pooled specimens was slightly greater than the time spent testing individual specimens. The cost of the extra time spent on pooled specimens ranged from £0.70 to £1.73.

Pooling specimens in pools of four and eight was less costly per specimen tested than testing individual specimens. The total costs of testing pooled specimens and the cost per positive specimen are estimated in the section 'Pooling of specimens' (p. 68).

Results

In total, 4731 specimens were returned to the study laboratories, of which 4729 had a completed consent form (*Figure 12*). The numbers of individuals included in analyses for each objective are shown below. There were 18 individuals for whom a result from one specimen had not been entered in the database. These were excluded from the analysis, but all individuals received a final result and appropriate treatment if necessary.

Comparison of PCE EIA plus negative grey-zone testing with Cobas PCR in male urine specimens

The results from this study have been published.[154] There were 1003 specimens that were tested by both PCE EIA and Cobas PCR. There were 32 specimens (3.2%) identified as true positives and 971 true negatives according to the algorithm in *Table 25*. Twenty-seven samples were initially PCE EIA reactive and 22 were confirmed positive by NAAT. Six samples were in the negative grey zone and two were confirmed positive by Cobas PCR. PCE EIA with negative grey-zone testing and confirmation by Cobas PCR therefore identified 24 out of 32 true positives (relative sensitivity 75.0%, 95% CI 56.6 to 88.5%, *Table 31*). Without negative grey-zone testing the

TABLE 27 *Hands-on time per test, by specimen type*

	PCE EIA		Cobas PCR		BD SDA	
	Urine	Swab	Urine	Swab	Urine	Swab
General activities, minutes (95% CI)	3.76 (2.88 to 4.64)	4.25 (3.21 to 4.54)	3.76 (2.88 to 4.64)	4.25 (3.21 to 4.54)	3.76 (2.88 to 4.64)	4.25 (3.21 to 4.54)
Test-specific activities, minutes (95% CI)	2.08 (0.77 to 6.78)	2.08 (0.77 to 6.78)	6.56 (4.53 to 16.00)	4.35 (2.00 to 13.00)	3.31 (1.82 to 9.73)	3.56 (1.26 to 12.60)[a]
Time per specimen tested, minutes (95% CI)	5.84 (3.65 to 11.42)	6.33 (3.98 to 11.32)	10.32 (7.41 to 20.64)	8.60 (5.21 to 17.54)	7.07 (4.70 to 14.37)	7.81 (4.47 to 17.14)

[a] Data only recorded on one occasion

TABLE 28 *Cost per test, by specimen type*

Cost[a]	PCE EIA		Cobas PCR		BD SDA	
	Urine	Swab	Urine	Swab	Urine	Swab
Consumable cost per specimen, £	1.02	1.29	3.90	4.07	4.85	4.85
Equipment cost per specimen, £	0.02	0.02	0.57	0.57	0.24	0.24
Consumables plus equipment, £	1.04	1.31	4.47	4.64	5.09	5.09
Average cost of hands-on time, £ (95% CI)[b]	1.84 (1.14 to 3.60)	1.99 (1.25 to 3.57)	3.25 (2.33 to 6.50)	2.71 (1.64 to 5.33)	2.22 (1.48 to 4.52)	2.46 (1.41 to 5.40)
Average cost per test, £ (95% CI)[c]	2.88 (2.18 to 4.61)	3.30 (2.56 to 4.88)	7.72 (6.80 to 10.97)	7.35 (6.28 to 10.17)	7.31(6.58 to 9.62)	7.55 (6.50 to 9.91)

[a] Costs inflated to UK pounds Sterling, 2005 prices.
[b] Hands-on time includes laboratory technician's time (hourly rate/time taken to complete test).
[c] Cost per test = cost of hands-on time + equipment and consumables cost per test.

TABLE 29 *Costs of pooling specimens using BD SDA assay*

Item	Four urines	Four swabs	Eight urines	Eight swabs
Average consumables cost per specimen, £	0.47	0.36	1.80	1.34
Average equipment cost per specimen, £	0.06	0.06	0.03	0.03
Total consumables and equipment cost per specimen, £	0.53	0.42	1.83	1.37
Hands-on time per specimen, £ (95% CI)[a]	3.95 (2.71 to 6.49)	3.45 (2.70 to 12.68)	3.95 (3.20 to 8.83)	3.45 (2.70 to 12.68)
Total cost per test, £ (95% CI)[b]	4.48 (3.24 to 7.02)	3.87 (3.12 to 13.10)	5.78 (4.54 to 8.32)	4.82 (4.08 to 14.05)

[a] Hands-on time includes laboratory technician's time (hourly rate/time taken to complete test).
[b] Cost per test = hands-on time + equipment and consumables cost per test.

TABLE 30 *Costs of pooling specimens using Cobas PCR assay*

Item	Four urines	Four swabs	Eight urines	Eight swabs
Average consumables cost per specimen, £	3.34	3.51	3.25	3.42
Average equipment cost per specimen, £	0.15	0.15	0.07	0.07
Total consumables and equipment cost per specimen, £	3.49	3.66	3.32	3.49
Hands-on time per specimen, £ (95% CI)[a]	3.95 (3.20 to 8.83)	3.45 (2.70 to 12.68)	3.95 (3.20 to 8.83)	3.45 (2.70 to 12.68)
Total cost per test, £ (95% CI)[b]	7.44 (6.68 to 12.32)	7.11 (6.35 to 16.33)	7.27 (6.52 to 12.16)	6.94 (6.20 to 16.17)

[a] Hands-on time includes laboratory technician's time (hourly rate/time taken to complete test).
Cost per test = hands-on time + equipment and consumables cost per test.

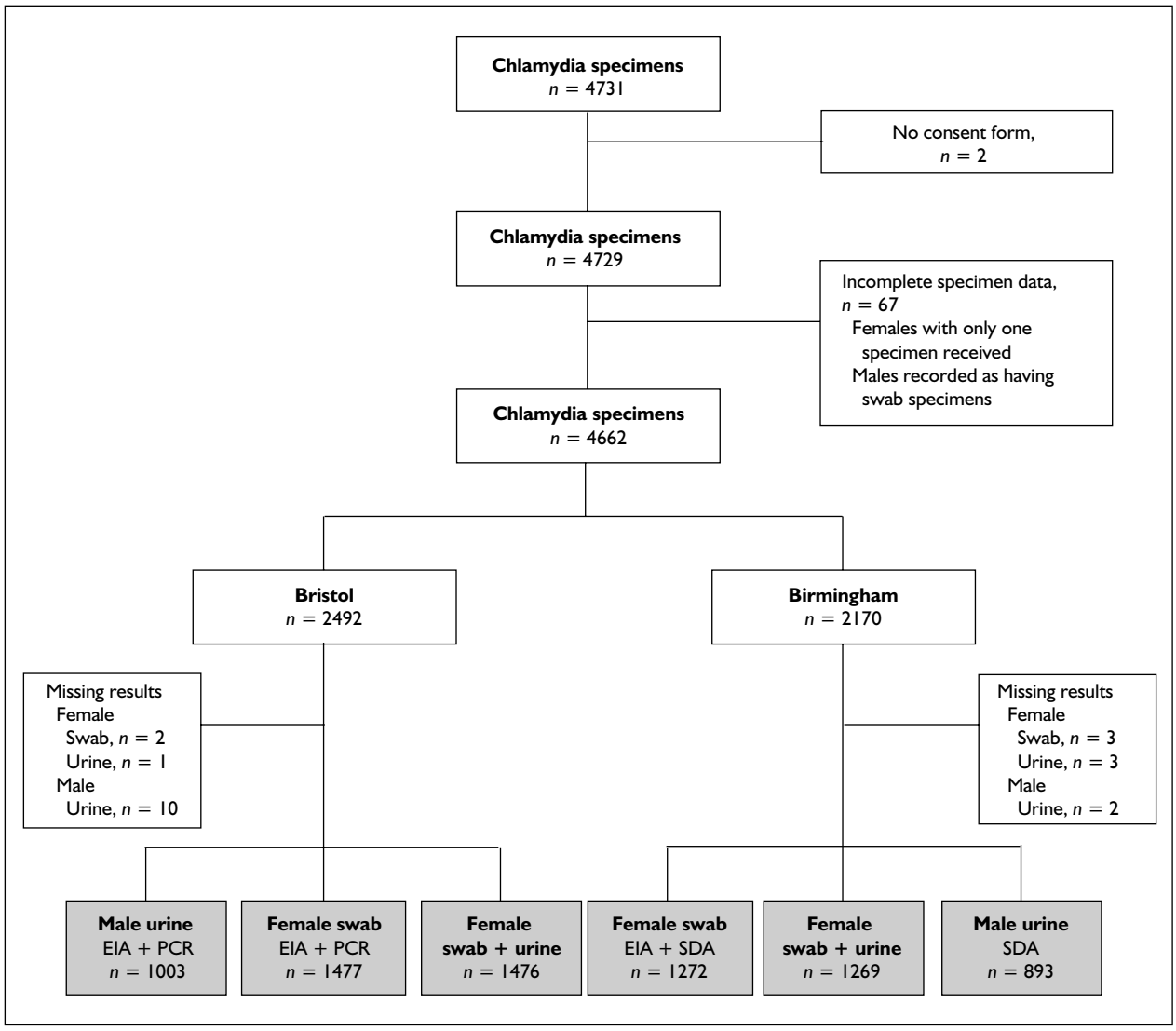

FIGURE 12 *Flowchart of individuals and specimens for laboratory studies*

relative sensitivity of PCE EIA was 68.8% (95% CI 50.0 to 83.9%). There were 962 PCE EIA negative specimens and a further five initially reactive specimens and four in the negative grey zone that were confirmed negative by subsequent NAAT. The specificity for the PCE EIA with a confirmatory NAAT was therefore 100% (95% CI 99.7 to 100%). Without NAAT for initially reactive specimens the specificity of PCE EIA was 99.5% (966/971, 95% CI 98.8 to 99.8%).

Cobas PCR identified 34 positives, including all 32 true positives (relative sensitivity 100%, 95% CI 89.1 to 100%). The other two (5.9%) Cobas PCR positives were negative by PCE EIA and real-time PCR, giving a specificity of 99.8% (95% CI 99.3 to 100%, *Table 32*). Nineteen (1.9 %) samples were initially Cobas PCR inhibitory. All were negative by PCE EIA and confirmed negative when retested by either BD SDA or real-time PCR. The estimate of specificity was unchanged if inhibitory specimens were excluded from the calculations (*Table 32*), or if it was assumed that no inhibitory control had been used and inhibitory specimens were classed as negative (data not shown).

Fifty-seven per cent of specimens were tested within 48 hours of sample collection. Increasing time from collection to testing did not affect the positivity rate (OR for specimens collected more than 96 hours before testing compared with less than 48 hours 1.0, 95% CI 0.4 to 2.3).

Performance of vulvovaginal swabs and first catch urine specimens tested with NAATs in women

Results from this study have been accepted for publication.[155] Overall there were 146 (5.3%)

TABLE 31 *Performance of PCE EIA with negative grey-zone testing in first catch urine specimens from men*

EIA result	True positive	True negative	Total
EIA confirmed positive[a]	22	0	22
EIA grey zone confirmed positive[b]	2	0	2
EIA negative	8	971	979
Total	32	971	1003
Relative sensitivity[c]	75.0% (95% CI 56.6 to 88.5%)		
Relative specificity[d]	100% (95% CI 99.7 to 100%)		
Positive predictive value	100% (95% CI 88.3 to 100%)		
Negative predictive value	99.2% (95% CI 98.4 to 99.6%)		

Source: Horner *et al.* (2005).[154] Reproduced with permission from the American Society for Microbiology Journals Department.

[a] There were 27 initially reactive samples by PCE EIA. Five specimens were negative by Cobas PCR. Of these, four were confirmed negative by a second NAAT and one was negative on repeat EIA testing.

[b] There were six PCE EIA results in the negative grey zone. The four true negatives were confirmed negative by a second NAAT on two specimens and two were EIA-negative on repeat testing.

[c] Calculated by including grey zone-positive specimens in EIA-positive results.

[d] Calculated by including unconfirmed EIA-positive and unconfirmed grey zone-positive specimens in EIA-negative results.

TABLE 32 *Performance of Cobas PCR in first catch urine specimens from men*

Cobas PCR result	True positive	True negative	Total
Positive	32	2	34
Negative	0	950	950
Inhibitory	0	19	19
Total	32	971	1003

	Inhibitory results resolved, *n* = 1003	**Inhibitory results excluded, *n* = 984**
Relative sensitivity, % (95% CI)	100 (89.1 to 100)	100 (91.1 to 100)
Relative specificity, % (95% CI)	99.8 (99.3 to 100)	99.8 (99.2 to 100)
Positive predictive value, % (95% CI)	94.1 (76.9 to 98.2)	94.1 (76.9 to 98.2)
Negative predictive value, % (95% CI)	100 (99.6 to 100)	100 (99.6 to 100)

Source: Horner *et al.* (2005).[154] Reproduced with permission from the American Society for Microbiology Journals Department.

infected women (74 in Bristol and 72 in Birmingham). There were 2745 paired urine and swab specimens, including 1476 pairs tested by Cobas PCR and 1269 tested by BD SDA. More swab and urine specimens were initially inhibitory by Cobas PCR (424/1476, 29%) than BD SDA (86/1269, 7%) (*Table 33*). Inhibition was equally likely in swab and urine specimens tested by Cobas PCR, but was more common in urine specimens tested by BD SDA than with vulvovaginal swabs.

Table 34 shows the results of testing with each specimen type and assay. After resolving the results of inhibitory specimens the performance of both NAATs on the two specimen types was virtually identical, with closely overlapping confidence intervals. Since the study populations, positivity rates and numbers of paired specimens in each centre in the two laboratories were similar, and protocols followed in the laboratories were identical, the results were pooled to increase precision, and the combined relative sensitivity and specificity of urine and swab specimens was estimated (*Table 35*).

Urine specimens correctly identified 134 out of 146 (91.8%, 95% CI 86.1 to 95.7%) chlamydia-infected women compared with 142 out of 146 (97.3, 95% CI 93.1 to 99.2%) identified using self-taken vulvo-vaginal swabs. Specificity for the two

TABLE 33 *Inhibitory specimens according to diagnostic test*

Diagnostic test and specimen	Inhibitory		Positive on retesting	
	n (%)	(95% CI)	*n* (%)	(95% CI)
Cobas PCR (*n* = 1476)				
Vulvovaginal swab	232 (16)	(14 to 18)	8 (5)	(2 to 11)
First catch urine	192 (13)	(11 to 15)	3 (2)	(0 to 6)
BD SDA (*n* = 1269)				
Vulvovaginal swab	1 (0)	(0 to 4)	0 (0)	(0 to 2)
First catch urine	85 (7)	(5 to 8)	2 (2)	(0 to 6)

Based on 2745 paired swab and urine specimens.

TABLE 34 *Results of testing first catch urine and vulvovaginal swabs with NAATs*

Specimen and test status	True positive	True negative	Total
Urine Cobas PCR			
Positive	64	0	64
Negative	7	1213	1220
Inhibitory	3	189	192
Total	74	1402	1476
Urine BD SDA			
Positive	65	4	69
Negative	5	1110	1115
Inhibitory	2	83	85
Total	72	1197	1269
Swab Cobas PCR			
Positive	64	5	69
Negative	2	1172	1174
Inhibitory	8	224	232
Total	74	1401[a]	1475
Swab BD SDA			
Positive	70	4	74
Negative	2	1192	1194
Inhibitory	0	1	1
Total	72	1197	1269

[a] Total excludes one specimen with an equivocal result that could not be resolved. The specimen was confirmed negative based on the urine specimen result.

specimen types exceeded 99.6%. The positive predictive value of swab-positive specimens (142/151, 94.0%, 95% CI 89.0 to 97.2%) was very slightly lower than that of urine-positive specimens (134/138, 97.1%, 95% CI 92.7 to 99.2%). When inhibitory specimens were excluded from the analysis, the performance of the tests was virtually identical (*Table 35*). If inhibitory specimens had not been tested further and a result had been issued as 'inhibitory', the system would have failed to identify 10.8% (4.8–20.2%, 8/74) of true-positive results from vulvovaginal swabs and 4.1% (0.8–11.4%, 3/74) of true-positive results from urine specimens using Cobas PCR. If inhibitory results with Becton Dickinson SDA had not been resolved, the system would have picked up all true-positive vulvovaginal swabs but missed 2.8% (0.3–9.7%, 2/72) of true-positive urine specimens.

PCE EIA compared with NAATs in vulvovaginal swabs

Paired vulvovaginal swabs tested by both PCE EIA and NAAT were available for 2749 women, including 1272 by BD SDA and 1477 by Cobas PCR. Overall, 146 women were considered positive (5.3%). PCE EIA correctly identified 97 of these results (66.4%, 95% CI 58.2 to 74.0%), six of which were in the negative grey zone and

TABLE 35 *Performance of first catch urine and vulvovaginal swabs tested with NAATs*

First catch urine	**True positive**	**True negative**	**Total**
Positive	129	4	133
Negative	12	2323	2335
Inhibitory	5	272	277
Total	146	2599	2745
	Inhibitory results resolved, *n* = 2745	**Inhibitory results excluded, *n* = 2468**	
Relative sensitivity, % (95% CI)	91.8 (86.1 to 95.7)	91.5 (85.6 to 95.5)	
Relative specificity, % (95% CI)	99.8 (99.6 to 99.9)	99.8 (99.6 to 99.9)	
Positive predictive value, % (95% CI)	97.1 (92.7 to 99.2)	97.0 (92.5 to 99.2)	
Negative predictive value, % (95% CI)	99.5 (99.2 to 99.8)	99.5 (99.1 to 99.7)	
Vulvovaginal swab	**True positive**	**True negative**	**Total**
Positive	134	9	143
Negative	4	2364	2368
Inhibitory	8	225	233
Total	146	2598[a]	2744
	Inhibitory results resolved, *n* = 2745	**Inhibitory results excluded, *n* = 2511**	
Relative sensitivity, % (95% CI)	97.3 (93.1 to 99.2)	97.1 (92.7 to 99.2)	
Relative specificity, % (95% CI)	99.7 (99.3 to 99.8)	99.6 (99.3 to 99.8)	
Positive predictive value, % (95% CI)	94.0 (89.0 to 97.2)	93.7 (88.4 to 97.1)	
Negative predictive value, % (95% CI)	99.8 (99.6 to 100)	99.8 (99.6 to 99.9)	

[a] Total excludes one specimen with an equivocal result that could not be resolved. The specimen was confirmed negative based on the urine specimen result.

subsequently confirmed positive after testing with a NAATs (*Table 36*). The performance characteristics of the two NAATs are shown in *Table 35* (lower panel). The performance of PCE EIA in the two laboratories, however, differed slightly. Although this might have been due to chance (test for heterogeneity, $p = 0.575$), it could also represent differences between laboratories, so the results are presented separately.

In the Bristol laboratory, PCE EIA identified 52 out of 74 true-positive individuals (relative sensitivity 70.2%, 95% CI 58.5 to 80.3%) (*Table 36a*). The relative specificity was 98.8% (95% CI 98.1 to 99.3%). After repeat testing of ten specimens in the negative grey zone, the relative sensitivity increased to 74.3% (95% CI 62.8 to 83.8%). In the Birmingham laboratory, PCE EIA identified 39 out of 72 true-positive individuals (relative sensitivity 54.2%, 95% CI 42.0 to 66.0%) (*Table 36b*). Negative grey-zone testing on eight specimens increased the relative sensitivity of the PCE EIA to 58.3% (95% CI 46.1 to 69.8%). The relative specificity after confirming reactive specimens was 99.4% (95% CI 98.8 to 100%). Positive predictive values of the PCE EIA test in the Bristol and Birmingham laboratories, after negative grey-zone testing, were 72.2% (95% CI 60.4 to 82.1%) and 85.7% (95% CI 72.8 to 94.1%), respectively.

Pooling of specimens

Methods

Extracted specimens were used and pooling was assessed on both urine and vulvovaginal swab specimens during the cross-sectional screening study. Pools of specimens were therefore tested simultaneously with the individual specimens. Pool sizes of four and eight were compared based on the optimum pool size at a given prevalence, and to use a 96-well plate efficiently (*Table 37*). Although four specimens per pool is not the most efficient below a prevalence of 7% the difference in numbers of tests required for pool sizes of four and five is small and four specimens per pool is more efficient. At very low prevalence, a pool size of eight is the optimum.

Dilution experiments with 20 positive urine specimens were performed to ensure that the assays were sensitive enough to identify one

TABLE 36 *Comparison of PCE EIA with NAATs on self-taken vulvovaginal swabs*

(a) Cobas PCR, Bristol

Test status	Cobas PCR		PCE EIA			
	+ve	–ve	+ve	–ve	NGZ	Total
True +ve	72[a]	2	52	19	3	74
True –ve	5	1398[b]	17	1379	7	1403
Total	77	1400	69	1398	10	1477

	Inhibitory results resolved	Including confirmed NGZ results	Treating NGZ results as negative
Sensitivity, % (95% CI)	97.3 (90.6 to 99.7)	74.3 (62.8 to 83.8)	70.2 (58.5 to 80.3)
Specificity, % (95% CI)	99.6 (99.2 to 99.9)	98.8 (98.1 to 99.3)	98.8 (98.1 to 99.3)
Positive predictive value, % (95% CI)	93.5 (85.5 to 97.9)	72.2 (60.4 to 82.1)	75.4 (63.5 to 84.9)
Negative predictive value, % (95% CI)	99.9 (99.5 to 100.0)	98.1 (97.3 to 98.8)	98.4 (97.6 to 99.0)

[a] 64 specimens were initially Cobas positive. The total includes eight specimens that were inhibitory and confirmed positive on repeat testing.
[b] 1173 specimens were initially Cobas PCR negative. The total includes 224 inhibitory results and one equivocal result that were negative on repeat testing.

(b) BD SDA, Birmingham

Test status	BD SDA		PCE EIA			
	+ve	–ve	+ve	–ve	NGZ	Total
True +ve	70	2	39	30	3	72
True –ve	4	1196[a]	7	1188	5	1200
Total	74	1198	46	1218	8	1272

	Inhibitory results resolved	Including confirmed NGZ results	Treating NGZ results as negative
Sensitivity, % (95% CI)	97.2 (90.3 to 99.7)	58.3 (46.1 to 69.8)	54.2 (42.0 to 66.0)
Specificity, % (95% CI)	99.5 (99.0 to 99.9)	99.4 (98.8 to 100.0)	99.0 (98.3 to 99.5)
Positive predictive value, % (95% CI)	94.5 (86.7 to 98.5)	85.7 (72.8 to 94.1)	84.8 (71.1 to 93.7)
Negative predictive value, % (95% CI)	99.8 (99.4 to 100.0)	97.5 (96.5 to 98.3)	97.3 (96.2 to 98.1)

[a] 1195 specimens were originally BD SDA negative. The total includes one indeterminate specimen that was negative on testing with Cobas PCR.

positive specimen in dilutions of 2, 4, 8 and 16. Since the antigenic load is less in urine than in swabs it was assumed that the results could be generalised to swabs.

Each sample was tested in a pool of four and a pool of eight (pools of eight consisted of the specimens from two pools of four). Pools were generated by mixing samples to obtain the required testing volume for each assay (*Table 38*). The pooled specimens were marked with a 'P' and the identification numbers of the constituent specimens noted. The pooled specimen was processed in parallel with the individual specimens and results for the pooled and individual specimens were recorded.

If the pool result was positive or equivocal but the pool contained no individual specimens with positive or equivocal results, the individual pool specimens were retested using lysed specimens. When there were insufficient specimens to make up a pool of four, residual urine specimens were stored at 4°C for up to 5 (BD SDA) to 7 (Cobas PCR) days and used to make pools with incoming fresh specimens.

The pool results were recorded as positive, negative or inhibitory. Inhibitory pools were not retested as it was assumed that further testing would identify any positive specimens. Concordance between pool and individual results was recorded as: 1, concordant; 2, pool positive

TABLE 37 *Relationship between prevalence and optimum pool size*

Prevalence, %	Pool size	Tests per 10^4 specimens n^a
2.0	8	2742
2.5	7	3053
3.0	6	3337
3.5	6	3636
4.0	6	3839
4.5	5	4056
4.5	4	4182
5.0	5	4262
5.5	5	4464
6.0	5	4661
6.5	5	4854
7.0	4	5019
7.5	4	5179
8.0	4	5336
8.5	4	5491
9.0	4	5643
10.0	4	5939

[a] Calculated from the number of pools expected positive plus the tests on individual specimens in those positive pools.

TABLE 38 *Volume of specimens required for pooling, by specimen type and assay*

Diagnostic test	Specimen type	Pool size	Volume of each specimen	Volume in assay
Cobas PCR	Urine	4	125 µl urine	50 µl
		8	65 µl urine from two consecutive pools of four	50 µl
	Vulvovaginal swab	4	25 µl swab eluate in 2SP	50 µl
		8	12.5 µl swab eluate in 2SP from two consecutive pools of four	50 µl
BD SDA	Urine	4	1000 µl urine	2 ml
		8	500 µl urine from two consecutive pools of four	2 ml
	Vulvovaginal swab	4	500 µl lysed swab extract	2 ml
		8	250 µl lysed swab extract	2 ml

2SP, 2-sucrose phosphate.

but no positive individual samples; or 3, pool negative but contained positive individual samples. The proportion (with 95% CI) of pools in which a positive specimen was missed, and concordant results between pool and individual results, were calculated.

Results

Overall, 1664 individual urine specimens and 980 individual vulvovaginal swab specimens were tested simultaneously in pools of four and eight (*Table 39*). In total, 106 out of 416 pools of four urine specimens contained a positive specimen. When combined to form pools of eight, 92 out of 208 pools had at least one positive specimen, and 14 pools of eight urine specimens contained two positive samples. For the swab specimens, 76 out of 245 pools of four swabs contained a positive specimen and 67 out of 122 pools of eight a positive, including nine with two positive swab specimens. There were 18 pools of urine specimens and four pools of swab specimens that were initially inhibitory and would have had to be retested to identify any positive specimens. In addition, six pools of urine specimens and six of swab specimens all tested with Cobas PCR were positive, even though there were no individual positive specimens in the pools.

In 16 pools out of 624 a positive urine specimen was missed, and in six pools out of 367 a positive vulvovaginal swab result was missed. The proportion of positive pools in which a positive specimen was missed was zero for swabs tested by Cobas PCR and from 5.4–9.8% for all other pooled specimens (*Table 40*).

TABLE 39 *Results of testing individual specimens and pools of four and eight*

Test, pool size	Positives in pool	Pool result					
		Urine specimens			Vulvovaginal swab		
		Positive	Negative	Inhibitory	Positive	Negative	Inhibitory
Cobas PCR							
4	Yes	45	4	2	35	0	1
	No	4	151	4	4	85	2
8	Yes	40	3	1	30	0	1
	No	2	57	1	2	30	0
BD SDA							
4	Yes	52	5	0	37	4	0
	No	0	144	7	0	77	0
8	Yes	45	4	0	35	2	0
	No	0	52	3	0	22	0

TABLE 40 *Concordance between individual and pooled specimen results*

Test and specimen	Pool size	Total pools	Pools with positives	Pools with missed positive	% (95% CI)	Concordant pools, *n*	% (95% CI)
Cobas PCR							
Urine	4	208	49	4	8.2 (2.3 to 19.6)	194	93.3 (88.9 to 96.3)
	8	104	43	3	7.0 (1.5 to 19.1)	97	93.3 (86.6 to 97.3)
Swab	4	127	35	0	0.0 (0.0 to 8.2)	120	94.5 (89.0 to 97.8)
	8	63	30	0	0.0 (0.0 to 9.5)	60	95.2 (86.7 to 99.0)
BD SDA							
Urine	4	208	57	5	8.8 (2.9 to 19.3)	196	94.2 (90.1 to 97.0)
	8	104	49	4	8.2 (2.3 to 19.6)	97	93.3 (86.6 to 97.3)
Swab	4	118	41	4	9.8 (2.7 to 23.1)	114	96.6 (91.5 to 99.1)
	8	59	37	2	5.4 (0.7 to 18.2)	57	96.6 (88.3 to 99.6)

With pooling in groups of four specimens, the number of tests required to identify the positive individual specimens ranged from 50 to 60% of the number required if the specimens were tested individually and reduced the cost per positive specimen by about half, but missed 5–9% of positive specimens (*Table 41*). With pools of eight the number of tests required was 45–51% of the number required for individual testing, the cost per positive specimen about 60% lower, with 3–8% of positive individuals missed. The cost per positive specimen, testing either individual or pooled samples, was lower for swabs than for urine specimens because of the lower number of inhibitory specimens with swabs.

Specimen stability at ambient temperatures

Methods

This study was conducted using specimens from women attending a GUM clinic, for logistical reasons. All women attending the Milne Centre, Bristol, were asked to provide a 25-ml first catch urine specimen and a double-headed vulvovaginal swab in addition to having nurse-taken cervical and urethral swabs. The time of specimen collection was recorded and the specimens were stored at ambient temperature during transport to the laboratory. The vulvovaginal swab was transported dry.

Specimens were tested on arrival in the laboratory using the PCE EIA on cervical specimens. Specimens from women with results that were PCE EIA reactive or in the negative grey zone were then divided: one aliquot of urine was immediately frozen at –20°C and one swab from the double swab was inserted into a tube with 1 ml of 2SP and frozen. The residual urine and swab samples were held at room temperature until 24 hours from collection of the specimen had elapsed and then also frozen at –20°C. Once the

TABLE 41 *Number of specimens required to identify positive specimens, and cost per positive specimen*

Test and specimen	Positives/total	Number of tests						Missed positives in pool *n* (%)	Cost per positive test, £[b]
		Positive	Inhibitory[a]	Negative	Confirm	Total	%		
Urine									
Individual	106/1664	106	166 + 166	1392	106	1936		0	137.35
4		101 + (101 × 4)	13 + (13 × 4)	302	97	969	50.1	9 (8.5)	70.93
8		87 + (87 × 8)	5 + (5 × 8)	66	99	993	51.3	7 (7.6)	61.89
Swab									
Individual	76/980	76	6 + 6	898	76	1062		0	104.10
4		76 + (76 × 4)	3 + (3 × 4)	166	76	637	60.0	4 (5.3)	42.66
8		67 + (67 × 8)	1 + (1 × 8)	54	76	474	44.6	2 (3.0)	34.68

[a] For individual specimen testing, 10% inhibitory urine specimens and 8% inhibitory vulvovaginal swab specimens are assumed (based on average of both assays, *Table 33*).
[b] Using average of cost per test for Cobas PCR and BD SDA for each specimen type and pool size (*Tables 29* and *30*). Cost per positive specimen = total tests × cost per test/number of positives detected.

TABLE 42 *Results of testing positive chlamydia specimens after 24 and 48 hours at room temperature: urine specimens*

Cobas PCR result at 24 hours	Cobas PCR result at 48 hours			
	Positive	Negative	Inhibitory	Total
Urine				
Positive	126	4	4	134
Negative	4	13	0	17
Total	130	17	4	151
Swab				
Positive	140	2	6	148
Negative	2	4	0	6
Total	142	6	6	154

initial PCE EIA result on the diagnostic sample had been confirmed by NAAT, the study samples were removed from the freezer. An aliquot was removed for batch testing using the Cobas PCR assay and the remainder of the specimen was left at ambient temperature. All samples from patients found to be negative were discarded. The laboratory temperature was recorded using a maximum/minimum thermometer and the outside temperature was also measured. Ethical committee consent for this part of the study was obtained from the United Bristol Healthcare Trust local research ethics committee.

Statistical analysis

It was assumed that women with a positive PCE EIA cervical specimen were infected with chlamydia. It was also assumed that the results of urine and swab specimens tested at 24 hours were the same as if they had been tested immediately on arrival in the laboratory. The stability of the specimens was assessed by comparing the results of urine and swab specimens at 24 hours and 48 hours using McNemar tests for paired data.

Results

Tests were carried out on 151 paired urine specimens and 154 paired swab specimens from women with chlamydia diagnosed by positive cervical specimens tested using PCE EIA. In urine specimens, 134 were positive at 24 hours by Cobas PCR. At 48 hours, 126 (94.0%, 95% CI 88.6 to 97.4%) remained positive, four were negative and four inhibitory (*Table 42*). Excluding inhibitory specimens, there were eight discordant pairs, four that were positive at 24 hours but negative at 48 hours, and four positive at 48 hours but negative at 24 hours ($p = 1.00$).

A total of 148 vulvovaginal swab specimens were confirmed positive at 24 hours by Cobas PCR. Of these, 140 (94.5%) were again positive at 48 hours, two were negative and six inhibitory (*Table 42*). There were four discordant pairs, two negative at 24 hours but positive at 48 hours, and two negative at 48 hours, but positive at 24 hours ($p = 1.00$). Of 13 inhibitory specimens at 24 hours, eight remained inhibitory at 48 hours.

Discussion

The laboratory studies undertaken in the ClaSS project found that, in a community setting, the performance of the PCE EIA on self-taken first catch urine specimens from men and vulvovaginal swabs in women was not adequate to recommend its use in screening programmes. The strategy of retesting specimens with results in the negative grey zone for PCE EIA by NAAT did not improve the sensitivity of the assay appreciably. In men, the Cobas PCR assay used in conjunction with an inhibitory control and with confirmation of positive results using a second independent test was an acceptable strategy, and identified all true-positive results. In women, the Cobas PCR and BD SDA assays performed equally well on urine specimens and on vulvovaginal swab specimens. There was some evidence to suggest that the sensitivity of vulvovaginal swabs was slightly better than that of first catch urine specimens. Pooling of specimens in groups of four and eight reduced the number of tests required to identify positive specimens but missed up to 10% of infected specimens. Leaving specimens at room temperature for 24–48 hours did not reduce the positivity appreciably.

Methodological issues

One strength of these studies is that they were performed under field conditions within a large population-based study. They used an unselected series of prospectively collected consecutive specimens and evaluated diagnostic strategies that would be used in practice, rather than simple test comparisons. In addition, simultaneous time and motion studies were carried out to obtain accurate data about the costs of testing. Testing was carried out under routine laboratory conditions and, for the pooling studies, pooling was carried out on fresh specimens at the same time as individual specimen testing. All specimens were tested with all of the tests that were being evaluated and infection status was based on the infected person rather than the infected specimen. This can result in lower estimated sensitivities for individual tests compared with assessments comparing performance at a single site, but provides a more realistic assessment of infection status.[154,156] For women, the reference standard did not include an endocervical specimen because this would have involved a speculum examination. The reference standard for positive and negative tests used a predetermined algorithm that required concordant results in two different tests (either biologically different, PCE EIA and NAAT, or different amplification technologies). Since the tests used to generate the final result were also those under investigation, the relative sensitivity and specificity of these assays were estimated. The results of the tests under evaluation were compared with the final result that was issued to the patient. In a small number of cases this required additional NAATs to resolve persistently discordant results, so there is a potential for bias.

The study had several weaknesses. For logistical and financial reasons, the final confirmatory NAAT (real-time PCR) could not be carried out on all specimens. For logistical reasons, the specimen stability study was carried out in a clinical population rather than the study population, and baseline results were performed with a different test (PCE EIA) from the tests at 24 and 48 hours (Cobas PCR). Further, the specimen exchange study could not be reported.

The best test for large-scale chlamydia screening

In these studies the PCE EIA had sensitivities of 75% in male urine[154] and 66% for female swabs when tested using an optimal strategy of NAATs on negative grey-zone results. This falls short of the 80% lower limit recommended in clinical effectiveness guidance from the British Association of Sexual Health and HIV[40] and precludes the use of EIAs for screening. Similar results from other studies prompted the CMO's letter of September 2003, 'Use of sub-optimal testing platforms for the detection of genital *Chlamydia trachomatis* infection in England' (www.doh.gov.uk) and £8 million was made available to enable PCTs to introduce NAATs across the country.[157] However, screening in low-prevalence populations raises issues about the specificity of tests and the predictive value of a positive test. In the present study in male urine specimens, the positive predictive value using Cobas PCR was 94%, which means that one in 15 samples were false positives. Repeat testing, either using the same assay or preferably using an alternative,[158] has been suggested to reduce the number of false positives and improve specificity; this is the approach advocated by the Health

Protection Agency (HPA) Chlamydia Diagnosis Forum and is now incorporated into the HPA standard operating procedure for *C. trachomatis* testing using NAATs.[159]

At the time of the study, two NAAT platforms were available, Cobas PCR and BD SDA. In female urine and vulvovaginal swab specimens the performance and cost per test of these assays were virtually identical, and both platforms and specimen types are acceptable for large-scale screening. A third platform is now available, the Aptima system (Gen-Probe). This uses transcription-mediated amplification (TMA) to detect ribosomal RNA from *C. trachomatis* and is also a semi-automated system. Throughput of samples varies for each platform and depends on how optimally they are used. In general, the Cobas PCR and BD SDA systems can cope with 50–100 samples per day, which gives a workload of around 20,000 samples per year, while the Aptima system (not assessed in this study) is reported to be able to achieve twice this number. Fully automated systems are planned for all platforms and this should result in increased throughput.

The presence of amplification inhibitors in clinical specimens, which can result in false-negative results, is a recognised potential disadvantage of NAATs.[158] Both of the tests used in the present study have an internal control. The Cobas PCR assay offers the option of not including the inhibition control. In this study eight positive swabs and three positive urines would have been missed had the control not been used. Only 2% of male urine samples tested with the Cobas PCR assay were inhibitory and all were subsequently found to be negative for chlamydia. However, the number of inhibitory samples in the Cobas system was high for both female swabs (16%) and urine (13%). Such high levels of inhibition with dry vulvovaginal swabs were not seen by Gaydos and colleagues, who observed less than 5% inhibition.[160] In the present study, less inhibition with the BD SDA system (7% of first catch urine specimens and one vulvovaginal swab) was observed. Again, there are contradictory studies: one study in routine clinical practice observed that 6–25% of vulvovaginal swabs gave initially indeterminate results.[161] It is generally agreed that inhibition controls should be used,[159] although this is costly. The costs of repeat testing of inhibitors specimens added about 30% to the cost of a positive test.

The stability study used specimens from chlamydia-positive women from the Bristol GUM clinic. Some urine and swab specimens tested at 24 hours were negative. This is to be expected, given that these specimens were not taken directly from the site of infection. Fewer patients were positive on first catch urine (89%) than on vulvovaginal swab (96%), which was consistent with observations in the cross-sectional study. However, the study was assessing the stability of these specimens when kept at ambient temperatures for longer than 24 hours, and the comparison between results for each specimen type at 24 and 48 hours showed that there was no difference. At 48 hours there was only a small loss in sensitivity (6% or less) with either specimen type compared with 24 hours. Given that some of these specimens will contain low levels of chlamydial DNA,[162,163] this small loss in sensitivity might have been a reflection of test performance at low levels of DNA.[164] In support of this, approximately one-quarter of either specimen type that was initially negative became positive on retesting at 48 hours. If stability did decrease with time it would not be expected for specimens initially negative, presumably owing to low DNA copy number, subsequently to become positive. The authors are in the process of investigating the chlamydial DNA load in these specimens to ascertain whether this is the case or not. The results of the stability study are also consistent with observations that there was no difference in positivity rate between those specimens, in the prevalence study, tested before 96 hours compared with those tested after 96 hours.

Vulvovaginal swabs as a non-invasive specimen in women

It is generally agreed that screening is facilitated by the use of non-invasive samples, so the study investigated self-taken male urine and female urine and self-taken vulvovaginal swabs. The relative sensitivities of female urine and swabs by both Cobas PCR and BD SDA were greater than 90%. Either sample would therefore be acceptable as a screening test from the technical point of view. The slightly higher sensitivities found with vulvovaginal swabs support the findings of other studies.[165–171] In addition, the cost per positive test was about 30% lower for vulvovaginal swab than for first catch urine specimens, largely owing to the lower number of inhibitory swab specimens tested by BD SDA. The time take to process the two specimen types was very similar, but urine specimens are thought to be more difficult for inexperienced staff to process,[172] and between-centre variation in estimated sensitivity might be greater for first catch urine specimens (range 50–100%) than for vulval swabs (range 70–100%, with only one centre less than 90%).[173] Published

studies performed with women attending STD and family planning clinics have shown that vulvovaginal swabs are acceptable, but the preferred specimen was urine in three studies[167,174,175] and vulvovaginal swabs in one.[176] A small proportion of women in this study, and others,[167] said that they did not take part in screening because they did not want to take a swab specimen themselves.

Potentials and pitfalls of specimen pooling

Pooling resulted in a loss in sensitivity with BD SDA on both first catch urine and vulvovaginal swab specimens, and on first catch urine with Cobas PCR but not vulvovaginal swabs. The sensitivity of the BD SDA compared with testing individual urine and swab samples was 90–95% and 91–93% for urines tested with Cobas PCR. This is consistent with the observations of Bang and colleagues on pooling swabs.[177] As pooling dilutes the original specimen target DNA levels may fall below the detection level of BD SDA, which may have a lower analytical sensitivity than other NAATs.[178] The level of target DNA in female first catch urine is lower than that in vulvovaginal swabs.[162] About 10% of female first catch urines, compared with less than 2% of vulvovaginal swabs, from a sample of 64 chlamydia-positive women in this study, had DNA levels that would mean that fewer than ten molecules of target would be present in either the BD SDA or Cobas PCR mixes.[163] This is approaching the lower limit of detection for NAATs. In some studies of pooling the sample to cut-off ratio has been reduced to compensate for the effects of dilution. This was not done in the present investigation, because preliminary studies showed that the tests picked up known positive specimens diluted at 1:8. One advantage of pooling was that, probably because of dilution, the number of inhibitory pools was lower than with individual specimens, and this further reduced the costs of pooling.

In summary, these results support existing data about the performance of NAATs on urine and vulvovaginal swab specimens. The performance of an amplified EIA with repeat testing of specimens in the negative grey zone was inadequate for population screening. Vulvovaginal swab specimens had slightly higher relative sensitivity than urine specimens, but the qualitative studies showed some concerns from women. A systematic review is required to determine whether there is a clinically important advantage for swab over urine specimens from women. The study using pooled urine specimens found that up to 10% of positive specimens would be missed using this method. Decisions about whether or not to pool specimens for chlamydia testing depend on whether the gains in time and money are considered to balance the loss in sensitivity. In screening programmes where the screening test is also a diagnostic test this may not be an acceptable balance.

Chapter 8

Systematic review of economic evaluations of chlamydia screening

There were three components to the economic evaluation of chlamydia screening. A systematic review of economic evaluations of chlamydia screening was carried out to inform primary studies collecting data about the costs of chlamydia screening, and the construction of a mathematical model of the transmission of chlamydia, from which the cost-effectiveness of chlamydia screening was investigated. The systematic review is reported in this chapter, and the patient cost and modelling studies are reported in Chapters 9 and 10.

Objectives

The objectives of this review were:

- to assess the evidence for the cost-effectiveness of different approaches to chlamydia screening in both men and women, with a particular focus on the appropriateness of the models used
- to assess the data requirements for a simulation economic and epidemiological model
- to identify areas of uncertainty that should be explored in a full economic evaluation of chlamydia screening.

A condensed version of this report has been published elsewhere.[253]

Methods

Eleven electronic bibliographic databases were searched from the earliest date available to August 2004 using a search strategy that included keywords such as chlamydia, pelvic inflammatory disease, economic evaluation and cost (Appendix 2).

Inclusion criteria

The following inclusion criteria were applied:

- **Participants:** males and/or females aged 14 years and above
- **Interventions:** any form of screening intervention for chlamydia, including both non-selective and selective opportunistic or population screening; also, studies that reported on diagnostic tests, contact tracing and treatment as part of a screening programme
- **outcomes:** cases of chlamydia identified and major outcomes averted (pelvic inflammatory disease, ectopic pregnancy or infertility)
- **studies:** formal economic evaluations, including cost-effectiveness analysis, cost–utility analysis, cost–benefit analysis and cost-minimisation analysis; primary studies of the costs and uptake of screening.

Selection of papers for review

The initial search was carried out in 2000 and was finally updated in August 2004. Two investigators (TR, SR) categorised papers independently in a two-stage process, resolving differences through discussion.[179] First, the title and abstract were used to allocate each paper to one of five categories (A–E) according to relevance (Appendix 3). All studies that reported primary research, including a formal economic evaluation (A) and reports including useful cost or utilisation data (B), were selected and read in full. The researchers reviewed in full a random selection of papers that included useful information but did not obviously fall into the first two categories (C), having agreed a priori to review all papers in this category if any was deemed to be relevant and to exclude all at this stage if none was.

Two investigators (TR, SR) extracted information about the study design, methods and results from each paper independently in a standardised manner, using an agreed pro forma, resolving differences by discussion. The quality of included studies was assessed using previously published criteria that were adapted from published guidelines (*Box 2*).[179,180] First, the quality of economic aspects of the studies was assessed. Papers failing more than two criteria were excluded. Papers failing two items were reviewed to identify key messages contained in the papers and marked with a query. Papers that failed one or none of the items were reviewed in full and marked with a pass. In the second stage the modelling approach was recorded and the appropriateness of the methods assessed

General quality criteria
- The research question is stated, implied or apparent and the rationale for the choice of alternative interventions for comparison should be given.
- The viewpoint(s) of the analysis are stated or implied.
- The source(s) of effectiveness estimates used are stated, implied or apparent, and appropriate.
- The primary outcome measure(s) are stated, implied or apparent.
- Quantities of resources are reported separately from their unit costs, or can be derived.
- Currency and price data are recorded.
- Details of currency or price adjustments for inflation or currency conversion are given (if appropriate).
- The discount rate is stated or is apparent, and is justified (if relevant).
- Details of any modelling used in the economic study are given.

Quality of modelling approach
- The choice of model used and the key parameters on which it is based are justified/appropriate.

Adapted from Roberts *et al*. (2002)[179] and Mugford (2001).[180]

BOX 2 *Quality assessment criteria*

qualitatively. The screening interventions were also categorised using the four categories described in the section 'Screening for chlamydia' (p. 3). The investigators used their own judgement to classify interventions unless study investigators clearly specified the type of screening intervention.

Results

The search identified 713 papers (*Figure 13*). Of these, 327 were potentially relevant and 190 papers were reviewed in full. None of those of uncertain relevance (category C) fulfilled the inclusion criteria and all other papers in this category were excluded. There were 57 formal economic evaluations and two cost studies. Of 59 papers that were assessed for quality, four were excluded.[181–184] No studies were excluded on the basis of an inappropriate modelling approach, but this was taken into account in the interpretation of the results.

Studies of chlamydia screening interventions

Twenty-nine papers had a primary focus of screening. The characteristics of these studies are summarised in *Table 43*. Further details of each study are summarised in Appendix 4. Eleven papers evaluated selective opportunistic screening,[131,185–192] including two cost studies.[144,193] These studies were based in settings such as general practice, family planning and antenatal clinics, and selected individuals based on specified criteria, including age. All used static models. Most economic evaluations in this group suggested that screening was cost-effective. Many specified an age range for which screening would be cost-effective, for instance under 30 years, 18–24 years, or for a given prevalence rate.

Fourteen papers evaluated non-selective opportunistic screening interventions, which typically included any individual visiting a general practice or gynaecology clinic.[25,194–206] The majority of these papers concluded that this type of screening was cost-effective. The majority of these studies (12/14) used static modelling approaches that were judged to be inappropriate for making policy recommendations. For example, Goeree and colleagues.[206] suggested that screening all women aged 15–24 years would be considerably more cost-effective than screening only high-risk women. This analysis was carried out using a Markov model with an outcome of cases of pelvic inflammatory disease and related sequelae avoided.

Only two papers used a transmission dynamic model that incorporated the effects on chlamydia transmission of reinfection and partner notification.[198,199] Welte and colleagues suggested that opportunistic screening of asymptomatic heterosexual men and women attending general practices would become cost-saving after about 5 years if over 90% of eligible individuals were screened annually.[198] Townshend and Turner evaluated various chlamydia screening scenarios, including opportunistic screening at general practices of men and women aged 20–40 years, using a hypothetical cohort and literature-based cost and effectiveness data.[199] This model informed the CMO's Expert Advisory Group report and concluded that screening was broadly cost-effective.[3] The report suggested that the proposed screening programme would prevent significant numbers of infertility cases annually, depending on the probability of infertility following an episode of pelvic inflammatory disease, and that the screening programme could pay for itself after 4 years.

Two studies evaluated selective population screening in female army recruits.[207,208] These studies considered screening of all recruits and only those under 25 years on entry to be cost-effective using static modelling approaches. Two

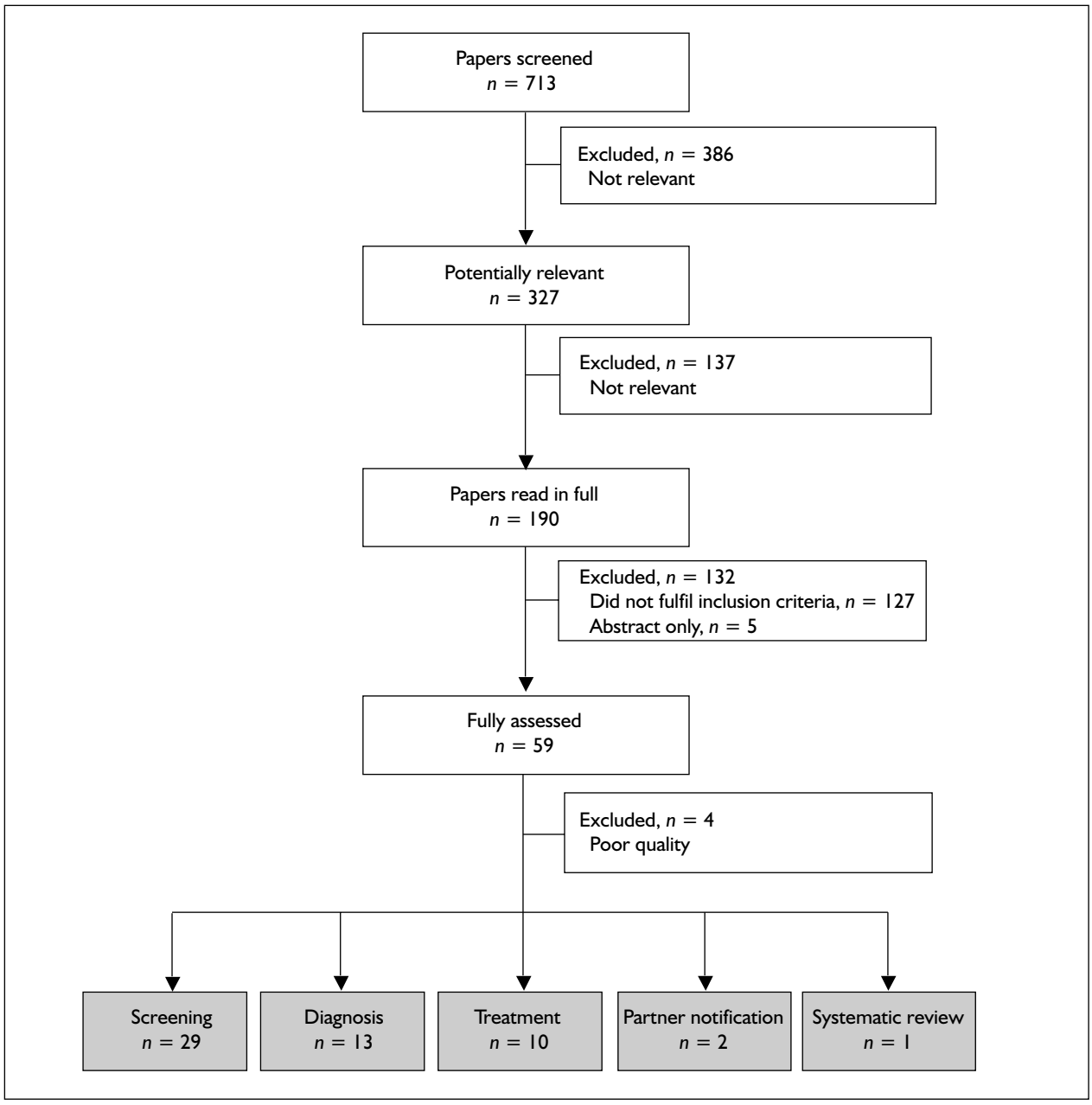

FIGURE 13 *Flowchart of selection of economic evaluations of chlamydia screening*

papers evaluated non-selective population screening.[92,209] Van Valkengoed and colleagues evaluated home-based postal chlamydia screening in women. Using a static model they concluded that postal screening with an uptake of 50%, even when targeted to 15–25 year olds, was not cost-effective at expected levels of prevalence.[92]

Partner notification

Three papers investigated partner notification in detail (*Table 44*).[186,210,211] The two studies evaluating cost-effectiveness did not use a transmission dynamic model. Howell and colleagues recommended that in STD clinics female partners of infected men should be notified when the prevalence of female infection exceeded 12% and that male partners of infected women should be notified when male prevalence was greater than 29%.[211] Postma and co-workers found that treating partners of chlamydia-infected women identified through opportunistic screening reduced the cost per major outcome averted by 50%.[186] They acknowledged the limitations of static models and proposed it as a first step to exploring the relative cost-effectiveness of successful partner notification. The study by Katz

TABLE 43 *Summary of characteristics of economic evaluations of chlamydia screening interventions, by publication year*

Study	Type of screening				Outcome		Model		Target population			Cost-effectiveness, screening recommended		
	SO	SP	NSO	NSP	MOA	Short term	Static	TDM	F	M&F	M	Yes	No	Comments
Adams, 2004[144]	✓				NA		None	✓				–		Cost study only
Hu, 2004[194]	✓				✓		✓		✓			✓		Annual screening women 15–29 years, cost-effective. Cost per QALY reported
Blake, 2004[185]	✓						✓				✓	✓		Universal NAAT screening most cost-effective
Ginocchio, 2003[196]			✓	✓	✓		✓				✓	–		Cost-effective if test costs <$18
Mehta, 2002[195]			✓			✓	✓			✓		✓		Mass treatment most cost-effective
Wang, 2002[209]				✓	✓		✓			✓		✓		School-based screening cost-saving
Postma, 2001[186]	✓				✓		✓			✓		–		Partner notification improves cost-effectiveness
van Valkengoed, 2001[92]				✓	✓		✓		✓				✓	NSP screening women 15–40 years not cost-effective
Goeree, 2001[206]	✓				✓		✓		✓			–		Screening high-risk women most cost-effective
Postma, 2000[197]			✓		✓		✓		✓			✓		Screen women under 30 years
Welte, 2000[198]			✓		✓			✓		✓				Screening may be cost-saving in long run. High estimated probability of complications
Townshend, 2000[199]			✓		✓			✓		✓		✓		Screening cost-saving after 4 years. Poor reporting of cost data
Howell, 2000[207]		✓			✓		✓		✓			✓		Screening army recruits is cost-effective
Shafer, 1999[187]	✓				✓		✓					–		ICER presented. Judgement unclear
Howell, 1999[208]		✓			✓		✓		✓			✓		Age-based screen cost-saving
Howell, 1998[200]			✓		✓		✓		✓			–		Age-based screening most cost-effective
Gunn, 1998[193]	✓					✓	None				✓	–		Result presented as cost per case
Paavonen, 1998[25]			✓		✓		✓		✓			✓		NSO screening cost-effective even at low prevalence
Genc, 1996[201]			✓			✓	✓			✓		–		Cost-effective under specific conditions
Marrazzo, 1997[202]			✓		✓		✓		✓			✓		Screening in FP/STD clinics cost-saving

continued

TABLE 43 *Summary of characteristics of economic evaluations of chlamydia screening interventions, by publication year*

Study	Type of screening				Outcome		Model		Target population			Cost-effectiveness, screening recommended		
	SO	SP	NSO	NSP	MOA	Short term	Static	TDM	F	M&F	M	Yes	No	Comments
Genc, 1993[203]			✓		✓		✓				✓	–		Cost-effective under specific conditions
Sellors, 1992[131]	✓					✓	NA		✓			–		SO screening cost-effective compared with NSP
Nettleman, 1991[188]	✓					✓	NA		✓				✓	Not cost-effective to screen all pregnant women
Buhaug, 1989[190]	✓				✓		✓		✓			✓		Testing cost-effective for women <24 years only
Buhaug, 1990[189]	✓				✓		✓		✓			✓		Testing cost-effective for women 18–22 years only
Begley, 1989[204]			✓			✓	NA			✓		✓		Screening in FP clinics is cost-effective
Skjeldestad, 1988[191]	✓					✓	NA		✓			–		Screening for women seeking abortion
Trachtenberg, 1988[192]	✓				✓		✓		✓			✓		Screening asymptomatic women is cost-effective
Phillips, 1987[205]			✓			✓	✓		✓			✓		Testing for *C. trachomatis* is cost-effective

F, females; FP, family planning; ICER, incremental cost-effectiveness ratio; M, males; MOA, major outcome averted; NSO, non-selective opportunistic screening; NSP, non-selective population screening; QALY, quality-adjusted life-year; SO, selective opportunistic screening; SP, selective population screening; TDM, transmission dynamic model.

TABLE 44 *Summary of characteristics of economic evaluations of partner notification for chlamydia infection, by publication year*

Study	PN strategy			Outcome		Model		Target population			Cost-effectiveness, PN recommended		
	M partners of F	F partners of men	Either	MOA	Short term	Static	TDM	F	M&F	M	Yes	No	Comments
Postma, 2001[186a]	✓			✓		✓		✓			✓		PN improves cost-effectiveness by 50%
Howell, 1997[211]			✓		✓	✓			✓		✓		PN more cost-effective for female partners of male cases than for male partners of female cases
Katz, 1988[210]			✓		✓	None			✓				Field follow up by trained investigators most cost-effective

PN, partner notification.
[a] Study also included in *Table 43*.

evaluated the best way of locating partners rather than the effectiveness of partner notification as part of a screening programme, so a dynamic model was not required.[210]

Diagnostic testing

Thirteen papers focused on diagnostic testing in chlamydia screening programmes (*Table 45*). The range of alternative testing procedures and samples made it impossible to identify the single most cost-effective test. The papers fell into two broad categories: those looking at short-term (restricted) outcomes such as test and treat only, and those attempting to use longer term outcomes such as major outcome averted. Nine papers were based on a restricted outcome of cost per case detected,[183,204,212–218] but only one paper explicitly acknowledged this type of analysis as a partial evaluation and recommended further work before robust policy recommendations could be made.[213] One paper used an appropriate transmission dynamic model, discrete event simulation, to compare two NAATs with an EIA.[219] There was, however, no clear measure of effectiveness and the results of the model suggested that an inadequate number of replications of the model was run.

Treatment

The ten papers with a primary focus of treatment are summarised in *Table 46*. Seven of these compared azithromycin (1 g single dose) with doxycycline (100 mg twice daily for 7 days).[220–226] All studies assumed 100% compliance for azithromycin in their base-case analysis, but 75–87% for doxycycline. Four studies recommended single-dose azithromycin as the treatment of choice[221,223–225] on cost-effectiveness grounds, assuming that incomplete adherence led to more treatment failures. Petitta and colleagues found that both azithromycin and a prepacked course of doxycycline reduced infection rates compared with a prescription for doxycycline, and acknowledged that cure is likely even without completing the 7-day course.[220]

Other characteristics of studies

In terms of analytical approach, 12 studies used no model, 34 studies used a static decision tree, two used Markov chain models,[190,206] one used an unspecified simulation model[189] and one used an undefined 'mathematical model'.[225] The most recent paper used a state-transition model.[194] Only three papers used an appropriate transmission dynamic model: one a system dynamic approach,[199] and two discrete event simulation models.[198,219] Of 31 studies that focused on screening or partner notification 18 considered programmes that screened women only. Only three studies considered screening both women and men.[198,199,204]

Overall, 23 studies used a restricted outcome of 'cost per case detected'. The remaining economic evaluations used 'major outcome averted' (MOA) or equivalent outcomes, which typically referred to cases of pelvic inflammatory disease, ectopic pregnancy and infertility. The three dynamic modelling studies used MOA.[198,199,219] Information about the risk of developing major outcomes was usually stated to be based on published literature. The probability of developing pelvic inflammatory disease following chlamydial infection was generally in the range of 0.25–0.30. Only one study conducted extensive sensitivity analyses according to assumptions about the number of pelvic inflammatory disease cases averted and the probability of infertility, and found that these have an important impact on the estimate of cost-effectiveness.[199]

Discussion

This systematic review identified a substantial number of economic evaluations addressing different aspects of chlamydia screening. Most of these studies found both opportunistic and population-based chlamydia screening to be cost-effective, partner notification to be an effective adjunct to a chlamydia screening programme, and testing with NAATs and treatment with azithromycin to be cost-effective. Three main methodological issues that were identified threaten the validity of these findings. First, most studies used a static modelling approach that is inappropriate for the study of infectious diseases. Secondly, restricted outcomes such as cost per case detected should not be used as a basis for policy recommendations. Thirdly, many studies did not acknowledge or investigate the uncertainty associated with probability estimates for the long-term sequelae associated with chlamydia infection.

Methodological issues

The strengths of this study are that, to the authors' knowledge, it provides the most comprehensive review to date of economic evaluations of screening, partner notification, diagnostic and treatment aspects of chlamydia screening programmes, and it is the first review in this area to critique the quality of modelling approaches used in the

TABLE 45 *Summary of characteristics of economic evaluations of diagnostic tests for use in chlamydia screening, by publication year*

Study	Diagnostic test			Outcome		Model		Target population			Cost-effectiveness, test strategy recommended		
	NAAT	EIA	Other	MOA	Short term	Static	TDM	F only	M&F	M only	Yes	No	Comments
Mrus, 2003[212]	C		✓		✓	✓			✓		–		Urine LE test produced lowest ICER
Sahin-Hodoglugil, 2003[227]			✓		✓	✓		✓			✓		Joint focus with treatment. Mass treatment with doxycline was most cost-effective strategy
Browning, 2001[216]	✓		C		✓	None		✓			–		SDA assay best test in GUM clinics
Scoular, 2001[213]	✓	C			✓	None		Not specified			✓		Testing with LCR would provide health gains
Nyari, 2001[228]			✓	✓		✓		✓			✓		Screen by amplified Gen-Probe is best
Knight, 2000[219]	✓			No outcome			✓	✓			–		Cost study only. LCR lowers costs but global screening not cost-effective
Kacena, 1998[51]	✓				✓	None					–		Pooling study. Pools of four reduce cost at prevalence <8%
Peeling, 1998[215]	✓		C		✓	None				✓	–		Targeted screening reduces costs in Canada
Howell, 1998[229]	✓	C	C	✓		✓		✓			–		LCR on cervical specimens most cost-effective
Dryden, 1994[217]		✓	C		✓	None			✓		–		Result presented as cost per infection cured
Sellors, 1993[218]	✓		C		✓	None				✓	–		LE urine strip accurate at lower cost than NAAT
Estany, 1989[230]			✓	✓		✓		✓			–		DFA test and EIA cost-effective for given prevalence
Nettleman, 1988[214]			✓		✓	✓			✓		✓		Culture compared with antigen testing not cost-effective

C, comparator; DFA, direct fluorescent antibody; LCR, ligase chain reaction; LE, leucocyte esterase.

TABLE 46 *Summary of characteristics of economic evaluations of chlamydia treatment, by publication year*

	Treatment		Outcome		Model		Target population			Cost-effectiveness, treatment recommended		
First author	**AZM vs Doxy**	**Other[a]**	**MOA[b]**	**Short term[c]**	**Static**	**TDM**	**F only**	**M&F**	**M only**	**Yes**	**No**	**Comments**
Gift, 2004[226]	✓		✓		✓		✓				✓	Coinfection with gonorrhoea. Routine dual treatment not a cost-effective replacement for testing
Moriarty, 2001[225]	✓			✓	✓		✓			AZM		AZM significantly more cost-effective
Petitta, 1999[220]	✓			✓	✓			✓				Both treatments decreased infection and costs
Marra, 1997[224]	✓			✓	✓		✓			AZM		AZM recommended treatment
Hueston, 1997[231]		✓		✓	✓		✓			AZM		AZM most cost-effective
Genc, 1997[222]	✓			✓	✓			✓				Doxy most cost-effective when compliance assumed >80%
Magid, 1996[223]	✓		✓		✓					AZM		AZM most cost-effective
Haddix, 1995[221]	✓			✓	✓		✓			AZM		AZM most cost-effective
Schiotz, 1992[232]		✓	✓		✓							Routine test of cure after treatment for chlamydia not cost beneficial
Washington, 1987[233]		✓		✓	✓		✓					Combined treatment more cost effective than tetracycline

AZM, azithromycin; Doxy, doxycycline.

evaluation. The main weakness of the review is that poor methodological quality, or at least reporting of the methodology, made it difficult to interpret the findings or to draw conclusions.

Comparison with other studies

One other systematic review was identified . Honey and colleagues reviewed economic evaluations of screening for chlamydia in women in primary care settings only.[91] The outcomes assessed were cases of pelvic inflammatory disease prevented or cases of chlamydia detected and the authors concluded that screening women for chlamydia in primary care is cost-effective. This conclusion is potentially misleading because the conclusions were based on the results of studies that used a restricted outcome such as cost per case detected, or whose results were derived from static models.[93] The authors did not discuss these limitations. This review highlighted the poor quality of data on long-term outcomes associated with chlamydia, which was supported by the findings of the present study.

Economic evaluations of infectious diseases

Infectious diseases such as chlamydia present specific challenges for economic evaluation. The interactions between individuals with STIs mean that the risk of infection depends on background prevalence; screened and treated individuals will not transmit infection, but are susceptible to reinfection, and sexual partners that remain untreated can also continue to transmit infection. Most healthcare interventions do not involve interactions between individuals receiving the intervention, and decision-tree analysis and Markov chain models, which assume that individuals are independent are ideal for these situations.[234] Two main approaches take into account the full economic consequences of interpersonal interactions: discrete event simulation (which works at an individual level) and system dynamics (aggregated level).[234] These methods provide more realistic representations of complex systems, but are computationally more complex.

Since 2000 both discrete event simulation[198,235] and system dynamics have been used to model the transmission of chlamydia and the cost-effectiveness of screening.[199] Despite increasing recognition of the importance of using an appropriate modelling approach,[194] the nine economic evaluations of chlamydia screening published since 2000 all used static models.[92,185,186,194–196,206,209,212] This may reflect publication lead time, but probably also reflects the view that the simplicity of static models outweighs the limitations of violating the assumption of independence. The most recent economic evaluation in this review attempted to incorporate the transmission dynamics of chlamydia into a (static) state-transition model by using population averages for variables such as rates of partner change and sexual mixing.[194] While there are circumstances, such as immunisation programmes, in which the results from static models approximate those of a dynamic model, and cohort models nearly always underestimate the cost-effectiveness of interventions,[236] the same conditions do not apply in chlamydia screening, where lasting immunity is not a strong feature of infection.

Cost-effectiveness of chlamydia screening

The two high-quality cost-effectiveness analyses based on the modelling approach suggested that opportunistic chlamydia screening would pay for itself or be cost-saving after 4–5 years.[198,199] These conclusions are, however, called into question by other methodological limitations. The study by Townshend and Turner, based on a hypothetical population, reported insufficient details of the cost data used, so the results are difficult to interpret.[199] The study by Welte and colleagues, which used empirical data about the coverage and uptake of opportunistic screening in primary care in The Netherlands, used published estimates for the risk of long-term sequelae, and unrealistic estimates of resource use (e.g. 10 days' hospital inpatient treatment for pelvic inflammatory disease) that might be overestimated.[198] Both of these assumptions would make screening appear more cost-effective.

The outcomes selected for economic evaluations are critical to the usefulness of the study for making policy recommendations. Almost half of the studies in this review used a restricted outcome such as 'cost per case detected' for their analysis. This kind of outcome should not be used as a basis for policy recommendations because it does not give any indication of the final success of the screening programme, particularly for an infectious disease where the consequences of transmission determine prevalence. Information on pathway, prognosis, final outcome and resources used after detection of the disease is required.[237] Nevertheless, studies using short-term outcomes continue to make policy recommendations about screening,[195,204,205] partner notification,[211] diagnosis[213,214,227] and treatment.[221,224,225] The use of major outcome

averted is also problematic in studies of chlamydia screening.[91] The uncertainty about the probability of developing sequelae associated with chlamydia was often not investigated in detailed sensitivity analyses, although cost-effectiveness estimates are highly sensitive to this assumption.[199]

The issue of who should be targeted for screening remains controversial. The majority of studies in this review focused on screening women only. A justification for this was not usually presented, but likely assumptions are that young women are most likely to access health services and that male partners would be picked up by partner notification programmes or develop symptoms and seek treatment. It is now known, however, that partner notification reaches only 50–60% of partners[136] and that asymptomatic chlamydia is as common in men as in women.[97] Thus, the focus on women only in screening programmes risks leaving a pool of infected men in the community who can continue to spread the disease.

On the basis of this review no firm conclusions could be drawn about the cost-effectiveness of alternative forms of chlamydia screening because of methodological flaws in most studies conducted to date. This review has highlighted the importance of appropriate modelling approaches and primary outcomes in economic evaluations that seek to make recommendations to influence health policy decisions. It has also drawn attention to fundamental gaps in the evidence about the probabilities of progression to long-term outcomes associated with chlamydia, which limit studies even when the appropriate model and outcomes are used.

Chapter 9

Primary study of the costs of population-based chlamydia screening

Objectives

The objectives were two-fold:

- to estimate the health service costs, including programme administration, of active chlamydia screening
- to estimate the private costs incurred by patients of active chlamydia screening.

A condensed version of this report has been published elsewhere.[254]

Methods

Health service costs

Decision-tree diagrams (Treeage Data 4, USA) were constructed to describe the flow of patients from initial screening invitation to treatment. Then, the unit cost of each component of the screening process was estimated and applied to the number of people passing through each stage of screening. For the screening test the costs of Cobas PCR, and for female specimens the costs of processing vulvovaginal swabs were used, because these were the cheapest NAAT and specimen type assessed (see *Table 28*, p. 63). Treatment costs included a consultation with a practice nurse and single-dose azithromycin (using the British National Formulary cost). The costs of partner notification done by a practice nurse at the general practice are reported, because this was as effective as referring patients to a health adviser at a genitourinary medicine clinic (see *Table 23*, p. 56).[136] The antibiotic costs were included for partners, who were all treated epidemiologically, but costs for chlamydia testing for partners were excluded, as this was defined as a separate screening episode.

The running costs of home-based population chlamydia screening were estimated by including the costs of reminders for non-responders and non-attenders, project management and other practice costs, including administration, overheads and training for practice nurses. Personnel costs were derived from salary costs including employer contributions directly from the study.

Patient costs

All patients attending their general practice were asked to complete a patient cost questionnaire, adapted from a published study.[238] The costs incurred by sexual partners were not measured. All participants provided information about their mode of transport, time spent travelling to the surgery (it was assumed that the return journey was the same duration) and out-of-pocket expenses such as car-parking, petrol and public transport. Consultation times for participants with positive results included the time taken to receive the result and treatment, and for the practice nurse to explain the RCT of partner notification, obtain consent, randomise and undertake partner notification herself or refer the patient to the GUM clinic.

Costs for private car travel were calculated using published motoring costs.[239] It was assumed that walkers and cyclists incurred no travel expenses. The distances travelled between participant and surgery postcodes were estimated using Multimap (www.Multimap.com). The opportunity cost of time lost from work was estimated from the mean gross weekly wage rate in Great Britain at April 2003 minus tax, pension and national insurance contributions (estimated at 35% of gross salary) and at the average hourly rate for a 37.5-hour week. It was assumed that employed patients under 18 years in employment, students and those looking after children had an opportunity cost approximating the minimum wage.
Other activities forgone were classified as 'leisure time' and valued at 40% of the mean average wage.[238]

Statistical analysis

Total health service costs at each stage of screening and treatment were estimated and the number of individuals at each stage was used to estimate the cost (with 95% CI) per screening invitation and per accepted offer. Mean travel, waiting and consultation times, and their associated costs (with 95% CI) were estimated from

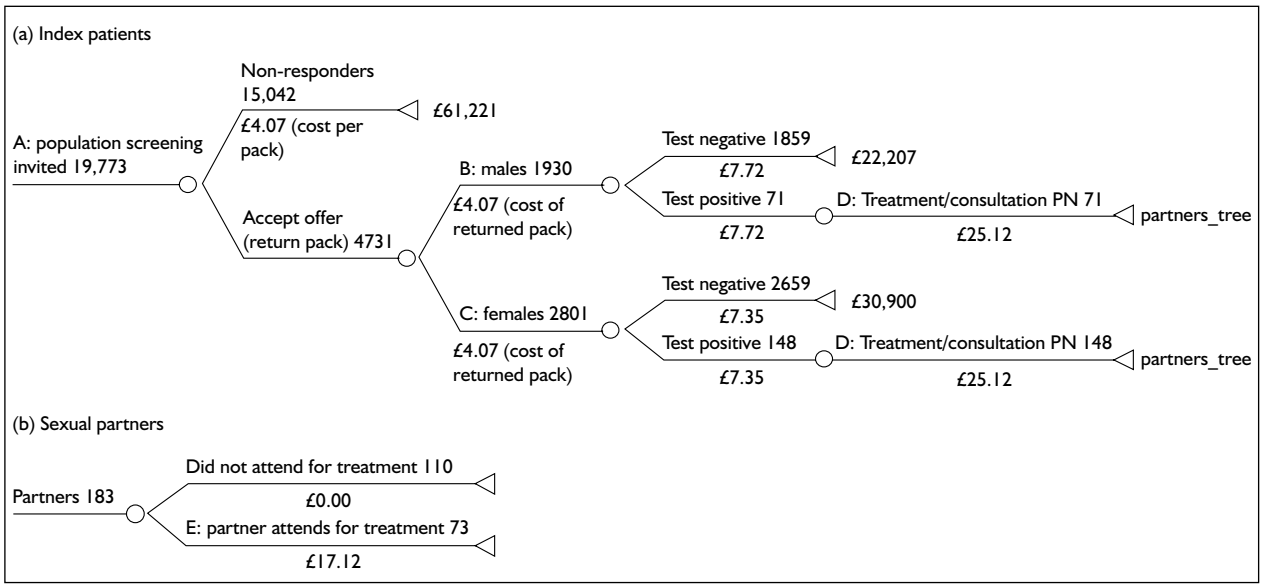

FIGURE 14 *Index patient pathway. For each branch option, the number who flowed through that branch is above the line and the unit cost is below. The aggregated costs of each stage are shown by the following letters: A, cost per screening invitation; B, cost per screening test in men; C, cost per screening test in women; D, cost of treatment per index case, including partner notification (PN); E, Cost treatment per sexual partner.*

the cost questionnaire. Travel and surgery waiting times for patients with both positive and negative chlamydia results were virtually identical, so these were combined to increase precision. Only consultation times from people with positive results were used. All costs were inflated to 2005 prices (£ sterling, *Table 47*).

A sensitivity analysis was conducted to explore the effects of applying the average wage rate to all participants, the minimum wage rate to all participants, the average wage to leisure time, and the current job seeker's allowance rate to all those not in employment. The effect of increasing the uptake rate, which was a major influence on the cost of opportunistic screening for chlamydia,[144] was also considered.

Results

Health service costs

Figure 14 shows the patient flow through each stage of the screening process, and the path followed by sexual partners. The cost of each returned pack includes only the cost of the packing and contents: the postage costs of returning the packs (B and C) were included in the test costs.

Table 47 shows the health service costs of each component of the screening process.

Table 48 shows the average costs for each screening invitation and for each person accepting the offer of screening. The average cost to the health service, including the cost of running the study, was £14.65 (95% CI £14.23 to 15.46) per individual screening invitation. The cost per person screened was £21.74 (95% CI £20.75 to 24.88). In sensitivity analysis, if the uptake of home-based screening had been 64%,[144] the average cost per screening offer would be £19.72 (£18.51 to 20.03).

Patient costs

In total, 411 responses (147 chlamydia positive, 264 negative) were received from 479 patients, a response rate of 86%.

Travel to the surgery

Most participants travelled to the general practice by car or on foot. Applying average travel costs to the estimated distances travelled, a car journey to and from the surgery was estimated at £1.49 (95% CI £1.46 to 1.57) per patient, and public transport at £1.06 (95% CI £0.77 to 1.40) per patient for the return journey. The overall average out-of-pocket expense per patient for all modes of transport was £0.26 (95% CI £0.16 to 0.72).

Time spent at the surgery

The average waiting time was 10.5 minutes (95% CI 8.5 to 12.5) (*Table 49*). For participants with positive chlamydia results, the consultation time

TABLE 47 *Health service costs of chlamydia screening using posted, home-collected specimens*

Resources used	Cost item	Unit cost, £[a]	*n*	Total cost, £ (95% CI)[a]
Screening invitation			19,773	
Invitation letter	Per letter	0.09		–
Postage	Per stamp	0.21		–
Study packs	Per pack	3.39		–
Result/appointment letter and postage	Per letter postage	0.38	–	
A: Cost per screening invitation		4.07		80,476.11
Laboratory costs				
Accepted screening offer[b]			4,731	
B: Cost per screening test, male	Per urine specimen	7.72	1,930	14,899.60 (13,122.22 to 21,175.42)
C: Cost per screening test, female	Per swab specimen	7.35	2,801	20,587.35 (17,590.16 to 28,477.33)
Treatment costs				
Index case			219	–
Antibiotics (azithromycin)	Per dose	12.71		2,783.49
Nurse consultation, including PN	Per consultation	12.41		2,717.79 (2,405.13 to 3,033.66)
D: Treatment of index case, including PN		25.12		5,501.28 (5,188.30 to 5,816.83)
Sexual partners			183	
Antibiotics (azithromycin)	Per dose	12.71		2,325.93
Consultation[c]	Per consultation	4.41		807.03
E: Treatment of partners		17.12		3,132.96
Total cost of screening episode				124,009.09 (121,243.45 to 134,827.95)
Screening programme costs				
Reminder letters	Per letter	0.09	11,462	1,031.58
Postage	Per stamp	0.21	11,462	2,407.02
Reminder packs	Per pack	3.39	809	2,742.51
Vouchers sent	Per voucher	10.00	2,171	21,710.00
Telephone calls[d]	Per call	1.55	124	192.20
Visits[e]	Per visit	31.77	17	540.09
General practice costs[f]				16,127.50
Project manager				120,299.72
F: Study expenditure cost				165,050.62

[a] Costs were inflated to £UK at 2005 rates.
[b] Cost of returning pack (£0.63) is included here.
[c] Personal Social Services Research Unit (PSSRU) cost of health adviser consultation at GUM clinic (PSSRU, 2004).
[d] Cost of telephone calls to people with positive chlamydia tests who defaulted from appointment to receive results (unit cost based on data from Bristol site only).
[e] Cost of follow-up visits to people with positive chlamydia tests who did not respond to appointments or phone calls (unit cost based on data from Bristol site only).
[f] Includes training of practice nurses and payments made to general practices to cover administration, running costs and overheads.

included the time taken to give the result and treatment, to explain the randomised trial of partner notification, obtain consent, randomise and either undertake partner notification at the surgery or explain the process of referral to a GUM clinic. Consultation times were similar for both partner notification strategies and for people who took part in or declined participation in the partner notification trial so data for all groups were combined: the average consultation time was 36.7 minutes (95% CI 35.7 to 41.2). The total time imposed upon individuals as a result of the screening programme was estimated to be 75.2 minutes (95% CI 71.3 to 82.5) per patient.

Opportunity cost

If patients had not been attending the general practice, almost 59% reported that they would have been in paid employment, 19.8% (81) patients said they would have been studying and

TABLE 48 *Average costs of screening invitation and offer*

	No. of individuals	Average cost, £ (95% CI)[a]
NHS cost per individual screening invitation[b]	19,773	14.65 (14.23 to 15.46)
NHS cost per accepted screening offer[c]	4,731	21.74 (20.75 to 24.88)
Patient cost	411	6.82 (5.43 to 10.22)
Total cost per screening invitation	19,773	21.47 (19.91 to 25.99)
Total cost per accepted screening offer	4,731	28.56 (22.10 to 30.43)

[a] Costs inflated to £UK 2005.
[b] Includes, from *Table 47*: (A+B+C+D+E+F)/19,773 patients invited.
[c] Includes, from *Table 47*: [(A/19,773) × 4731 + B+C+D+E+(F/19,773) × 4731]/4731.

TABLE 49 *Patient time and travel costs of attending GP surgery*

Activity	Time in minutes, mean (95% CI)	Cost, £ mean (95% CI)[a]
Travel to surgery	27.98 (26.40 to 29.55)	2.45 (2.16 to 2.73)
Surgery waiting time[b]	10.47 (9.27 to 11.68)	0.90 (0.23 to 2.03)
Surgery consultation time[a]	36.74 (35.67 to 41.23)	3.21 (2.88 to 3.56)
Out-of-pocket expenses	–	0.26 (0.16 to 0.72)
Lost income[c]	–	6.56 (5.76 to 7.77)
Cost per patient[d]		6.82 (5.48 to 10.22)

[a] All costs inflated to £UK 2005.
[b] Estimated from participants who completed the patient cost questionnaire. Consultation time differs slightly from times estimated by practice nurses (41.9 minutes, 95% CI 37.0 to 46.7) during partner notification study.
[c] Average cost = (Travel, waiting and consultation time) × (Wage rate for each patient)/Total number of patients.
[d] Average lost income + out-of-pocket expenses.

10.2% (42) would have been looking after children. Of 242 patients in paid employment, 234 reported arrangements they had made with regard to taking time off work. The largest group (33%, 80) came outside work time or took paid leave (21%, 51). Taking into account out-of-pocket expenses related to travel and the opportunity costs associated with the time spent travelling and at the surgery, the average estimated cost was £6.82 (95% CI £5.48 to 10.22) per patient (*Table 49*). In sensitivity analysis this cost varied from £5.16 (95% CI £4.63 to 7.40) when the current UK job seeker's allowance rate was applied to patients who were not in employment to £10.95 (95% CI £8.34 to 13.92) when the average wage rate was applied to all participants (*Table 50*).

Discussion

In this study, which simulated a single round of home-based population screening for chlamydia, the average costs to the health service were £14.65 (95% CI £14.23 to 15.46) per screening invitation and £21.74 (95% CI £20.75 to 24.88) per person screened, which are comparable to opportunistic screening in England.[144] Out-of-pocket patient expenses averaged £6.82 (95% CI £5.43 to 10.22).

Methodological issues

The advantages of this study were that cost data were collected prospectively as part of a large screening study, which included both men and women, and the costs of participation to patients were estimated. In addition, patients documented the duration of consultations, which was only estimated in other studies.[144] One limitation of this research study was that some of the costs of the research process could not be disaggregated from those of the intervention. For example, the consultation with the practice nurse included the time taken to explain an RCT and alternative interventions, and conduct randomisation in those giving consent, so the estimated health service costs are somewhat higher than they would be in a real screening programme.

TABLE 50 *Sensitivity analysis for patient costs*

Activity	Base case, £ (95% CI)[a]	Average wage rate applied[a,b] to all, £ (95% CI)	Average wage rate[a,b] applied to leisure time, £ (95% CI)	Minimum wage rate[a,c] applied to all, £ (95% CI)	Benefit rate[a,d] applied to all those not in employment, £ (95% CI)
Travel time	2.45 (2.16 to 2.73)	3.97 (3.74 to 4.19)	3.08 (2.77 to 3.39)	2.09 (0.56 to 4.03)	1.80 (1.61 to 2.08)
Surgery waiting time	0.90 (0.23 to 2.03)	1.49 (0.21 to 3.20)	1.16 (1.02 to 1.31)	0.78 (0.12 to 1.68)	0.62 (0.36 to 1.61)
Surgery consultation time	3.21 (2.88 to 3.56)	5.23 (4.89 to 5.57)	4.25 (3.90 to 4.62)	2.73 (2.54 to 2.91)	2.48 (2.11 to 2.87)
Out-of-pocket expenses	0.26 (0.16 to 0.72)	0.26 (0.16 to 0.72)	0.26 (0.16 to 0.720)	0.26 (0.16 to 0.72)	0.26 (0.16 to 0.72)
Total lost income	6.56 (5.76 to 7.77)	10.69 (8.57 to13.93)	8.49 (8.01 to 9.00)	5.60 (3.92 to 7.75)	4.90 (4.63 to 6.36)
Total patient cost[e]	6.82 (5.48 to 10.22)	10.95 (8.34 to13.92)	8.75 (8.26 to 10.77)	5.86 (4.19 to 8.77)	5.16 (4.63 to 7.40)

[a] Costs inflated to £UK 2005.
[b] Average wage rate £8.26.
[c] Weekly job seeker's allowance rate 2003 (37 hours per week).
[d] Minimum wage 22 years and over £4.50, under 22 years £3.80.
[e] Including out-of-pocket expenses (£0.26 per person).

TABLE 51 *Studies reporting the private patient costs associated with screening programmes in the UK*

Study	Type of screening	Setting	Cost, mean £[a]
This study	Chlamydia	General practice	6.82
Henderson, 2002[238]	Foetal anomalies	Hospital	Minimum: 10.61 Maximum: 18.87
Frew, 1999[240]	Colorectal cancer	Clinic	20.62
Bryan, 1995[241]	Aortic aneurysm	Clinic General practice Hospital	7.28 5.61 9.15
Sculpher, 1993[242]	Breast cancer, diabetic retinopathy	Hospital General practice	Minimum: 9.00 Maximum: 13.19 Minimum: 6.79 Maximum: 13.20

[a] All cost data inflated to £UK 2005 prices.

Comparison with opportunistic chlamydia screening

The estimate of the health services cost of proactive chlamydia screening was comparable to that estimated for opportunistic screening in England. Adams and colleagues estimated the costs of the National Chlamydia Screening Programme using data from the pilot studies in Portsmouth and the Wirral.[144] They found that offering chlamydia screening to women in healthcare settings cost £16.49 per screening offer (at 2005 prices), if 64% accepted the screening offer. The authors acknowledge the omission of societal costs. In the present study, the cost was £14.65 per screening offer with an uptake of 34%, and £19.72 if uptake was 64%. The costs of screening invitations, laboratory testing, giving results, providing treatment and administration in this study were also comparable to those estimated from a previous population-based study in Amsterdam.[92]

In an opportunistic screening programme, the screening test is only offered to eligible patients who are already having a consultation, so administrative costs are presumed to be limited. Nevertheless, the opportunistic pilot screening programme required some infrastructure and incurred over £75,000 of administrative and running costs, which accounted for around 39% (£7.30) of the average cost per test offered.[144] In the present study, the running costs accounted for around 57% (£8.35) of the average NHS cost per screening invitation. This study is the first to collect private patient costs associated with a chlamydia screening programme. These costs should be generalisable to opportunistic screening if partner notification takes place in the setting where the results and treatment are given: referral of index cases to a GUM clinic would increase patient costs because of the additional journey and time off work.

Comparison with other patient cost studies

The patient costs reported in this study were similar to those reported by other studies of screening in general practice, but lower than those of screening in hospital settings (*Table 51*). This may be due in part to the greater distances travelled to hospitals compared with local surgeries.

The costs of screening in this study were similar to those of screening for abdominal aortic aneurysm.[241] The low private costs of hospital and general practice screening might be because most men were retired. Productivity losses may also be higher where the condition screened for affects older adults in full-time employment (e.g. colon or breast cancer),[242] as opposed to chlamydia, which is most common in young adults with lower incomes. The results suggest that the private costs to individuals who participate in home-based chlamydia screening, in which positive cases are managed at general practices, are likely to be lower than those imposed by more centralised screening programmes. There was no evidence to suggest that the reduction in patient costs occurred at the expense of cost shifting to the NHS. The costs imposed on patients should be included in future economic evaluations of chlamydia screening.

Implications for policy and research

Detailing the costs of different components of a screening programme is required for the rational development of screening policies and good organisation is essential. The infrastructure required by the English National Chlamydia Screening Programme,[112] and implemented in the pilot studies, contributed substantially to the costs of opportunistic screening. Rescreening in both opportunistic and active programmes will also need to be compared in the future. For active screening the costs of the population register have already been incurred, but systematic recall in an opportunistic programme would involve additional administrative costs. This study shows that, contrary to popular assumptions, active chlamydia screening is not more expensive than opportunistic screening.

Chapter 10

Economic evaluation of active screening for chlamydia using a transmission dynamic model

Objectives

The objectives of this economic evaluation were:

- to develop a dynamic model representing the transmission of *C. trachomatis* in the population
- to use epidemiological and economic data from the ClaSS project and other empirical studies to parameterise the model
- to examine the cost-effectiveness of active chlamydia screening approaches in preventing major clinical outcomes.

Selecting a modelling approach

The importance of using an appropriate model for the transmission of *C. trachomatis* to allow for interaction between individuals was explained in Chapters 1 and 8. Of the available dynamic modelling approaches discrete event simulation, an individual-based approach, was chosen because this was the only approach that would allow the effects of partner notification to be examined. System dynamics, which use aggregated data, would only permit the estimation of average effects, whereas discrete event simulation allows records of partners attached to specific individuals to be kept. Mirjam Kretzschmar (University of Bielefeld, Germany) is a leader in the field of stochastic simulation models for studying the transmission of bacterial sexually transmitted infections.[198,235,243,244] In these models a population is simulated over time, with individual characteristics changing as necessary on a daily basis. A mathematical model for the ClaSS project was developed based on Kretzschmar's framework, and modified in discussion with her and with Dr Robert Welte (Institute of Health Economics and Health Care Management, Neuherberg, Germany). The authors planned to parameterise the model, wherever possible, using empirical data collected in the ClaSS project (active screening),[97,98,136,154] chlamydia screening pilot studies and RCTs (opportunistic screening)[144,245] and Natsal 2000 (sexual behaviour).[108] One substantial improvement in the ClaSS project model was the introduction of dynamic modelling of the incidence of long-term complications associated with chlamydia. In the original model the occurrence of these sequelae was modelled statically because the most cited literature about the complications of chlamydial infection provides the data as a fixed probability.[24] Data were used from the Uppsala Women's Cohort Study, in which the cumulative incidences of pelvic inflammatory disease, ectopic pregnancy and infertility were estimated for a population of over 40,000 young women in Uppsala County, Sweden.[20]

Methods

The main features of the model are divided into the following sections: ageing and replacement; partnership formation and dissolution, chlamydia transmission and progression, testing and treatment, and sequelae associated with pregnancy. The sequelae associated with chlamydia include inflammatory complications such as pelvic inflammatory disease in women and epididymitis in males, sequelae associated with pregnancy such as infertility, ectopic pregnancy and neonatal complications, conjunctivitis and pneumonia. In modelling terms, the inflammatory sequelae were modelled as part of the progression of chlamydia, while the sequelae associated with pregnancy, including neonatal complications, were treated as a separate part of the model.

Ageing and replacement

The initial population consists of a number of virtual individuals with ages drawn from a uniform distribution between lower and upper limits. As the model runs, individuals in the model die (from 'other causes') in line with standard UK life tables and new individuals at the minimum age are added to the model. Mortality from chlamydia-related causes such as ectopic pregnancy was deemed to be negligible and excluded from the model.

Partnership formation and dissolution

The initial population does not contain any partnerships. During the running of the model, new partnerships form and are dissolved.

Properties of the partnership include frequency of unprotected sexual contact. Only opposite-sex partnerships were included, because of the scarcity of data on chlamydia transmission in same-sex relationships. Individuals were categorised into three sexual activity groups according to rates of sexual partner change. Individuals' propensity to form new partnerships is determined in part by their activity group and existing partner status, and the age difference between prospective partners.

Chlamydia transmission and progression

At any time in the model an individual's chlamydia status is one of the following: no chlamydia, latent chlamydia, asymptomatic chlamydia, symptomatic chlamydia or inflammation (pelvic inflammatory disease in women, epididymitis in men). Initially, a small proportion of the population is infected with chlamydia. If one member of a partnership is infected, but the other is not, then there is a risk of transmission on each (unprotected) sexual contact. Different figures were used for male-to-female and female-to-male transmission. The probability of transmission on any day was obtained by multiplying the frequency of sexual contact by the probability of transmission per contact.

An individual who is infected enters a period with latent chlamydia, which is assumed to last for a fixed number of days (different for male and female), and then may become asymptomatic or symptomatic. Individuals with latent chlamydia cannot pass on the infection. Individuals with asymptomatic chlamydia may recover or progress to inflammation. Those with symptomatic chlamydia may recover, progress to inflammation or seek treatment. In either case they may also be treated after screening or partner notification. Individuals with pelvic inflammatory disease or epididymitis were assumed to seek treatment on the day after progression to that condition. Note that the definitions of the terms used here require that they are symptomatic.

Testing and treatment

In the absence of a population screening programme, individuals may be treated either by presenting with symptoms or through background opportunistic screening, here called 'no screening'. As well as a no-screening option, two different screening populations were considered: screening women only and screening men and women, both within a defined age group. For both situations it was assumed that active population screening started on a given date after the start of running the model.

For women-only screening, women are invited for screening on reaching any of a given set of ages. If invited, a woman may then accept the offer of the screening test. If so, she receives a screening result at a fixed delay after testing. Allowance is made for the sensitivity and specificity of the test used to be below 100%. A woman who screens negative is not treated, but may be called for screening in the future. A woman testing positive will be treated, and asked to notify partners. If she complies with partner notification, she will inform current and former partners within a specified time interval (in the baseline scenario, for simplicity, it was assumed that notification was either zero or complete). Each partner individually may then comply with a request to attend for treatment. Any partner attending will be treated without waiting for a test result. The process for screening men and women is the same as above, but both genders are selected for screening at the given ages.

Compliance is an important issue for both screening methods. The term compliance is used here as a general term that refers to the uptake rate to the invitation for screening, treatment and partner notification. In the model compliance with treatment (single-dose azithromycin) is assumed to be 100%. The model allows for varying patterns of compliance among individuals. At one extreme, some individuals always comply and others never comply. At the opposite extreme, each call for screening and testing is regarded as a separate occasion and the probability that the individual will comply is fixed and independent of other occasions. Intermediate positions between these extremes are also allowed.

Sequelae associated with pregnancy

Sequelae currently considered in the model are infertility, ectopic pregnancy and neonatal complications. To allow these to be modelled, pregnancy needs to be modelled explicitly within the model. The probability that a woman becomes pregnant on any given day is a product of three factors: her total frequency of unprotected sexual contact is multiplied by an age-dependent factor, which represents a combination of varying fertility and use of non-barrier contraception; this is then multiplied by a factor representing reduced fertility as a result of chlamydia-related damage. Instances of infertility are recorded as occasions when a woman does not become pregnant, but would have done so had her fertility not been

TABLE 52 *Live births per 1000 women per year*

Age range of mother (years)	Results from model	ONS data
15–20	28.17	30.9
20–25	74.03	75.5
25–30	117.93	102.2
30–35	113.24	89.9
35–40	45.57	39.8
40–45	7.73	7.5
45–50[a]	0.27	0.3

[a] ONS data reported as '45 years and over'.

reduced by the effect of chlamydia-related damage.

The probability that any pregnancy is ectopic is taken to be proportional to the total time that a woman has been infected with chlamydia, while neonatal complications occur (with a fixed probability) only if the woman is infected with chlamydia at the time of her child's birth. For simplicity, it is assumed that ectopic pregnancies are discovered, and the pregnancy terminated, at a fixed time after conception, and that all other pregnancies go to full term, which again is assumed to be constant length.

Calibration of the model

A common problem with modelling, which applies particularly to the ClaSS model, is that the data available often relate to model outputs rather than model inputs. For example, although the model requires some individuals to have chlamydia at the start of a model run (input), the steady-state prevalence of chlamydia in the model (output) without population screening is a function of the transmission dynamics, and the same steady-state prevalence is reached for different starting patterns of chlamydia. Another example is that the model inputs relate to propensity to form a new partnership on a given day. In contrast, the pattern of partnership formation that actually takes place is a model output to be compared with these data.

Thus, instead of direct incorporation of data points as input parameters to the model, it is necessary to calibrate the model by adjusting the input parameters until a reasonable fit to the available data is obtained. This raises the question of how closely it is desirable to fit the existing data. The purpose of the model is to estimate the effects over time of introducing a screening policy, in terms of the difference between the costs and outcomes under different policies (including a policy of no population screening). Given that sexual behaviour patterns vary over time, but that it is not feasible to reflect such variation in a model, there is limited value in producing an extremely close fit to current behaviour patterns. It is more important to test how robust policy decisions would be to variations in such patterns. It is also worth noting that it is possible to produce similar observed outputs from a variety of different patterns of input: again, it is important to test the robustness of conclusions to such variation.

The determination of the input set used to produce the current set of results for the ClaSS model is described in detail in the following sections. This input set is determined by a process of calibration. The data shown in *Tables 52–54* represent outcomes rather than model inputs, and so the model is calibrated to these.

Calibration of the model to existing data

Tables 52–54 show the results of calibrations to the model. *Table 52* shows the observed live births per 1000 women per year in a single run of the model using each input set, running for 7500 days after a 7500 day warm-up period. This is compared with ONS data for England and Wales in 1998. The fit is reasonable.

Table 53 shows comparisons with ClaSS data applying the ClaSS prevalence survey to the model at the end of the run. Here the general patterns are approximately preserved.

For long-term sequelae in women, data from the Uppsala Women's Cohort Study were used.[20] Information from this was extracted into Kaplan–Meier curves, from which a failure function could be estimated by age. This represents the probability that an individual will have experienced a given event at least once by the age stated. This process was replicated by the

TABLE 53 *Comparisons between model outputs and ClaSS prevalence study data*

	Results from model		ClaSS prevalence study	
	M	**F**	**M**	**F**
Mean age difference with partner (years)				
Age range (years)				
16–19	0.83	–2.42	0.37	–2.21
20–24	1.65	–1.74	1.41	–2.10
Percentage reporting ever having had sex[a]				
Age range (years)				
16–19	57.78	85.81	54.2/65.1	80.6/81.8
20–24	94.16	99.63	92.1/92.5	95.4/96.3
Mean length of reported partnership (months)				
Age range (years)				
16–19	7.80	10.98	7.61	8.44
20–24	16.82	17.81	17.86	32.24
Sexual activity groups (%)[b]				
16–24 years				
Periphery	71.71	72.64	72.6	79.2
Adjacent	16.03	21.36	17.4	15.1
Core	12.26	6.00	10.0	5.7
25–39 years				
Periphery	84.21	89.20	80.5	91.0
Adjacent	13.23	8.05	12.7	6.6
Core	2.56	2.75	6.8	2.4

[a] Two sets of data figures are given for percentages reporting ever having had sex. In each case, the first figure is from the case-control study, the second from the prevalence study.
[b] Laumann and Youm use activity groups defined by the number of partners in the past 12 months, calling those with 0 or 1 partner the 'periphery', those with 2 or 3 the 'adjacent' and those with 4 or more the 'core'.[246]

TABLE 54 *Comparisons of incidence of sequelae associated with chlamydia in ClaSS project model and Uppsala Women's Cohort Study*

	ClaSS model		Uppsala	
	Age 25	**Age 35**	**Age 25**	**Age 35**
PID				
Never screened	0.0167	0.0194	0.0165	0.0292
Always –ve	0.0158	0.0182	0.0132	0.0404
At least one +ve	0.0600	0.0886	0.0278	0.0561
Infertility				
Never screened	0.0024	0.0143	0.0041	0.0308
Always –ve	0.0038	0.0125	0.0044	0.0471
At least one +ve	0.0527	0.1670	0.0052	0.0671
Ectopic pregnancy				
Never screened	0.0034	0.0169	0.0051	0.0187
Always –ve	0.0041	0.0177	0.0038	0.0202
At least one +ve	0.0656	0.1946	0.0053	0.0272

PID, pelvic inflammatory disease.

model. *Table 54* shows the results from the model and from the Swedish study, allowing a comparison to be made. The overall level of sequelae is approximately the same. The good matching in the never-screened groups and the fact that ClaSS has higher results for women with at least one positive suggest that the ClaSS model overestimates the relationship between chlamydia

TABLE 55 *Initial percentage allocation of sexual activity groups*

	Male, %	Female, %
Group 1	54	81
Group 2	30	14
Group 3	16	5

Group 1 least active, group 3 most active.

TABLE 56 *Mixing factors for activity groups*

Female/male	Group 1	Group 2	Group 3
Group 1	1	0.2	0.1
Group 2	0.2	1	0.2
Group 3	0.1	0.1	1

and sequelae (as based on the Swedish data[20]) and therefore is likely to lead to relatively more optimistic results.

Basic population characteristics

The initial population is evenly distributed in age between 12 and 62 years, and is assumed to be 50% female, although this proportion can be altered as a model input. The population is allocated to activity groups according to sexual partner change in proportions shown in *Table 55*. The allocation of activity groups for the ClaSS model is designed so that the outputs of the model are broadly in line with the data from the lifestyle questionnaire collected in the ClaSS case–control study (Chapter 5), but also broadly in accordance with groups defined by Laumann and Youm (see *Table 53*).[246]

To ensure that there is some chlamydia in the model, an initial arbitrary age-related prevalence of chlamydia is applied: zero at age 15, 3% at age 20, 4% at age 25, 1% at age 30 and zero at age 40. The values of these are unimportant as the steady-state prevalence in the model after the warm-up period depends on the transmission dynamics within the model, not on the initial state. Each individual is given chlamydia or not, with probabilities appropriate to the starting age. Linear interpolation is used between the ages given; for example, the probability of a 21-year-old starting the model with chlamydia is 3.2%. Everyone outside the age range 15–40 starts chlamydia negative.

Each day of simulated time, new 12-year-olds may be added to the model. The number to be added each day is drawn from a Poisson distribution with mean appropriate for the size of the initial population. New additions to the model are assumed to be chlamydia negative, and are assigned to activity groups in the same proportions as the initial population. Individuals remain in the model until death. As no chlamydia-related death is included in the model, the date of death can be sampled at the time of including the individual in the model. Appendix 5 gives the basic survival curves used. These are based on tables obtained from the Government Actuary's Department website (http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm), truncated to 101 years of age.

Propensity to form new partnerships

The propensity to form a new partnership for males and females was estimated according to sexual activity group (Appendix 6). The main driver for the pattern in these model inputs was the prevalence data obtained from the ClaSS project survey (Chapter 3). The values in these tables are determined as part of the calibration process described above. The values given approximate the probability that the individual will form a new partnership on any given day. Values are calculated by linear interpolation between the ages given; for example, the propensity to form a new partnership for a male aged exactly 17 years, in activity group 1, with no current partners, is 0.001. Note that the earliest age for sexual activity in this data set is 14 for males and 12 for females. The full process by which partnership formation is modelled is described later.

Mixing factors

An important part of the model is the extent to which partners are drawn from the same activity group as each other. The main problem here is that no data are available on the activity groups to which the partners of index cases belong. In the ClaSS model, this is handled by a mixing factor dependent on the activity groups, as shown in *Table 56*. This has the equivalent function to 'mixing matrices' used in other, similar chlamydia models.

Age effects on mixing are defined in terms of two parameters, μ and σ. They represent an assumed underlying normal distribution of age difference between partners, with a positive value of μ indicating males on average older than their female partners, which was a finding of the ClaSS prevalence study (see *Table 53*). This distribution is distorted by the age-varying propensity to form a new partnership, and the values used ($\mu = 3$, $\sigma = 2.5$) are calibrated to the data.

TABLE 57 *Partnership duration*

Basic mean partnership duration (days)	**950**
Multiplier for activity groups of partners	
Both partners group 1	1
Female group 1, male group 2	0.5
Female group 1, male group 3	0.3
Female group 2, male group 1	0.5
Both partners group 2	0.3
Female group 2, male group 3	0.15
Female group 3, male group 1	0.3
Female group 3, male group 2	0.15
Both partners group 3	0.12

TABLE 58 *Inputs relating to chlamydia transmission and progression*

Parameter	**Value**	**Source**
Probability of transmission male to female	0.154	*K*
Probability of transmission female to male	0.122	*K*
Incubation period male (days)	10	*K*
Incubation period female (days)	12	*K*
Probability asymptomatic female	0.7	*K*
Probability asymptomatic male	0.25	*K*
Recovery rate per day asymptomatic female	0.005	*K*
Recovery rate per day symptomatic female	0.005	*K*
Recovery rate per day asymptomatic male	0.025	*K*
Recovery rate per day symptomatic male	0.03	*K*
Progression per day chlamydia to epididymitis	0.0001	*W*
Progression per day chlamydia to PID[a]	0.00008	Calibration

K, parameter sustained from Kretzschmar *et al*. (2001)[235]; *W*, estimated from proportion progressing to epididymitis in Welte *et al*. (2000).[198]
[a] The model input is calibrated to the PID incidence presented in *Table 54*.

Partnership formation

The full process by which partnership formation is modelled may now be described. A partnership is formed by an initiator and a responder. For symmetry, the initiator may be male or female. Each day of simulated time, each individual is selected an initiator with a probability one-half of that individual's propensity to form a new partnership (Appendix 6) (the factor 0.5 allows for the fact that the same individual may enter a new partnership as a responder and thus ensures that the propensity approximates to the probability of forming a new partnership). Once an individual is selected as an initiator, a partner of the opposite sex must be found. Individuals of the opposite sex are selected at random. Any individual is accepted with a probability which is (proportional to) the product of three factors: the potential responder's own propensity to form new partnerships, the mixing factor and an age-difference factor,

$$\exp\left(-\tfrac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2\right)$$

which represents an assumed normal distribution, where x is the difference between ages (male minus female), and μ and σ are as defined above.

Partnership duration

It is a logical assumption that partnerships involving high-activity groups will be, on average, shorter in duration than those involving low-activity groups. This is modelled by setting a baseline duration which applies when both partners are in activity group 1 (the least active), and applying a multiplier for other combinations of activity groups. The values used are shown in *Table 57*. These were determined as part of the calibration process. Mean lengths of reported partnerships are presented in *Table 53*.

Chlamydia transmission and progression

The main inputs relating to chlamydia transmission and progression are summarised in *Table 58*. These parameters were kept from the original models.[198,235]

TABLE 59 *Assumed daily probability of background screening*

Age	Groups 1 and 2		Group 3	
	Male	Female	Male	Female
15	0.0002	0.0002	0.0004	0.0004
20	0.0004	0.0004	0.0008	0.0008
25	0.0002	0.0002	0.0004	0.0004
30	0.0002	0.0002	0.0004	0.0004
35	0.0001	0.0001	0.0002	0.0002
40	0	0	0	0

TABLE 60 *Parameters for population screening*

Parameter	Value	Source
Compliance with screening (female)	0.39	ClaSS
Compliance with screening (male)	0.29	ClaSS
Waiting time for result of screening (days)	30	Assumption
Sensitivity of screening test (male)	0.99	ClaSS
Specificity of screening test (male)	0.99	ClaSS
Sensitivity of screening test (female)	0.97	ClaSS
Specificity of screening test (female)	0.99	ClaSS
Range in days for recent partner	120	Assumption
Probability that a partner will attend for treatment	0.45	ClaSS
Delay in days for partner to receive treatment	3	Assumption
Screening tests are Cobas PCR on urine specimen for men and vulvovaginal swab for women. The probability of partner attending for treatment was applied independently to each partner.		

TABLE 61 *Age-related pregnancy risk*

Age, years	12.5	17.5	22.5	27.5	32.5	37.5	42.5	45
Risk of pregnancy per day	0	0.00035	0.0007	0.0019	0.0019	0.0004	0.0001	0.000002

Testing and treatment

Even in the no-screening arm, some background screening is assumed. It is assumed that those in the highest activity group are more likely to receive background screening. The daily probability of background screening is dependent on age, gender and activity group, as shown in *Table 59*. This is subject to a minimum gap of 200 days since last screened. These inputs are largely arbitrary, but are informed by the data from the Uppsala Women's Cohort Study (see *Table 54*).[20] Part of the justification for the model inputs presented in *Table 59* is that the Swedish data are applied to a Swedish population with opportunistic screening only, so differences between the never-screened and screened groups are likely to depend on the level of baseline screening.

Parameters relating to the population screening programme are shown in *Table 60*. The parameters that were assumptions were based on consensus within the ClaSS project team.

Sequelae associated with pregnancy

With the exception of neonatal complications, all inputs here have been calibrated to the best available data, using British ONS data for pregnancy rate and the Uppsala Women's Cohort Study for risk of sequelae.[20] *Table 61* shows the parameters relating to pregnancy risk, defined as age-related risk of pregnancy per episode of unprotected intercourse. This is assumed to take into account variation in both fertility and use of non-barrier contraception. *Table 62* shows the other parameters used.

It is generally accepted that repeat infection increases the risk of ectopic pregnancy and infertility, but it is not clear whether this is due to separate number of episodes or simply

TABLE 62 *Other parameters relating to pregnancy*

Parameter	Value	Source
Ectopic pregnancy risk factor (days)	0.00003	Calibration
Ectopic pregnancy risk factor (episodes)	0.001	Calibration
Infertility risk factor (days)	0.00003	Calibration
Infertility risk factor (episodes)	0.0005	Calibration
Probability of neonatal complication[a]	0.45	*W*
Duration (in days) of ectopic pregnancy	50	Advice
Duration (in days) of normal pregnancy	280	Advice

W, parameter obtained from Welte *et al*. (2000).[198]
[a] Applied to women who are chlamydia positive at the time of giving birth.

cumulative effects of the time infected. The model allows either theory to be applied; the figures give a combination of the two. Consider, for example, a woman who has had two separate episodes of chlamydia infection, lasting for a total of 50 days. With the input parameters above, her risk of ectopic pregnancy (if she becomes pregnant) is $(50 \times 0.00003) + (2 \times 0.001) = 0.0035$. For the same woman, her fertility is reduced by a factor $1 + (50 \times 0.00003) + 2 \times 0.0005) = 1.0025$. In the model, an instance of infertility is recorded when a woman who would become pregnant does not become so as a result of reduced fertility.

Costs used in the model

Unit costs used in the model are shown in *Table 63*. The actual figures differ slightly from those in the text in corresponding chapters because costs here were estimated at 2003 prices. All costs elsewhere in the report have been inflated to 2005 prices.

Results

The model was run with input set 1, as described above. The model uses random numbers throughout and therefore it is necessary to rerun the model a sufficient number of times, with different random numbers, to ensure that the effects of randomisation are reduced. The model was run 60 times, on a population of 50,000 individuals, with no screening (background screening only), for a total of 15,000 (simulated) days each time. The prevalence of chlamydia was recorded every 20 days by gender and 5-year age bands.

The baseline results are shown in *Figure 15*. The vertical line is at 7500 days and indicates the end of the warm-up period. The part of the graph to the left of the line is the model reaching a steady state of prevalence. Note that the steady-state prevalence was determined by the transmission dynamics of the model and not by the initial

TABLE 63 *Unit costs in the model*

Resource-use data required	Unit cost, £	Source	
Cost per screening invitation (including administration)	11.82	ClaSS	Chapter 9
Planned screening tests male	7.29	ClaSS	Chapter 9
Planned screening tests female	6.94	ClaSS	Chapter 9
Background screening tests male	6.66	ClaSS	Chapter 9
Background screening tests female	6.31	ClaSS	Chapter 9
Treatment of index case including PN	30.16	ClaSS	Chapters 7, 9
Treatment of partners	22.60	ClaSS, PSSRU	Chapters 7, 9
Infertility[a]	428	NICE guidelines	
Ectopic pregnancy[b]	2319	HRG costs	
PID	2846	HRG costs	
Epididymitis	790	Welte[c]	
Neonatal complications	708	HRG costs	

HRG, Health Resource Groups.
[a] National Institute for Health and Clinical Excellence (NICE) baseline costs for one cycle converted to 2003 costs.
[b] NICE baseline costs converted to 2003 costs.
[c] Weighted average of Welte *et al*. (2000),[198] converted to 2003 UK costs.

prevalence incorporated. It can be seen that the prevalence after the warm-up period remains constant over time.

The mean prevalence after the warm-up period is shown as prevalence from model compared with ClaSS survey. Compared with the results from the ClaSS cross-sectional survey, all prevalence figures were within the 95% confidence intervals of the survey, except for the 25–29-year-old males, where prevalence in the survey was much lower than in the model, and it was necessary to compromise between fitting the prevalence pattern and the activity pattern (*Table 64*).

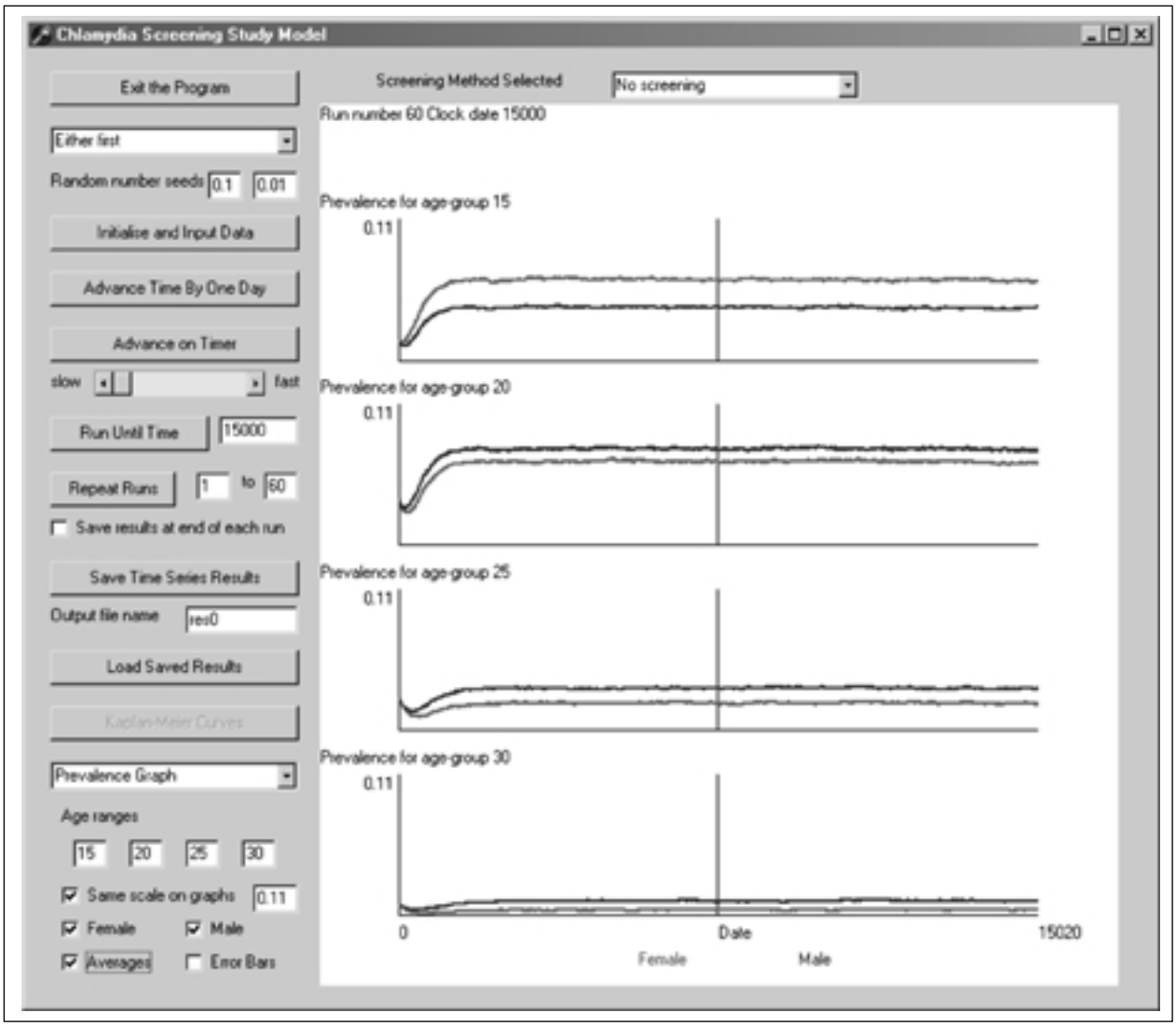

FIGURE 15 *Baseline results of the ClaSS model*

TABLE 64 *Prevalence from model compared with ClaSS survey*

	Model results, %		ClaSS survey, % (95% CI)	
	Male	**Female**	**Male**	**Female**
15–19[a]	4.09	6.25	3.41 (2.26 to 5.15)	6.20 (4.80 to 8.59)
20–24	7.51	6.53	6.92 (5.22 to 8.98)	6.15 (4.93 to 8.35)
25–29	3.30	2.13	0.62 (0.20 to 1.86)	3.27 (2.01 to 6.65)
30–39	0.63	0.23	0.44 (0.06 to 2.94)	0.32 (0.05 to 2.34)

[a] ClaSS survey results for age group 16–19 years.

Incorporating population screening

The model was rerun, introducing population screening annually from the ages of 16–24 years after the 7500-day warm-up period. The results for screening women only and men and women are shown in *Figure 16*.

As in *Figure 15*, there is a vertical line marking the end of the warm-up period. After the introduction of home-based postal screening, with uptake of 39% in women and 29% in men, prevalence dropped to a new equilibrium value, particularly in the younger age group where screening is likely to have more effect. The prevalence dropped slightly more in the case of screening both women and men (*Table 65*), but did not decline persistently.

Costs and major outcomes averted

In a dynamic model such as the ClaSS model, the results are likely to depend on the time-horizon used for calculations. All calculations were taken from the end of the warm-up period, costs and outcomes being discounted to that point. In line with current guidelines, costs were discounted at 3.5%. Because the outcomes were counts of events (avoided), these were left undiscounted.

Figure 17 shows the cumulative difference in cost between the three strategies, taken over a period of up to 20 years from the start of population screening.

All the figures resulting from the model give three comparisons: screening women versus no screening,

a

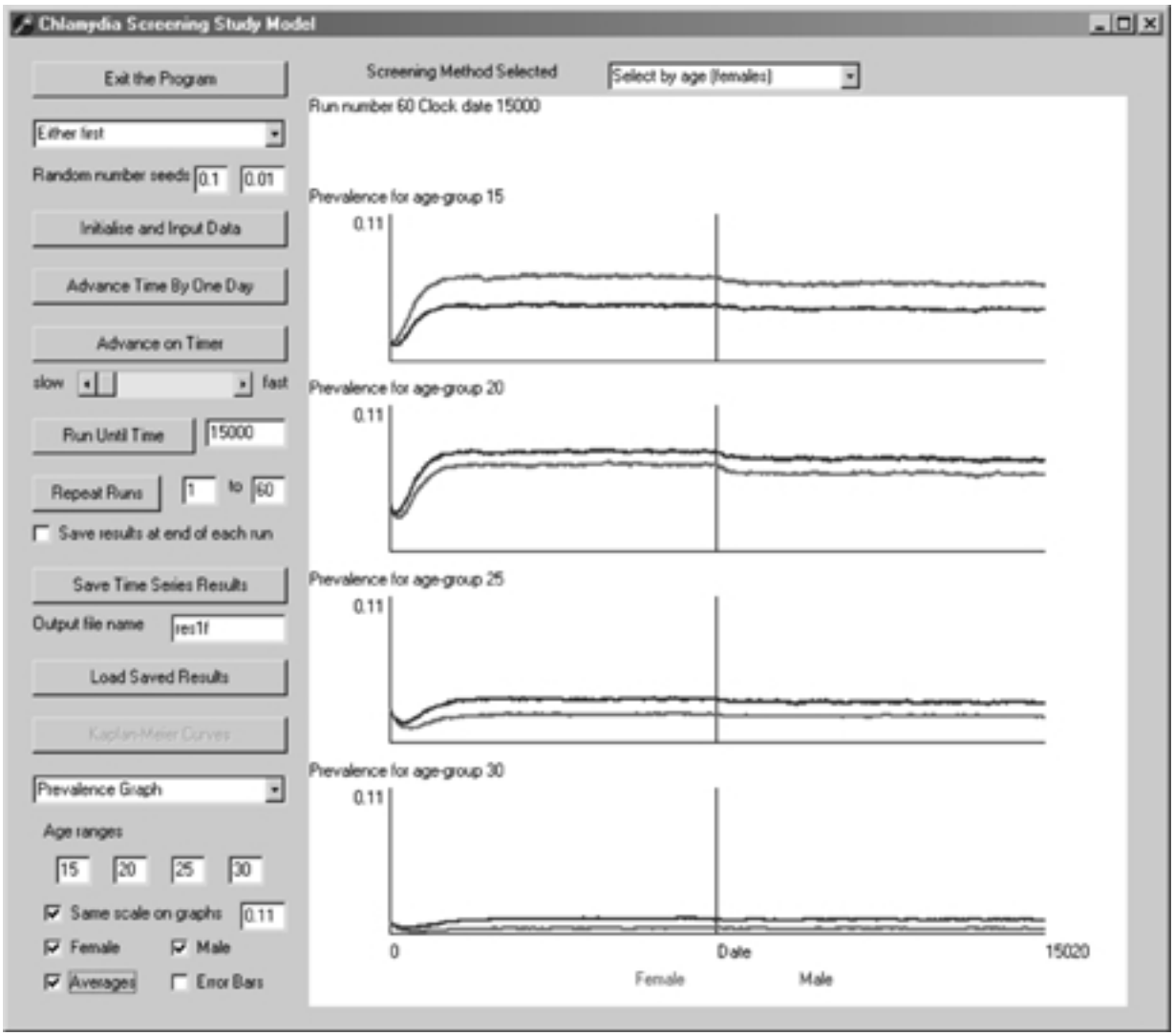

FIGURE 16 *Base-case results for screening (a) women only*

b

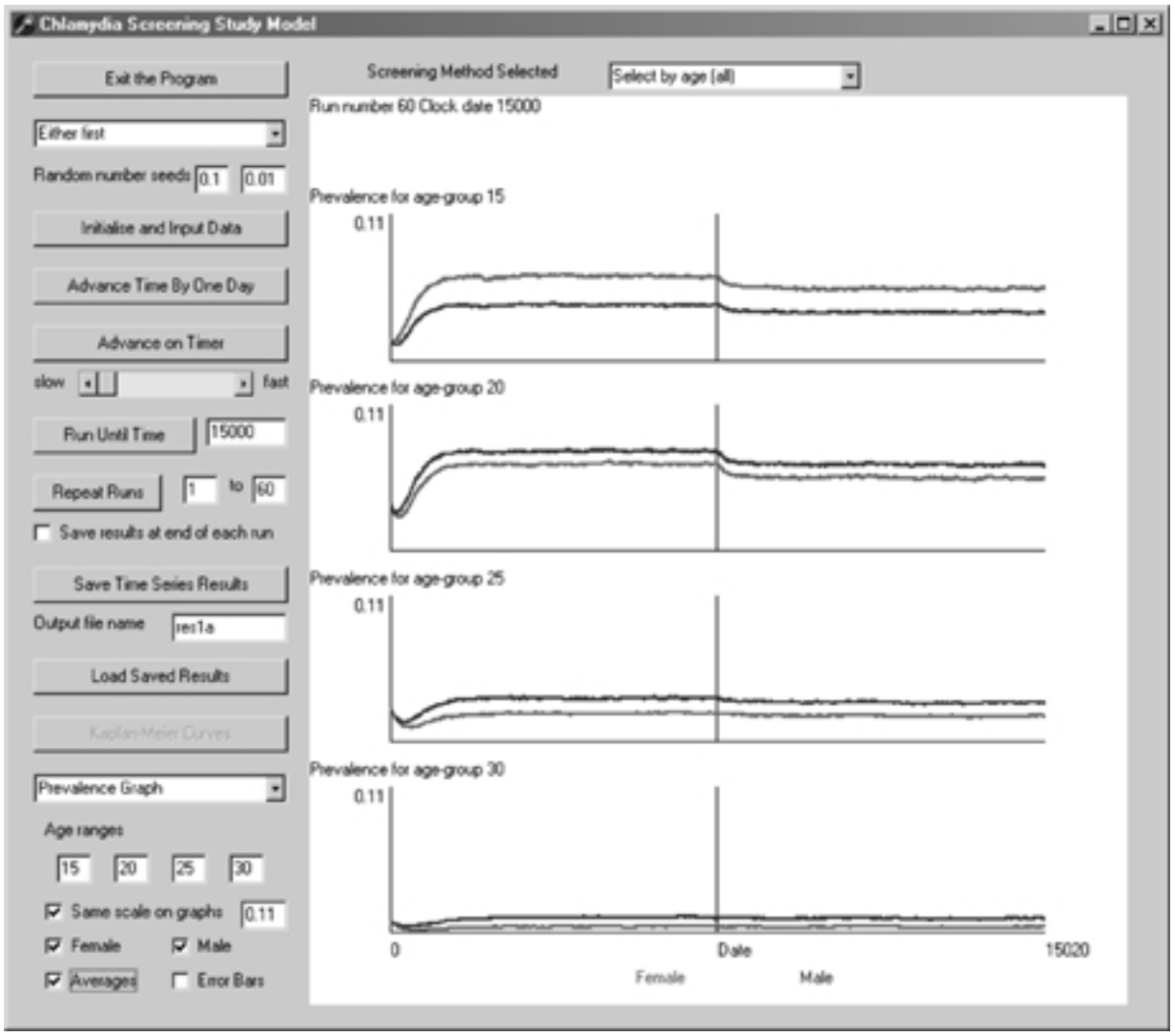

FIGURE 16 *Base-case results for screening (b) men and women*

screening men and women versus no screening, and screening men and women versus screening women only. Outputs from only the first two comparisons are reported because these represent direct changes from a policy of no screening. *Figure 18* shows the difference in the aggregated major outcomes pelvic inflammatory disease, infertility, ectopic pregnancy and neonatal complications (given as major outcomes averted). *Figure 19* shows the individual outcomes. Pelvic

TABLE 65 *Steady-state prevalence for baseline run of the model*

Age, years	No screening[a]		F only		M and F	
	M, %	F, %	M, %	F, %	M, %	F, %
15–19	4.07	6.24	3.85	5.75	3.60	5.37
20–24	7.50	6.52	6.96	5.86	6.50	5.50
25–29	3.29	2.14	3.04	2.01	2.93	1.92
30–39	0.63	0.24	0.59	0.22	0.58	0.22

[a] Slight variations from *Table 64* because of randomness in the model.

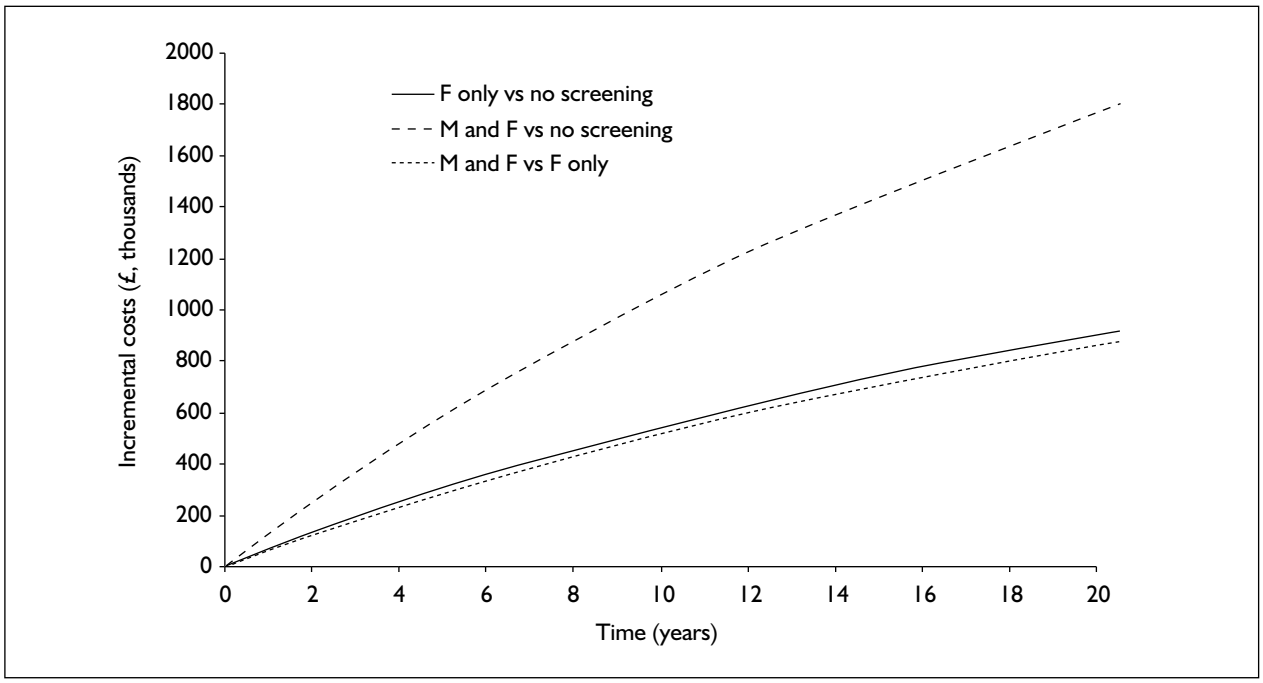

FIGURE 17 *Cumulative difference in costs*

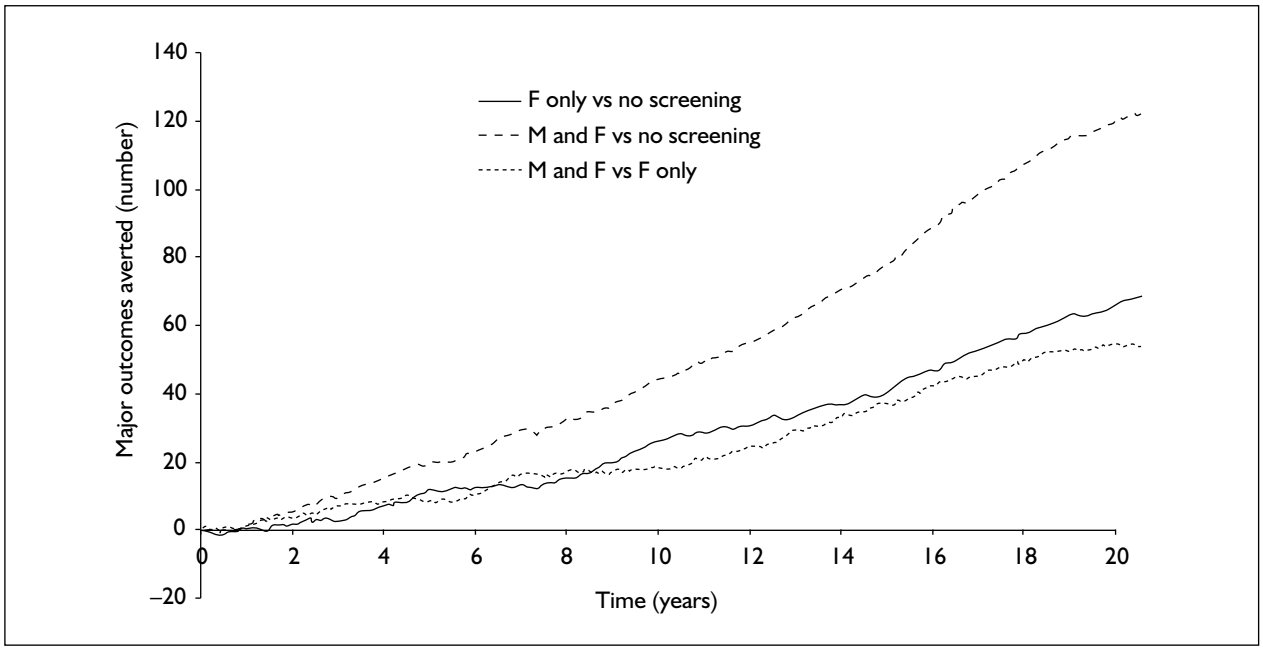

FIGURE 18 *Cumulative aggregated major outcomes averted (includes cases of PID, ectopic pregnancy, infertility and neonatal complications)*

inflammatory disease and neonatal complications were the most frequent outcomes and dominated the overall picture. In each of these diagrams, cumulative costs and outcomes refer only to those incurred up to the given time. Thus, the time-horizon is such that nothing is considered beyond that point. The model is built on the assumption that a screening programme, once introduced, would remain in place indefinitely.

If the screening programme were to be stopped at any time, the prevalence of chlamydia would return to the original steady-state value, but there would be some delay. The incidence of sequelae

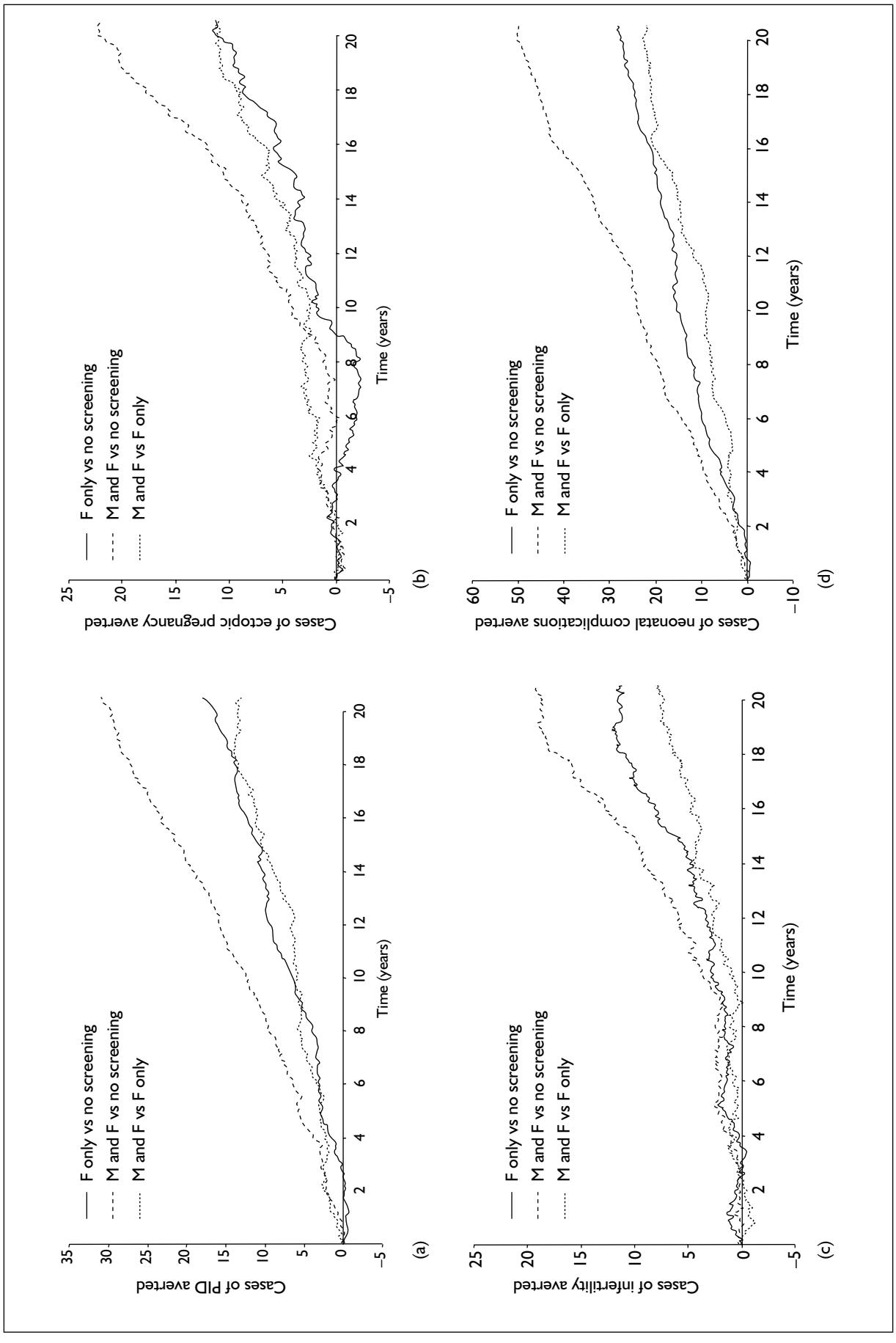

FIGURE 19 *Major outcomes averted by chlamydia screening, disaggregated: (a) PID; (b) ectopic pregnancy; (c) infertility; (d) neonatal complications*

would also be expected to return to the steady-state-value without screening, but after a somewhat longer delay. The effect on costs would be that the additional costs of the screening programme would cease immediately, but that the costs of managing sequelae would return gradually to a higher figure. The overall effect of this is that the costs immediately after the withdrawal of a fixed-length screening programme would be slightly lower than would be the case if the screening programme had never taken place. Thus, the net present value of the difference in costs between a fixed-length screening programme and no screening would be slightly lower than the value plotted against that length of time in *Figure 16*. Because there would be fewer major outcomes immediately after the withdrawal of a screening programme than would be the case if the screening programme had never taken place, the total expected number of major outcomes averted by a fixed-length screening programme would be slightly higher than the value plotted in *Figure 18*.

Cost-effectiveness analysis

Table 66 shows the results of the runs of the ClaSS model, taken to an illustrative (arbitrarily chosen) period of 8 years after the introduction of population screening. These calculations give the estimated results for the first 8 years of a screening programme intended to continue indefinitely. For reasons given above, they give a slightly conservative estimate of the costs and effects of a screening programme lasting for 8 years only.

These results are shown graphically in *Figure 20*. Here, the screening options are shown in

TABLE 66 *Summary of results for 8 years' follow-up*

(a) Results from running individual strategies			
	Cost, £000	**Major outcomes**	
No screening	1720	596	
F only	2154	580	
M and F	2561	563	
(b) Comparison between strategies			
	Difference in cost, £000	**MOA**	**ICER, £ per MOA**
F only vs no screening	434	16	28,000
M and F vs no screening	840	33	25,700

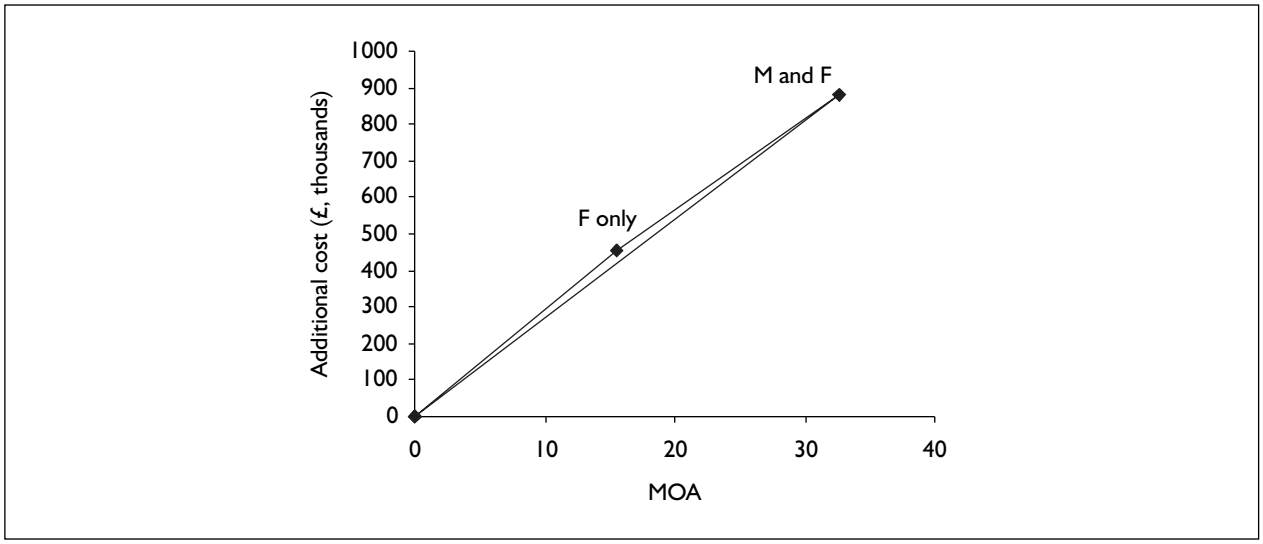

FIGURE 20 *Results over 8 years on the cost-effectiveness plane*

comparison to no screening. The ICER for screening men in addition to women is lower (more favourable) than that for screening women compared with no screening. That means that, under the assumptions included in this run of the model, if it is considered desirable to screen women, then it is more desirable to screen men as well as women. This phenomenon is known as weak or extended dominance; dominated means that the option is cheaper and more effective than the comparison. Weak dominance relates to a situation where two options are both more expensive and more effective than some third option, but the more effective of the two initial options has a lower ICER than the other two. The option of screening women only is said to be weakly dominated by the option of screening men as well as women.

Figure 21 shows the results for a range of time-horizons from 4 to 20 years. The gradual fall in the ICER over time reflects the delay inherent in a screening programme in which there is a lag before the full effect of the major outcomes averted as a result of screening becomes apparent. The values of the ICER were consistently high, suggesting that population screening is unlikely to be cost-effective under the conditions built in to this version of the model.

Sensitivity analysis

The ClaSS model has a running time of 3–5 hours per replication (one run of 20 years simulated time). The sensitivity analysis was conducted with fewer replications, for logistical reasons. This explains minor differences between graphs, which otherwise would be expected to be the same. The results of the sensitivity analysis are summarised in *Table 67* and the graphs (*Figures 23–32*) are shown in Appendix 7.

Varying the response rate

The base-case analysis used a response rate to screening invitations of 39% for women and 29% for men, as found in the ClaSS screening survey. With a response rate of 39% for men as well as women, the pattern of weak dominance was maintained for all time-horizons beyond 6 years. If the response rate increased to 60% for women and 40% for men it was relatively more cost-effective to screen women only. At an uptake of 60% for both men and women the pattern of weak dominance reappeared after about 10 years.

Varying the screening interval

The base-case scenario involved annual screening. Reducing the screening interval to 6-monthly did not affect the ICER.

Use of alternative screening test

Screening using PCE EIA resulted in higher ICERs. In this analysis, to maintain the same baseline prevalence patterns, Cobas PCR testing was still used for background screening. The reduced sensitivity of the PCE EIA (*Table 68*)

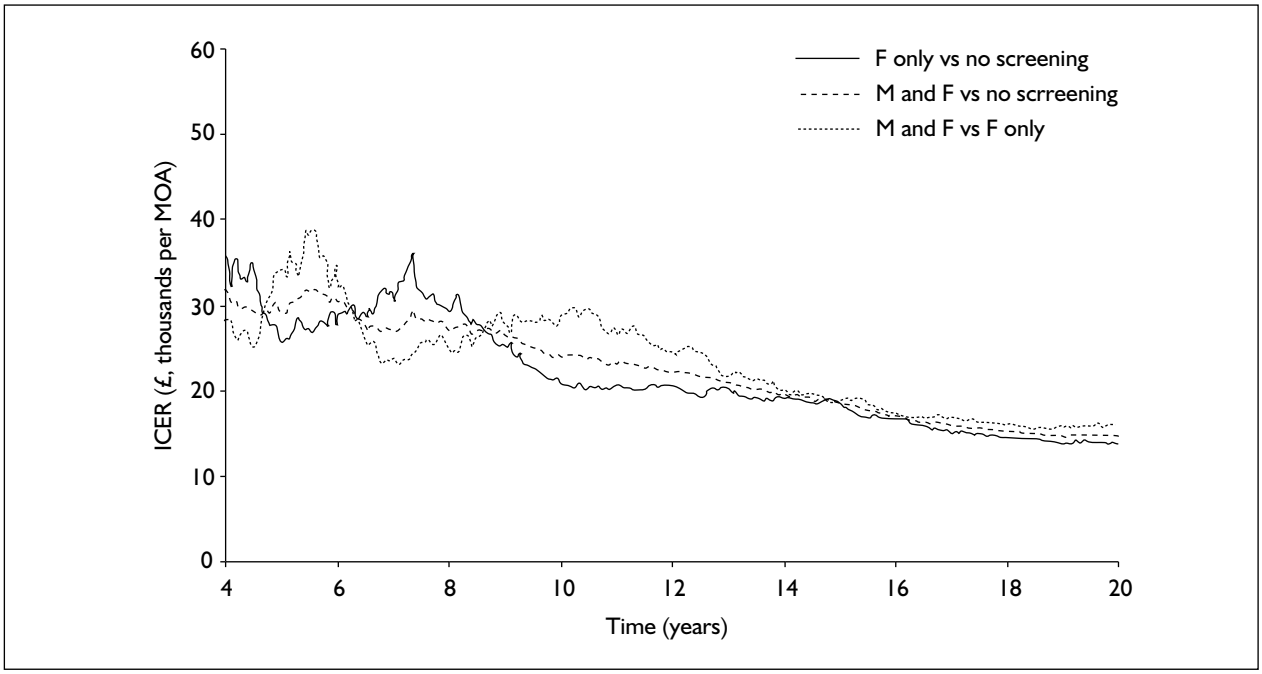

FIGURE 21 *Base-case results for a range of time-horizons*

TABLE 67 *Summary of ICERs over time under different conditions*

Scenario	ICER, £ per MOA				Figure number
	8 years		12 years		
	F vs none	M&F vs none	F vs none	M&F vs none	
Base case[a]	29,000	27,000	21,000	22,000	21[b]
Equal response rate 39%	34,000	21,000	22,000	17,000	23[c]
Response 60% female, 40% male	13,000	17,000	11,000	13,000	24[c]
Equal response rate 60%	13,000	15,000	11,000	11,000	25[c]
6-monthly screening	29,000	28,000	21,000	23,000	26[c]
6-monthly screening, equal response rate 39%	29,000	27,000	21,000	21,000	27[c]
2-yearly screening	45,000	27,000	27,000	17,000	28[c]
EIA testing	92,000	41,000	34,000	29,000	29[c]
Incidence of PID equivalent to Welte	4,700	6,800	4,400	6,400	30[c]
Base case, outcomes discounted at 1.5%	31,000	29,000	23,000	25,000	31[c]
Base case, outcomes discounted at 3.5%	34,000	31,000	26,000	28,000	32[c]
Best case: PID 25%, and 60% response rate for men and women	2,900	3,700	2,900	3,400	22[b]

F, screening women only; M&F, screening men and women; none, no population screening; MOA, major outcome averted; ICER, incremental cost-effectiveness ratio
[a] Base-case response rate, 39% women, 29% men.
[b] This chapter.
[c] Appendix 7.

TABLE 68 *Alternative model parameters for EIA testing*

	PCR			EIA		
	M	F	Source	M	F	Source
Cost of planned screening test (UK £ 2003)	7.29	6.94	ClaSS	2.72	3.12	ClaSS
Sensitivity of planned screening test	0.99	0.97	ClaSS	0.73	0.65	ClaSS
Specificity of planned screening test	0.99	0.99	ClaSS	0.99	0.99	ClaSS

meant that the effectiveness of the screening programme was substantially reduced compared with using Cobas PCR. The cost saving of using the cheaper test applied only to those who responded to the screening programme, and the saving in diagnosis and treatment costs is offset by increased costs of sequelae. Thus, the overall reduction in cost of the screening programme using PCE EIA compared with Cobas PCR was small.

Varying the incidence of sequelae

The model was based on the incidence of severe major complications associated with chlamydia observed in the Uppsala Women's Cohort Study.[20] In this sensitivity analysis these estimates were compared with the value used by Welte and colleagues for pelvic inflammatory disease.[198] It was not possible to use their figures for ectopic pregnancy and infertility because they were based on the assumption that these followed from pelvic inflammatory disease, whereas the ClaSS model regarded ectopic pregnancy and infertility as due to tubal damage and sets incidence based on infection history.

Welte and colleagues used a probability of 0.25 that an asymptomatically infected woman would develop pelvic inflammatory disease, and a further conditional probability of 0.4 that this would be symptomatic.[198] The definition of pelvic inflammatory disease in the present study only included symptomatic cases. This converts to a probability of 0.1 that an asymptomatic woman would develop pelvic inflammatory disease. For the ClaSS model this converts to a daily probability of progression of 0.0005 from asymptomatic chlamydia to pelvic inflammatory disease. This analysis used the same probability for progression from symptomatic chlamydia to pelvic

inflammatory disease. Not surprisingly, the much higher incidence of pelvic inflammatory disease among chlamydia-infected women led to an increase in the number of major outcomes averted and lower ICERs.

Varying the discount rate

It has been suggested that outcomes as well as costs should be discounted. Current Treasury recommendations are that non-monetary outcomes should be discounted at 1.5%, while NICE recommends a discount rate of 3.5% for all outcomes. The results of applying these two discount rates made little difference to the pattern of results.

Best case analysis

The uptake rate and incidence of sequelae had the most impact on ICERs. If it was assumed that the risk of pelvic inflammatory disease was 0.25 and that the uptake of population screening was 60% for both men and women, the ICERs dropped dramatically and there was no dominance at any time-horizon (*Figure 22*).

Discussion

The ClaSS chlamydia transmission model suggests that chlamydia screening using posted home-collected specimens, at uptake levels achieved in empirical studies, and assuming a low incidence of chlamydia-associated complications, was not cost-effective. Provided that the response rate in men is not much lower than in women, screening men and women is preferred to screening women only. If the uptake of screening and the incidence of complications are assumed to be high, screening appears cost-effective.

The strengths of this study are that it used an individual-level dynamic mathematical model that gave the closest approximation to real-population sexual behaviour together with empirical data for as many parameters as possible. Many replications of the model were conducted to achieve replicable results and wide-ranging sensitivity analyses were undertaken. The results of calibrating the model were generally consistent with the empirical data, but there were some discrepancies. The ClaSS model showed a higher prevalence rate in 25–29-year-old men than was found in the prevalence survey. This might be because of the small number of participants in this age group and selection in those responding. A limitation of the results was that they were based on a single input set. Owing to the long running time of the current model, use of these additional input sets was beyond the remit of the current study. In terms of the level of uncertainty surrounding the illustrative cost-effectiveness results, confidence intervals were not presented. The most appropriate method for exploring uncertainty in these figures is by rerunning the model with

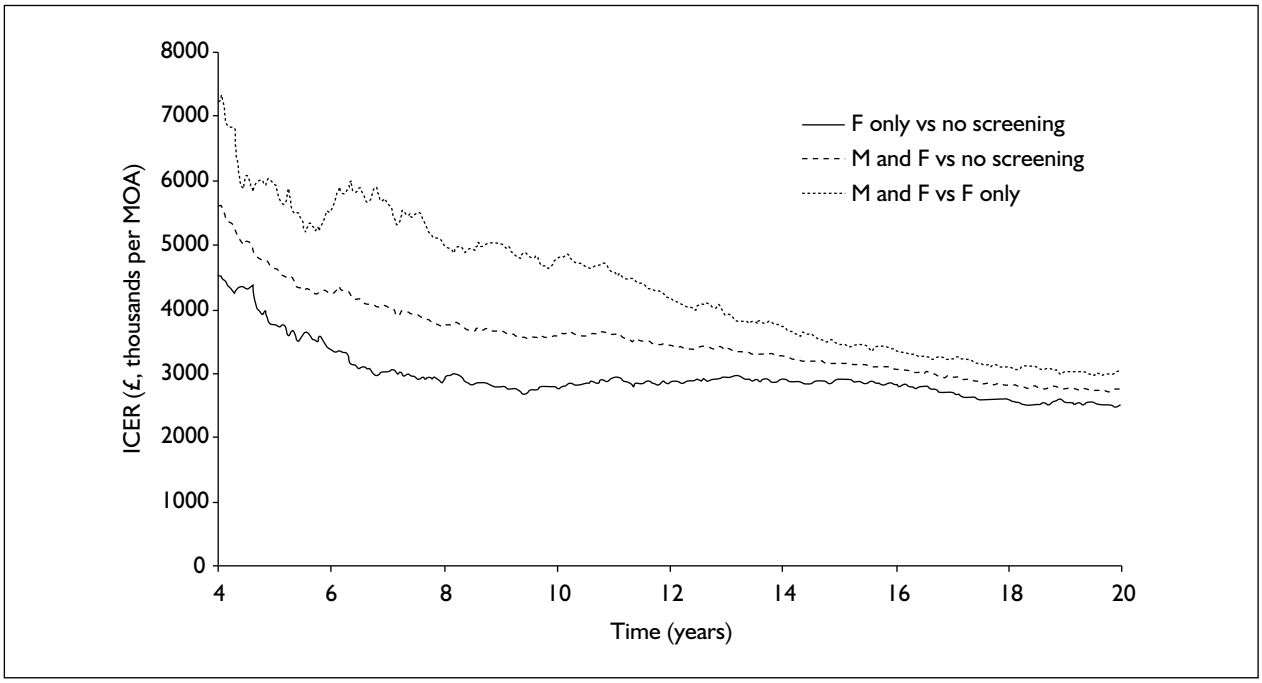

FIGURE 22 *Best case scenario*

another input set. Thus, the model needs to be rerun with different input sets to test the robustness of the conclusions. Compared with the model by Kretzschmar and colleagues,[235] this study did proportionally more replications. This is important for the ClaSS model because of the inclusion of sequelae. Future work is planned to examine the impact on the robustness of these results by using a number of other input sets. The full economic impact of alternative methods of partner notification has not been completed yet and will be reported separately.

The incidence of long-term sequelae used in this model was approximated through the calibration process to be comparable with the results of the Uppsala Women's Cohort Study.[20] These data showed a lower incidence than those used in virtually all other cost-effectiveness analyses found in the literature or used in other studies (Chapter 8). The sensitivity analysis showed that varying the incidence of pelvic inflammatory disease to that used in other published studies produces lower cost-effectiveness ratios. However, increasing the uptake of screening was also necessary to make chlamydia screening using active approaches cost-effective.

To the authors' knowledge, the ClaSS model is the first to attempt to incorporate some concept of tubal damage caused by repeated or persistent chlamydial infection into the stochastic model. The dynamic models of Welte[198] and Turner[247] appear to have done this using fixed probabilities. This leads to an increased variance within the model which necessitates a proportionally larger overall number of runs. The exact numbers presented in the summary table should therefore be interpreted with caution and the patterns presented in the graphs provide more qualitative information. In addition, the authors acknowledge the limitations to using data only from hospital-diagnosed episodes of sequelae.

The implications of this study are discussed further in Chapter 11.

Chapter 11

Discussion and recommendations

The results of the ClaSS project, described in Chapters 3–10, challenge some assumptions about chlamydia epidemiology, screening and management of infection. Each of these chapters includes a discussion about the component studies. The overall strength of this large, complex, multicentre, multidisciplinary project was that it was able to explore the entire process of a first round of chlamydia screening under realistic field conditions. This design was also a weakness: the unexpectedly low uptake of the active screening intervention meant that the number of people with chlamydia was lower than anticipated and some subsequent studies lacked statistical power. This concluding chapter discusses the relevance of findings from the ClaSS project to current chlamydia screening policy in the UK and provides recommendations for future research.

Effectiveness of chlamydia screening

The primary aims of the National Chlamydia Screening Programme are to prevent female reproductive tract morbidity and chlamydia transmission.[1] The ClaSS project was not designed to demonstrate the effectiveness of chlamydia screening in preventing these outcomes, which would require an RCT. The cross-sectional screening survey examined the uptake of proactive chlamydia screening, an intermediate outcome for screening programmes. High uptake is desirable in any screening programme but, for chlamydia screening, the level required to have an impact on prevalence or complications is disputed. Two randomised trials of active screening both led to reductions in the incidence of pelvic inflammatory disease of about 50%, a clinically important effect. Uptake of screening differed markedly between these studies, however: 64% in women in the USA,[29] but only 32% in women and 20% in men in Denmark.[62] A mathematical model with inputs from the Danish trial suggested that this level of uptake could result in a reduction in prevalence.[109] In the ClaSS project, uptake in 16–24-year-old women and men was similar to the Danish trial. The mathematical model, however, suggested that this would not have an appreciable impact on either prevalence (see *Figure 16*, pp. 106 and 107) or complication rates (see *Figure 18*, p. 108). Both studies used similar screening interventions and similar dynamic models. The different outputs are presumably due to differences in the assumptions used and, perhaps, calibration in these models. Taken together, the findings suggest that only further empirical studies will be able to determine whether long-term reductions in female reproductive tract morbidity and chlamydia prevalence are realistic goals for chlamydia screening programmes, and to improve the parameterisation of mathematical models.

Approaches to chlamydia screening

In the absence of evidence for the long-term effectiveness of screening, making access to chlamydia testing and treatment widely available in an equitable manner may be the most appropriate medium-term goal. Proactive screening for chlamydia in women and men under 25 years using home-collected specimens was feasible and acceptable, but the uptake of this method was lower than had been expected from an early pilot study (Chapter 3).[96] The low uptake might have been partly related to the novelty of the intervention. This approach to screening might become more acceptable and popular if it were more widely implemented and publicised. In common with studies using the same screening approach,[123] the qualitative research showed that people who took actually part in screening liked the convenience and privacy of taking specimens at home.

Maximising chlamydia screening uptake

Opportunistic testing in healthcare settings is being implemented in the National Chlamydia Screening Programme in England. In the pilot studies for this programme, screening was estimated to have reached 50% of sexually active women aged 16–24 years in the Portsmouth area, where the number of healthcare providers participating throughout the study period was greatest.[60,61] Such high coverage probably represents the upper limits of what could be achieved in real life, because the high levels of general practice participation in the pilot areas are

unlikely to occur nationally. GPs received generous financial incentives for each patient enrolled in the pilot study. GPs in the rollout of the programme have not been paid so far and participation in local chlamydia screening is voluntary.

Mixed models of chlamydia screening should be considered if they achieve higher consistent levels of screening uptake than either active or opportunistic screening alone. The ClaSS project approach to screening included features that could enhance the uptake of opportunistic screening, even though uptake as a single strategy was modest. The effectiveness of any kind of enhanced approach to screening should be determined through RCTs.

- Practice registers could be used by central chlamydia screening offices to ensure that multiple tests in different healthcare settings are not being done in the same individuals, to invite individuals to be screened if they have not presented during the year, and to recall individuals who have been screened once to invite them for regular annual screening. Population registers kept by GPs are already used by PCTs for administering the cervical cancer screening programme. The experience with high numbers of 'ghost' patients shows that registers needs to be updated regularly to increase their accuracy.
- Home-based specimen collection can be offered by post as an alternative to clinic-based screening for individuals who do not wish to go to a healthcare setting, to individuals attending general practices or other screening venues if they do not wish to accept the offer of a screening test at that visit, and to improve partner notification rates (see next section).
- Unfortunately, the examination of risk factors for chlamydia in the prevalence and case–control studies did not find any factors, other than young age, that would help to target screening more easily.

Screening young men for chlamydia

Chlamydia prevalence in asymptomatic young men was the same as in women (Chapter 3) and the economic evaluation showed that screening young men as well as women was the preferred option (Chapter 10). Active screening by invitation reached equivalent populations of young women and men. Although acceptance was lower in men than in women in the ClaSS project, about 20% of men aged 16–24 years were screened. Evidence for the best way to increase chlamydia screening uptake in young men in the National Chlamydia Screening Programme in England is lacking because the pilot studies only included women.[60,61] In the first year of the programme's implementation, when the target population was extended to include men, they accounted for fewer than 10% of chlamydia screening tests. Offering testing in workplaces, as piloted by the Men's Health Forum, has low uptake rates.[248] Pharmacy testing has low uptake among women,[249] and uptake in men is not yet known. When general practice attendances in the ClaSS project population were examined, it was found that nearly two-thirds of men aged 16–24 years (and three-quarters of women) attended their general practice in one year. If opportunistic screening in healthcare settings is the chosen approach to chlamydia screening then general practice is the setting best placed to offer screening to the majority of young men.

Repeat screening

Practice registers could be used to ensure regular repeat screening and to monitor long-term programme coverage. Screening is a continuous process, but there are limited data about repeat chlamydia screening because most research studies, including the ClaSS project, only investigate the first round. The results of a reinfection study from the National Chlamydia Screening Programme[137] suggest an annual screening interval for people with negative tests, and repeat screening within 6 months for those with a positive test.[137] Well-organised screening services that ensure consistently high coverage are essential if these programmes are to do more good than harm.[250] This is a major challenge for opportunistic screening programmes, where the onus is on providers to offer testing at every consultation so that people are rescreened regularly. Data from opportunistic chlamydia screening activities in Sweden suggest that, although most women were screened once, few were screened more frequently and only about 1% were screened annually.[20] Peto and colleagues have shown that, for cervical cancer screening, mortality only began to fall substantially when practice registers were used to call and recall women regularly.[251] In an opportunistic chlamydia screening programme, practice registers could be used to invite people who accepted an opportunistic offer of a test for rescreening at an appropriate interval, and to monitor programme performance. In the ClaSS project the qualitative research showed that there were very few instances in which the postal invitation caused serious offence. Further research about the ideal

frequency for rescreening, and about the uptake of regular chlamydia screening in the long term, is needed.

Reducing inequalities

Both active and opportunistic screening approaches have the potential to increase inequalities in sexual health. In the ClaSS project, no strong evidence was found of differences in prevalence according to individually measured ethnic group or area-level measures of deprivation. This lack of difference might, in part, have been due to the differential coverage and uptake: screening invitations were less likely to reach people in areas with high numbers of residents from non-white minority ethnic groups, and the uptake of the screening invitation was lower in more deprived areas (Chapter 3). If, however, there are no marked differences before screening was introduced, a screening programme that is less likely to be available and accessible, and less acceptable to people from vulnerable and disadvantaged groups could create or widen existing inequalities. Opportunistic screening might also be less available in deprived areas if GPs in those areas are less likely to offer chlamydia screening as a locally enhanced service. This is an issue that requires further research.

Partner notification

It is suggested that nurse-led partner notification, with support from specialist health advisers should be implemented within the National Chlamydia Screening Programme. Practice nurse-led partner notification was as effective a strategy for ensuring treatment of the sexual partners of people diagnosed with chlamydia in primary care as referral to a GUM clinic. The strategy was no more expensive than referral to a specialist GUM clinic and was preferred by patients. The strategy could be extended to nurses in family planning clinics, youth sexual health clinics and NHS walk-in centres. Home-based specimen collection could be offered to eligible patients as an alternative to clinic-based screening, and can be given to individuals diagnosed with chlamydia to improve partner notification rates. This intervention is being implemented in Denmark.

Laboratory diagnosis

EIAs, even when used with strategies to enhance their performance, were inadequate for performing chlamydia screening using male urine and female vulvovaginal swab specimens. Female vulvovaginal swab specimens are likely to become more popular for screening women using NAATs. They had high sensitivity and specificity, and lower levels of inhibition (with Becton Dickinson BD ProbeTec ET system) than with female urine specimens, and the cost per positive test was marginally lower than for urine specimens. The qualitative findings do, however, need to be taken into consideration before recommending vulvovaginal specimens as the female specimen of choice. Women were clearly unfamiliar with this type of specimen. Some confused it with a cervical smear, and others said that it had put them off taking part in the study altogether (Chapter 4). Even in studies performed in sexually transmitted disease and family planning clinics, most have shown that women prefer to give urine rather than vulvovaginal specimens.[167,174,175] More education of the public about the benefits of vulvovaginal specimens should improve the acceptability of these types of specimen. Systematic reviews of the increasing literature comparing female vulvovaginal and urine specimens are required to establish whether there is a clinically important gain in sensitivity. Pooling of specimens for screening is not recommended if resources to carry out individual testing are available. Pooling of self-taken urine and vulvovaginal swab specimens reduces costs and workload, but misses an appreciable proportion of positive tests.

Recommendations for research

There is still a need for a large, multicentre RCT to determine whether chlamydia screening prevents female reproductive tract morbidity and chlamydia transmission in the long term. Existing RCTs have only evaluated population-based (proactive) screening with a maximum follow-up of 1 year. No high-quality RCT has demonstrated any impact on the population incidence and prevalence of infection. Any new RCT would have to include opportunistic screening as one of the interventions, because this is current practice in the National Chlamydia Screening Programme, and would have to measure long-term primary outcomes.

Further research about the mathematical modelling of interventions to control chlamydia and other STIs is required. Detailed comparisons of static and dynamic modelling approaches should be carried out to determine the magnitude and direction of biases in both types of model.[255] Different types of dynamic mathematical model

should also be compared to determine the assumptions to which the models are most sensitive. These evaluations should use empirical data where possible and should carry out extensive sensitivity analyses.

Studies to determine the best ways of engaging young men in chlamydia screening should be carried out. Comparisons of the coverage and uptake of offering screening to young men in general practice and postal, Internet or outreach activities would be of value. All such studies need to use appropriate denominators to measure coverage, and to determine whether the intervention reaches men who would not otherwise have an opportunity of being screened.

The risks of reinfection following screening and treatment, the appropriate screening interval and the uptake of repeat screening have not been well established. Annual rescreening is currently recommended in the National Chlamydia Screening Programme and in the USA, but it is not known how often this offer is taken up in an opportunistic programme. The impact on chlamydia prevalence of different rescreening rates also needs to be examined in modelling studies.

Research to monitor and investigate the effects of chlamydia screening on inequalities in sexual health should be done. The impact of differential uptake of screening by vulnerable and disadvantaged groups should be examined.

A systematic review of studies comparing the performance of female urine and vulvovaginal specimens for *C. trachomatis* diagnosis should be undertaken to determine whether the increase in yield with vulvovaginal specimens is clinically important.

Better data about the likelihood of progression of chlamydial infection to pelvic inflammatory disease, ectopic pregnancy, tubal infertility and chronic pelvic pain are required. Systematic reviews should be conducted first to synthesise the evidence. Future studies need to take into account the fact that diagnosing chlamydia necessitates treatment, which alters the natural history, but that not offering treatment is unethical.

Studies about quality of life associated with chlamydia, and its long-term consequences in women, men and newborn children, are required so that cost-effectiveness studies can use cost per QALY as the outcome.

Acknowledgements

Contribution of authors

Nicola Low (Senior Lecturer, Epidemiology and Public Health) was acting principal investigator, co-chair of the partner notification workstream, oversaw the overall project, contributed to conception and design, data analysis and interpretation, coordinated and drafted the final report, and was guarantor of the final report. Anne McCarthy (Senior Research Fellow, Social Medicine and Primary Care) was project manager, Bristol, was responsible for overall running of project, and contributed to data acquisition, interpretation of data and drafting the report. John Macleod (Senior Lecturer, Primary Care) was co-chair of the prevalence and case–control workstreams, Birmingham, oversaw the project in Birmingham, and contributed to conception and design, data interpretation, and drafting and revising the final report. Chris Salisbury (Professor, Primary Care) was co-chair of the prevalence workstream, Bristol, oversaw the prevalence study in Bristol, and contributed to conception and design, data interpretation, and drafting and revising the final report. Rona Campbell (Professor, Health Services Research) was chair of the social research workstream, oversaw the social research studies, and contributed to conception and design, data collection, analysis and interpretation, and drafting and revising the final report. Tracy Roberts (Senior Lecturer, Health Economics) was chair of the economics workstream, oversaw the economic evaluation, conducted the systematic review of economic evaluations, and contributed to conception and design, data acquisition, analysis and interpretation, and drafting and revising the final report. Paddy Horner (Consultant, Genitourinary Medicine) was co-chair of the laboratory workstream, Bristol, after the retirement of Dr Herring, oversaw laboratory studies in Bristol and the department of genitourinary medicine part of the partner notification trial in Bristol, and contributed to conception and design, data interpretation, and drafting and revising the final report. Sue Skidmore (Consultant, Microbiology) was co-chair of the laboratory workstream, Birmingham, oversaw the laboratory studies in Birmingham, and contributed to conception and design, data interpretation, and drafting and revising the final report. Jonathan Sterne (Reader, Epidemiology and Medical Statistics) oversaw all statistical analyses, and contributed to the analysis and interpretation of data, and drafting and revising the final report. Emma Sanford (Research Assistant, Medical Statistics) conducted statistical analyses for the prevalence, social research, partner notification and laboratory workstreams, and contributed to data analysis and drafting the final report. Fowzia Ibrahim (Research Assistant, Medical Statistics) conducted statistical analyses for the prevalence and case–control workstreams, and contributed to data analysis and drafting the final report. Aisha Holloway (Lecturer, Nursing) was assistant Project Manager, Birmingham, was responsible for running the project in Birmingham, and contributed to data acquisition, interpretation of data and revising the final report. Rita Patel (Research Assistant, Primary Care) conducted fieldwork for the prevalence study in Bristol, and contributed to data acquisition and revising the final report. Pelham Barton (Lecturer, Mathematical Modelling) developed the mathematical model with advice from Mirjam Kretzschmar and Robert Welte, conducted mathematical modelling for economic evaluation, and contributed to drafting and revising the final report. Suzanne Robinson (Lecturer, Health Economics) conducted the primary health service and patient cost studies and systematic review of economic evaluations, and contributed to data acquisition, analysis and interpretation, and drafting and revising the final report. Nicola Mills (Training Fellow, Social Medicine) conducted qualitative interviews in the social research workstream, and contributed to data acquisition, analysis and interpretation, and drafting and revising the final report. Anna Graham (Lecturer, Primary Care) was a member of the case–control and social research workstreams, conducted qualitative interviews in the social research workstream, and contributed to data acquisition, analysis and interpretation, and revising the final report. Alan Herring (Consultant, Microbiology) was co-chair of the laboratory workstream, Bristol, oversaw laboratory studies in Bristol, and contributed to conception and design, and revising the final report. He retired in 2004. Owen Caul (Virologist) contributed to conception and design. He retired shortly after the project began. George Davey

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Contribution of other collaborators and members of the ClaSS project team, in alphabetical order

All practice nurses in the study practices participated in training, and undertook chlamydia management, recruitment into a randomised trial and partner notification. All general practitioners in the study practices facilitated the successful integration of the ClaSS project into practice work and provided support for practice nurses. Stirling Bryan (Professor, Health Economics) was an economic adviser, provided advice on the economic evaluation and commented on drafts of the economic sections of the report. Gavin Daker-White (Research Fellow, Social Medicine) conducted qualitative interviews in the social research workstream, and contributed to data acquisition, analysis and interpretation. Debbie Hawkings (Secretary) provided secretarial and administrative support throughout the ClaSS project. Martin House (Database Manager) developed the database for importing and managing general practice lists. Mia Huengsberg (Consultant, Genitourinary Medicine) was co-chair of the partner notification workstream, Birmingham, and contributed to the department of genitourinary medicine part of the partner notification trial in Birmingham. Mirjam Kretzschmar (Mathematical Modeller) developed the original dynamic model for modelling chlamydia transmission, consulted with the authors on refinements to adapt to the ClaSS project, and made comments on the draft chapter for economic evaluation. Philippa Matthews (Principal, General Practice) developed and delivered the training programme for practice nurses. Andrea Morcom (Research Assistant, Primary Care) contributed to data acquisition for the prevalence study and partner notification trial in Birmingham. Ian Paul (Laboratory Manager) oversaw diagnostic testing in Bristol. Tim Peters (Professor, Medical Statistics) supervised statistical analysis for the quantitative study of psychological effects of screening, and contributed to data analysis, interpretation and writing up of quantitative social research study. Karl Pye (Health Adviser) was the research health adviser in Bristol, was responsible for partner notification procedures and contributed to training, data acquisition and interpretation of the partner notification trial. Jo Sell (Biomedical Scientist) conducted diagnostic testing in Bristol. Jane Thomas (Biomedical Scientist) conducted diagnostic testing in Birmingham. Robert Welte (Health Economist) consulted with the authors to make refinements to the ClaSS transmission dynamic model. Mark Young (Health Adviser) was the research health adviser in Birmingham and contributed to data acquisition in the partner notification trial.

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Appendix 1

Assessment of National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme for chlamydia

The criteria, which are set out below, are based on the classic criteria first promulgated in a WHO report in 1966, but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the adverse effects of healthcare; regrettably, some people who undergo screening will suffer adverse effects without receiving benefit from the programme.

These criteria have been prepared taking into account international work on the appraisal of screening programmes, particularly that in Canada and the USA. It is recognised that not all of the criteria and questions raised in the format will be applicable to every proposed programme, but the more that are answered will obviously assist the NSC to make better evidence-based decisions.

All of the following criteria should be met before screening for a condition is initiated.

The condition

1. *The condition should be an important health problem*.
   Genital tract infection due to *Chlamydia trachomatis*, chlamydia, is an important public health problem. Chlamydia is the most common bacterial sexually transmitted infection worldwide, with an estimated 89 million new cases every year. In England, Wales and Northern Ireland the number of diagnosed infections has been increasing since 1995, with 104,155 new cases reported from GUM clinics in 2004.
   Chlamydia infection that ascends in the genital tract from the endocervix in women can cause pelvic inflammatory disease, which is an important cause of ectopic pregnancy, tubal infertility and chronic pelvic pain. In men, ascending infection can cause epididymitis. Chlamydia can be transmitted during labour to cause neonatal ophthalmia and pneumonitis. The presence of chlamydia in the genital tract facilitates the transmission of HIV infection.
2. *The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker and a latent period or early symptomatic stage*.
   The epidemiology of chlamydia is understood. Chlamydia is a sexually transmitted infection primarily affecting young adult men and women. Chlamydia is frequently asymptomatic in both men and women, facilitating continuing transmission. Chlamydia is widely distributed in the general population; about 2–6% of men and women under 25 years are infected. The prevalence of infection increases with increasing numbers of sexual partners, but is not strongly associated with socio-economic factors.
   The natural history of chlamydia is not adequately understood. Chlamydia in the lower genital tract is a strong risk factor for pelvic inflammatory disease. Host immunological factors are thought to be important in determining which women will develop complications. The latent period and incidence of complications are, however, not defined. The diagnosis of pelvic inflammatory disease is also invasive and not well defined, so it is not known how often endocervical chlamydia infection ascends into the upper genital tract, whether symptomatic lower genital tract chlamydia is more likely to ascend, how often pelvic inflammatory disease resolves spontaneously, or whether symptomatic pelvic inflammatory disease is more likely than asymptomatic or mild pelvic inflammatory disease to cause tubal damage. Clinic- and hospital-based studies might have overestimated the incidence of complications of chlamydia by selective inclusion of women

with more severe disease. These risks therefore may not be applicable to asymptomatic chlamydia infections diagnosed in the community using nucleic acid amplification tests, or to cases of pelvic inflammatory disease managed in primary care (which may account for 90% of all diagnosed pelvic inflammatory disease).

3. *All the cost-effective primary prevention interventions should have been implemented as far as practicable*.
   High-quality health promotion and sex and relationships education in schools should contribute to reducing levels of high-risk sexual behaviour. Condoms, used consistently and correctly, protect against chlamydia transmission.

The test

4. *There should be a simple, safe, precise and validated screening test*.
   Nucleic acid amplification tests for the detection of *Chlamydia trachomatis* are safe and precise. They have been validated, mainly in clinical populations. They are technologically complicated, but are becoming increasingly automated. They perform well when used on non-invasively collected specimens such as urine and vulvovaginal specimens in women, which makes testing simpler than collecting endocervical and urethral specimens.
5. *The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed*.
   The cut-off level for a positive test has been defined and agreed. It is not known whether results close to the cut-off for a positive test represent low numbers of copies of *C. trachomatis*, which may be less infectious and pathogenic.
6. *The test should be acceptable to the population*.
   Chlamydia testing using non-invasive specimens is acceptable to the population. Collecting specimens at home and posting them to a laboratory was acceptable to those who participated in screening.
7. *There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals*.
   For chlamydia screening, the screening test is also the diagnostic test. All positive test results should be regarded as presumptive evidence of infection. Positive screening test results should be confirmed in the laboratory, particularly when the prevalence in the target population is low. The screening test should include a control to detect specimens that contain inhibitors so that further tests can be carried out. Screening test results that are indeterminate should be repeated. The individual can choose whether to provide a second specimen or to take presumptive antibiotic treatment.

The treatment

8. *There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment*.
   Several antibiotic regimens have cure rates of 95% or higher. There is no evidence about the effectiveness of antibiotic treatment according to the duration of chlamydial infection because there is no way of determining the duration of infection in most cases.
9. *There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered*.
   All individuals with positive tests for chlamydia should be offered appropriate antibiotic treatment. If there is evidence that infection has spread to the upper genital tract the treatment regimen should include antibiotics that cover other possible causes of pelvic inflammatory disease in women or epididymitis in men.
10. *Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme*.
    Clinical guidelines for the management of chlamydia are published in the UK by the British Association for Sexual Health and HIV. Partner notification is an integral part of the management of chlamydia. For chlamydia infections diagnosed through screening in non-GUM clinic settings this study shows that partner notification using patient referral by general practice nurses who have received appropriate training and are supported by specialist health advisers is as effective as referral to a GUM clinic.

The screening programme

11. *There must be evidence from high-quality randomised controlled trials that the screening*

programme is effective in reducing mortality or morbidity.

Screening for *C. trachomatis*, an infectious disease, has two aims: (1) to reduce morbidity and mortality from the upper genital tract complications of chlamydia infection in women; and (2) to control the transmission of *C. trachomatis* in the population so that incidence and prevalence are reduced and infection can be eliminated.

Chlamydia screening can be done using an opportunistic approach (individuals offered chlamydia screening during a healthcare consultation) or an proactive (register-based) approach where individuals are invited specifically to take part in the screening programme.

There is no evidence from RCTs that an opportunistic screening programme for chlamydia reduces the risk of pelvic inflammatory disease or reduces the incidence and prevalence of chlamydia in the population.

Two RCTs have found that proactive (register-based) screening for chlamydia can reduce the incidence of pelvic inflammatory disease in women by around 50% 1 year later.

Methodological limitations in both studies have been documented: these might have resulted in an overestimate of the effectiveness of screening and the choice of study populations and screening methods may limit the generalisability of the findings.

There is no evidence from existing programmes that any form of screening has controlled chlamydia transmission.

The ClaSS project did not evaluate the effectiveness of chlamydia screening, but examined questions about screening programmes based on an evidence-based model of proactive population-based screening.

Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Not applicable.

12. *There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public*.

    Qualitative research was used to investigate the acceptability of chlamydia screening using home-collected specimens mailed to the laboratory. Participants in the screening survey found home-collection of urine and vulvovaginal swab specimens acceptable, receiving negative test results by post and positive tests at their general practice acceptable, and preferred the possibility of having partner notification done at the general practice at the time of diagnosis to being referred to a GUM clinic. Primary care professionals also found the programme acceptable.

13. *The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)*.

    The collection of non-invasive specimens at home did not cause any physical harm. This study showed that, among individuals with negative test results there were no negative effects on levels of anxiety, depression or self-esteem.

14. *The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money)*.

    The cost per accepted offer of an active chlamydia screening programme (including testing, diagnosis, treatment, administration and partner notification) was similar to that estimated for the National Chlamydia Screening Programme, an opportunistic screening programme.

    Evaluating the cost-effectiveness of chlamydia screening is more complicated. There are three specific factors that need to be taken into consideration in interpreting economic evaluations: (1) the need to use an appropriate mathematical model for an infectious disease, which takes into account interactions between individuals and the indirect effects of screening on disease transmission; (2) the need to use realistic assumptions about the incidence of complications (if these are high, the costs averted by screening will be overestimated); and (3) the need for realistic assumptions about the uptake and frequency of screening (if these are overestimated the benefits of screening will also be overoptimistic).

    For proactive screening using home-collected specimens posted to a laboratory a transmission dynamic model was used. Observational data from a large cohort in

Sweden were used to estimate the incidence of complications, which were considerably less common than suggested by hospital and clinic-based studies. The uptake of screening obtained in a cross-sectional screening survey and was used as the annual uptake. With these baseline assumptions, the ICER for screening men and women compared with no screening was about £25,000 after 8 years of screening. This would be considered an expensive intervention. In sensitivity analyses the cost per major outcome averted was reduced by: increasing uptake, to £13,000; increasing pelvic inflammatory disease incidence, to £7000; and with high uptake and incidence of complications, to about £3500.

15. *There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards*.
    Not applicable. The programme assessed by the ClaSS project will not be implemented in England, where the National Chlamydia Screening Programme is using an opportunistic approach.
16. *Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme*.
    Not applicable. See above.
17. *All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available*.
    Not applicable. See above.
18. *Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice*.
    The information obtained from the ClaSS project would enable this information to be provided.
19. *Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public*.
    Not applicable.

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Appendix 2

Search strategy for systematic review of cost and cost-effectiveness

The keyword search was based on the following strategy (including truncation of terms where appropriate):

Chlamydia OR chlamydia infections OR chlamydia exp OR pelvic inflammatory disease

AND

Economics OR economic evaluation OR cost benefit analysis OR cost OR cost analysis OR cost effectiveness analysis OR cost utility analysis OR cost minimisation OR quality of life OR QALY

Electronic bibliographic databases searched included the following:

- MEDLINE
- CINAHL
- EMBASE
- Econlit
- Science Citation Index (SCI)
- Social Science Citation Index (SSCI)
- Cochrane Library
- Database of Abstracts of Reviews of Effectiveness (DARE)
- NHS Economic Evaluation Database
- ASSIA
- OHE Health Economic Evaluation Database (OHE-IFPMA).

To ensure comprehensive coverage of relevant material, additional searches were undertaken These included:

- citation checking of all articles obtained
- Internet searches using the terms chlamydia or sexually transmitted infection and screening
- conference proceedings and abstracts.

Appendix 3

Categorisation process for all papers identified in the search strategy

Stage 1: initial categorisation based on title and abstract

A. Primary research is reported on the costs or utilisation of care and includes formal economic evaluation.
B. Economic aspects of care are discussed and useful primary or secondary cost or utilisation data included.
C. Contains useful information, but does not obviously fall into category A or B.
D. Economic aspects of polices for care are discussed, but the study is not in either category A or B.
E. The study does not have any relevance to the economic evaluation of *C. Trachomatis* screening.
F. The studies categorised as A, B and C were considered relevant to the systematic review. Those in categories D and E were not considered further.

Stage II: further categorisation of studies, after full review

All studies in categories A, B and C were reviewed in full and further classified into the categories below:

1. economic evaluation (cost-effectiveness, cost–utility, cost-minimisation, cost–benefit)
2. other cost study
3. effectiveness study with some assessment of implications for cost or quantity of resources used
4. description of methods used in aspects of economic evaluation of chlamydia screening
5. review of economic aspects of care
6. other, such as survey of resources and facilities, survey of utilisation, estimate of economic burden of disease, discussion of health finance or policy
7. not relevant to the economic evaluation of chlamydia screening
8. foreign language: to be reviewed by relevant linguist.

All studies classified as A(1), A (2), B(1), B(2), C(1) or C(2) were included in the quality assessment section of the review. All studies that did not fall into the above categories were rejected.

Appendix 4

Systematic review summary table

TABLE 69 *All studies included in the systematic review, in alphabetical order*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Adams, 2004[144] UK B(2) Pass	**Screening** (selective opportunistic) Women 16–24 years	Healthcare system	NA	UK £ sterling, 2001	NA	LCR	Azithromycin (1 g single dose) or doxycycline (alternatives for pregnant women)	Average cost per screening invitation	Average cost (with partner management) £14.88 per screening offer, £21.83 per testing episode, £38.36 per positive episode	High-quality cost study (not an economic evaluation) presenting costs of the UK opportunistic screening programme
Begley, 1989[204] USA A(1) Pass	**Screening** (non-selective opportunistic) Adolescents 12–19 years	Healthcare system	Own primary study	Own primary study US$, 1987	No model	Not specified	Oral tetracycline (7 days, q.d.s.)	Cost per test, screen or treatment	Chlamydia screening of asymptomatic patients in FP clinic cost-effective	No model: analysis insufficient to make policy recommendations
Blake, 2004[185] USA A(1) Pass	**Screening** (selective opportunistic) Young men in detention 14–18 years	Healthcare system	Primary (own study) and secondary	Department of Youth Services salary data and literature No currency or price year specified	Static: decision-analytic model	LE test strips (Chemstrips 9) LCx, or BD ProbeTec	Azithromycin (1 g single dose)	Cost per case of PID prevented	Three strategies: universal screening (urine NAAT); NAAT testing LE positive urines; no screening. Universal NAAT screening most cost-effective for prevalence 2.8% or higher	Comprehensive study, well reported. Model takes no account of reinfection and population effects so results may be misleading
Browning, 2001[216] UK B1?	**Diagnosis** GUM clinic Men and women	Healthcare system	Observed data	Local costs £ sterling	None	BD ProbeTec on urine specimens vs culture of genital swabs	None	Case detected	BD ProbeTec superior to culture for identifying chlamydia in GUM clinic	Good analysis of cost per true case detected. Limited because does account for long-term cost and effect of false negatives
Buhaug, 1989[190] Norway A(1) Pass	**Screening** (selective opportunistic) FP, or routine GP gynaecological visit Women 15–39 years	Societal (implied, not stated)	Own primary study	Own costs from GP and University of Trondheim NKr, £ sterling, 1987	Static: Markov model	Not specified	7-day treatment, drug not specified	Sequelae avoided	Testing cost-effective for 18–24 year-olds only	Model used takes no account of reinfection and population effects and therefore results may be misleading

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Buhaug, 1990[189] Norway A(1) Pass	**Screening** (selective opportunistic) FP, or routine GP gynaecological visit Women 15–35 years	Societal (implied, not stated)	Own primary study	Own costs from GP and University of Trondheim NKr, £ sterling, 1987	Simulation model, details unspecified	Not specified	Lymecycline (7 days)	Sequelae avoided	Testing cost effective for 18–24-year-olds only	Limited information provided on simulation model approach
Dryden, 1994[217] UK A(1) ?	**Diagnosis** (selective opportunistic) Men and women 16–65 years	Healthcare system	Observed data	Local costs £ sterling	None	EIA, DFA Urine specimens	Doxycycline (7 days)	Chlamydia cases detected	Cost per case cured £245. The authors state that the cost of missing a diagnosis of chlamydia was not included because there were too many variables to consider	Correct result for this approach. Partial study reporting cost of detecting chlamydia. Did not incorporate long-term outcomes
Estany, 1989[230] A(1) Pass	**Diagnosis** (non-selective screening) Non-pregnant women	Societal	Literature	Literature and national publication, observational data (from hospital charts) Canadian $, 1987	Static: decision-analytic model	EIA, DFA	Tetracycline, (7 days)	Cost per PID prevented (analogous to MOA)	Early detection with DFA and EIA cost-effective if prevalence exceeded 6% and 7%, respectively	The study compares dated diagnostic techniques. Model takes no account of population effects
Genc 1993[203] Uppsala, Sweden A(1) ?	**Screening** (non-selective opportunistic) Routine health check Adolescent men	Healthcare system	Literature	Own primary costs US$, no year (SKr1 = $7)	Static: decision-analytic model	LE-EIA, EIA	Azithromycin (1 g single dose)	Cure for men, including contact tracing and costs associated with PID, ectopic pregnancy, infertility	Compared with no screening, screening adult men reduced overall costs when chlamydia prevalence was above 2% for LE-EIA and 10% for EIA alone	Model used takes no account of reinfection and population effects and therefore results may be misleading

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Genc 1996[201] Uppsala, Sweden A(1) ?	**Screening** (non-selective opportunistic) Youth clinic, GP, FP Women and male partners Age not specified	Healthcare system	Literature	Own costs US$, no year	Static: decision-analytic model	Culture, EIA, NAAT	Azithromycin (1 g single dose)	Cost per case identified and treated	Screening with NAAT combined with azithromycin for positive patients was the most cost-effective strategy when the prevalence was 6%	Outcome is right for this model, but study is trying to suggest that individuals will be cured and does not take into account reinfection
Genc, 1997[222] Sweden A(1) ?	**Treatment** (gonorrhoea with chlamydia coinfection) Women and men	Societal	Literature	Average Swedish salaries and medical care costs US$ no year	Static: decision-analytic model	Not specified	Doxycyline (7 days, 100 mg b.d.), Azithromycin (1 g single dose)	Cost per cured patient	Doxycycline more cost-effective than azithromycin if compliance >80%. Azithromycin more cost-effective if compliance low	Model takes no account of population effects
Gift 2004[226] USA A(1) Pass	**Treatment** (gonorrhoea with chlamydia coinfection) Women Age not specified	Healthcare system	Literature	US$, 2000	Static: decision-analytic model	Nucleic acid hybridisation test (PACE 2), LCR Endocervical specimens	Doxycycline + azithromycin	PID cases prevented	Dual treatment alone not cost-effective replacement for chlamydia testing, but increased cases treated when combined with testing. Dual treatment resulted in more over treatment	Comprehensive study. Model adequate for objective
Ginocchio, 2003[196] USA) A(1) Pass	**Screening** (non-selective opportunistic) Adolescent men	Healthcare system	Literature	US$, 2000	Static: decision-analytic model	LE-LCR vs LCR Urine specimens	Not specified	PID cases prevented	LCR alone prevented 104 more cases of PID than LE-LCR, but cost $22.62 more per male screened. For this to be more efficient than LE-LCR, the LCR cost needs to decline to <$18	Comprehensive study, well reported. However, model used takes no account of reinfection and population effects and therefore results may be misleading

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Goeree, 2001[206] Canada A(1) Pass	**Screening** (selective opportunistic) Women; 15–24 years	Healthcare system	Literature	Various sources in Ontario Canadian $, 1999	Markov model	Seven combinations of test and samples performed on symptomatic, asymptomatic and high-risk women	Not specified	Prevention of chlamydia cases over 10 years (including sequelae)	Screening all women aged 15–24 years considerably more costly and only moderately more effective than screening only high-risk women	Outcome unclear. Probabilities of long-term sequelae not presented explicitly. Distinguished diagnostic testing in this study (symptomatic) and screening (asymptomatic). Model takes no account of reinfection and population effects and may be misleading
Gunn, 1998[193] USA A(2) Pass	**Screening** (selective opportunistic) Outreach clinic High-risk adolescent males	Healthcare system	NA	Own primary study US$, 1996	No model	LCR	Azithromycin (1 g single dose)	Cost per specimen obtained and cost per case identified	Cost per specimen obtained $103; cost per case identified $1677	Correct approach for the objective of evaluating an intermediate outcome
Haddix, 1995[221] USA A (1)?	**Treatment** Women	Healthcare perspective, publicly funded clinic perspective	Literature	Consumer Price Index US$, year not given	Static: decision-analytic model	Laboratory-confirmed diagnosis (test not specified), presumptive diagnosis	Azithromycin (1 g single dose), doxycycline (7 days, 100 mg b.d.)	PID case prevented	Azithromycin is a cost-effective alternative to doxycycline. However, the cost of azithromycin must decrease markedly for it to be less costly to public clinics	Model takes no account of population effects
Howell, 1997[211] USA A(1) Pass	**Partner notification** Women and men	Healthcare system	Literature	US$, 1994	Static: decision-analytic model	Not stated	Azithromycin (single dose)	Locating and treating partners	Contact tracing of female partners of male cases with chlamydia more cost-effective than contacting male partners of women to prevent reinfection	Inadequate modelling approach given attempt to look at population effects of chlamydia spread as a result of partner notification

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Howell, 1998[229] USA A(1) Pass	**Diagnosis** (selective opportunistic screening); FP clinics Women <30 years	Healthcare system	Literature, direct observation, expert opinion	Local standard costs, literature US$, 1995	Static: decision-analytic model	Cell culture, EIA, non-amplified probe assay, PCR (cervical specimens), PCR (urine), LCR (cervical specimens)	Doxycycline (7 days)	Additional case of PID prevented (analogous to MOA)	LCR on cervical specimens on women receiving pelvic examinations most cost-effective. LCR on cervical specimens without pelvic examination would also prevent more disease than EIA	Model takes no account of population effects and therefore results may be misleading
Howell 1998[200] USA A(1) Pass	**Screening** (non-selective opportunistic) FP Women 11–68 years (median 25 years, focus age <30 years)	Healthcare system	Own primary study	Baltimore City hospital and literature US$, 1995	Static: decision-analytic model	PCR tests on cervical swab and/or urine	Doxycycline	Sequelae prevented in men, women and infants, but considers consequences of longer term sequelae	Age-based screening provided the greatest cost saving of the three strategies examined. Universal screening cost-effective at a prevalence >10.2%	Model used takes no account of reinfection and population effects and therefore results may be misleading
Howell, 1999[208] USA A(1) Pass	**Screening** (selective population) Female army recruits 17–39 years	Military (modified payer)	Own primary study	TRADOC and own costs US$, 1995	Static: decision-analytic model implied (but not presented or made explicit)	LCR	Azithromycin (1 g single dose)	PID avoided	Screening by age provided a cost saving to the Army over a 1-year period	Model used takes no account of reinfection and population effects and therefore results may be misleading

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Howell, 2000[207] USA A(1) Pass	**Screening** Selective population screening Female US army recruits, Focus age <25 years	Military and civilian	Own primary study	TRADOC and own costs US$, 1998	Static: decision-analytic model	LCR	Azithromycin (1 g single dose)	Sequelae avoided	Screening army recruits was cost-effective. From a military perspective screening under 25 years provided greatest cost saving	Model used takes no account of reinfection and population effects and therefore results may be misleading
Hu, 2004[194] USA A(1) Pass	**Screening** (selective opportunistic) Women only 15–29 years	Modified societal	Literature	US$, 2000	State-transition simulation model	NAAT (unspecified) Urine specimens	Azithromycin (1 g single dose)	Cost per QALY	Four alternative screening strategies. Annual screening followed by semi-annual screening for those with a history of infection was the most effective and cost-effective strategy. It consistently had an ICER <$25,000 per QALY	State-transition model with cycle time 6 months. Attempts to incorporate issues that require a dynamic model by using population averages. This does not reflect reality. No mention of partner notification. QALY outcome not described. Results should be viewed with caution
Hueston, 1997[231] USA A(1) Pass	**Treatment** Pregnant women	Healthcare provider	Literature	Local charges US$, 1996	Static: decision-analytic model	NA	Amoxicillin (7 days 500 g t.d.s.), erythromycin (7 days q.d.s.), clindamycin (14 days q.d.s.), azithromycin (1 g single dose)	Cost per case cured	Amoxicillin (500 mg t.d.s. for 7 days) followed by a single dose of azithromycin for non-responders was the most cost-effective strategy for treatment	Partial study. Does not include reinfection or long-term outcomes (including of neonates). Model takes no account of population effects

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Kacena, 1998[51] USA B(1) ?	**Diagnosis** (selective population screening) Army recruits Women	Healthcare system	Observational data	Local costs US$, year not given	None	LCR Pooled urine specimens	NA	Cost per specimen tested	At 8% prevalence, pooling by four would reduce costs by 39%. At 2% prevalence pooling by eight samples would reduce costs by 59%	Cost study only, but only paper identified on the subject of pooling specimens
Katz, 1988[210] USA A(1) ?	Partner notification (field follow-up or two self-referral strategies) Army recruits Men with non-gonococcal urethritis	Healthcare system	Own study	US$, 1985	None	Culture	Not specified	Locating partners	Field follow-up by trained investigators proved to be the most cost-effective method of locating patients with chlamydia	The data are old, but the methods for partner referral similar to current patient referral. The model used is not an issue in this evaluation because the objective was to look at the methods of locating partners and not the population effects of the consequences
Knight, 2000[219] UK A(1) Pass	**Diagnosis** (non-selective opportunistic screening) Women (men through partner notification) 16–25 years	Healthcare system	Observational data, literature	Local costs £ sterling, 1997	Dynamic: simulation approach	ELISA, PCR/LCR Type of specimen not stated	Included but not specified	No outcome measure used; costing study only	Testing with LCR would reduce the cost of testing and treating by around the second year of implementation. Cost savings due to the increased sensitivity of the test. Global screening not cost-effective	Acceptable basic dynamic structure, but monthly cycle is a potentially serious defect. Some dubious assumptions, e.g. all partners are positive. The absence of an effectiveness measure means that conclusions about the cost-effectiveness of screening should not be drawn from this study

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Magid, 1996[223] USA A(1) Pass	**Treatment** Women; non-pregnant, childbearing age	Payer perspective	Expert, literature, assumptions	National charges and prices (Blue Cross and Blue Shield) average wholesale drug prices US$, 1993	Static: decision-analytic model	NA	Azithromycin (1 g single dose), doxycycline (7 days 100 m g b.d.)	Major complication averted	Azithromycin strategy more cost-effective than doxycycline	Model takes no account of population effects. Paper did incorporate different levels of compliance
Marra, 1997[224] USA A(1) ?	**Treatment** Women Hypothetical cohort of 5000	Third party payer	Literature, expert opinion	Hospital costing departments US$, currency year not stated	Static: decision-analytic model	Laboratory-confirmed diagnosis (test not specified) and presumptive diagnosis	Azithromycin (1 g single dose) doxycycline (7 days 100 mg b.d.)	Cost per cure	Concluded that azithromycin should be used to treat laboratory cases. Azithromycin for presumptive cases if probability of chlamydia and PID >19%, doxycycline effectiveness <78%, or cost of azithromycin <$19	Model takes no account of population effects and therefore results may be misleading. (Based model on Haddix[221])
Marrazzo, 1997[202] USA A(1) Pass	**Screening** (non-selective opportunistic) FP, STD clinics Women Mean 22–25 years	Societal	Own primary study	Own costs from region office of family planning US$, 1993	Static decision-analytic model	DFA, culture, EIA, DNA probe	Doxycycline (compliance estimated at 70–100%; see Washington[233])	Sequelae avoided	At the given prevalence it would be cost-saving to screen universally in FP clinics and selectively in STD clinics	Model used takes no account of reinfection and population effects and therefore results may be misleading
Mehta, 2002,[195] USA A(1) Pass	**Screening** (non-selective opportunistic) Emergency department (gonorrhoea and chlamydia) Men and women; 18–31 years	Healthcare system	Literature	US$, 1999	Static: decision analytic model	LCR Urine specimens	Azithromycin (1 g single dose) + ciprofloxacin (500 mg single dose)	Cost to prevent case	Five strategies, including standard, enhanced, mass treatment. Mass treatment most cost-effective strategy among men and women	Comprehensive study which was well reported. However model used takes no account of reinfection and population effects and therefore results may be misleading

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Moriarty, 2001[225] New Zealand A(1) ?	**Treatment** Women	Healthcare system	Literature, medical records, experts, arbitrary	National pricing schedules	Extended mathe-matical model	EIA confirmed by DFA, LCR	Doxycyline (7 days 100 mg b.d.), azithromycin (1 g single dose)	Cost per patient cured	Azithromycin regimens more cost-effective. Single-dose azithromycin both ensured compliance and minimised side-effects	Main aim was to discuss the modelling approach. Needs more detail of model to assess properly
Mrus, 2003[212] USA A(1)?	**Diagnosis** Adolescents in juvenile detention 13–18 years	Societal	Cohort study, literature	US$, 1998	Static: decision-analytic model	Urine LE test and LCR, additional sample and swab test for all testing positive on urine	Azithromycin (1 g single dose)	Cost per case treated; cost minimisation comparing estimated total cost of diagnosing and treating chlamydia as well as associated with complications	Urine LE results produced the lowest ICER. In the extended time-horizon treating males on the basis of urine LE results was the least expensive strategy	Inappropriate use of longer time-horizon cost-minimisation analysis, which implies treating. Takes no account of the different sensitivities of tests. The valuation of these outcomes has not been included, leading to potential bias. Model takes no account of population effects
Nettleman, 1991,[188] USA A(1) ?	**Screening** (selective opportunistic) Pregnant women not specified but pregnant	Healthcare system	Literature	Literature Currency and year not stated	Static: decision-analytic model	Culture, DFA	Erythromycin (7 days)	Cost per complication (salpingitis, neonatal pneumonia)	Screening all pregnant women was not cost-effective, although this depended on the test	Model used takes no account of reinfection and population effects and therefore results may be misleading
Nettleman, 1988[214] USA A(1) Pass	**Diagnosis** (non-selective opportunistic) Student health clinic	Healthcare system	Observed data, literature	Local standard cost US$	Static: decision-analytic model	Culture, ELISA, indirect immuno-fluorescent antibody test (IFA), microimmuno-fluorescence test (MIF), year not given	NA	Cost per case detected	Screening with DFA more cost-effective than no screening. Culture alone or as confirmation less cost-effective	Study compares dated diagnostic techniques. Model takes no account of population effects

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Nyari, 2001[228] Hungary A(1) ?	**Diagnosis** (non-selective opportunistic) Women 15–19 years	Healthcare system	Observational data, literature	Not stated, presume local costs US$, year not stated	Static: decision-analytic model	ELISA, Gen-Probe Type of specimen collection not stated	Doxycyline	Cost per case prevented (analogous to MOA)	Screening by amplified Gen-Probe assays (followed by treatment of positive patients) was the preferred screening strategy for young women in Hungary	Model takes no account of population effects and therefore results may be misleading
Paavonen, 1998[25] Finland A(1) ?	**Screening** (non-selective opportunistic) Women Age not specified	Healthcare system	Literature, expert opinion	National Research and Development Centre for Welfare and Health Finland US$, year and exchange rate not specified	Static: decision-analytic model	PCR on urine; EIA on swabs	Azithromycin (1 g single dose)	Cure; cost per case detected; looks at longer term outcomes	Population screening using PCR was cost-effective even in low-prevalence populations. Net saving for population screening in Finland $3.5m	Model used takes no account of reinfection and population effects and therefore results may be misleading
Peeling, 1998[215] Canada A(1) ?	**Diagnosis** (selective) Chlamydia and gonorrhoea Men 15–68 years	Healthcare system	Observed data	Local costs Canadian $, year not given	None	PCR or LE for urine specimens, culture for urethral specimens	Not stated	Cost per case detected	Targeted screening using risk assessment recommended in the Canadian STD guidelines would detect the same number of cases as universal screening, but with reduced costs	Partial evaluation. No discussion or analysis of reinfection or infection of others or of issue of false negatives
Petitta, 1999[220] USA A(1) ?	**Treatment** Men and women	Healthcare system	Literature, arbitrary, own primary study, expert opinion	Hospital charges, literature US$ implied, year not given	Static: decision-analytic model	NA	Azithromycin (1 g single dose), prescription for doxycycline (7 days, 100 mg b.d.), prepacked doxycycline	Assume cost per case cured	Prepacked doxycycline and azithromycin decreased re-infection and overall costs compared with prescription doxycycline. Azithromycin decreased relapse compared with prepacked doxycycline, but incremental impact on cost was inconclusive	Model takes no account of population effects and therefore results may be misleading. The paper compared prescription vs complete package for doxycycline

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Phillips, 1987[205] USA A(1) Pass	**Screening** (non-selective opportunistic) Gynaecological visit Women Age not specified	Healthcare system	Literature	Local charges US$, 1984	Static: decision-analytic model	DFA or EIA Endocervical specimens	Tetracycline (7 days q.d.s.)	Cervicitis	Testing women for cervical chlamydia was cost-effective	Model used takes no account of reinfection and population effects and therefore results may be misleading
Postma, 2000[197] Netherlands A(1) Pass	**Screening** (non-selective opportunistic) General practice Women 15–34 years	Societal	Own study: this is the Amsterdam pilot study	Short-term costs from primary study. Long-term costs from published literature US$, 1996	Static decision-analytic model	LCR	Azithromycin (1 g single dose)	Major outcome averted	Screening sexually active women under 30 was cost-effective	Model used takes no account of reinfection and population effects and therefore results may be misleading
Postma, 2001[186] Netherlands A(1) Pass	**Screening/ partner notification** (selective opportunistic) Women and male partners in general practice 15–29 years	Societal	Amsterdam pilot study	Dutch sources and published literature Euros, 1996	Static: decision-analytic model	LCR	Azithromycin (1 g single dose)	Net cost per MOA	Partner treatment reduced net costs per major outcome averted of the screening programme by 50%. Thus, partner notification significantly improved cost-effectiveness	Inadequate inclusion of population effects. Authors argue that this is a justifiable first step and do not attempt to make policy recommendations
Sahin-Hodoglugil, 2003[227] USA A(1) Pass	**Diagnosis** Gonorrhoea and chlamydia Women in sub-Saharan Africa	Healthcare system	Literature (based on sub-Saharan Africa where possible)	US$, 2002	Static: decision-analytic model	Syndromic management vs mass treatment	Doxycycline or azithromycin for chlamydia, ciproflaxin for gonorrhoea, vs mass treatment with doxycycline	Cost per cure	Mass treatment with doxycycline for chlamydia most cost-effective strategy	Comprehensive paper focusing on African women. Syndromic management rather than aetiological diagnosis. Model used appropriate for objective of this paper

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Schiotz, 1992[232] Norway A(1) ?	**Treatment** Women	Health service	Literature	Norwegian medical charges and published studies using Norwegian prices US$ (NKr), year not given	Static: decision-analytic model	Culture	Lymecycline (10 days, 300 mg b.d.)	PID case prevented	Routine test of cure of asymptomatic chlamydia after treatment not cost beneficial	Model takes no account of population effects and therefore results may be misleading
Scoular, 2001[213] UK B(1) Pass	**Diagnosis** Laboratory receiving tests from all settings Women and men All ages	Healthcare system	Observational data	Local costs £ sterling, 2000	None	LCR, EIA Urine and urethral swabs	None	Cost per case detected	Substantial health gains are likely to be achieved at both an individual and a public health level as a result of introduction of LCR testing	Authors acknowledge that this is a partial evaluation. Costs and effects of false-positive and false-negative tests not considered
Sellors, 1992[131] Canada A1 Pass	**Diagnosis** (non-selective opportunistic) Men 16–35 years	Healthcare system	Observed data	Local costs Canadian $, 1992	None	LE, EIA and PCR urine specimens in the first instance, positives were recalled for further collection using both urine and urethral specimen collection	NA	Cost per case detected	LE urine strip accurate screening test. Used to preselect urine specimens for chlamydia testing would be less costly per case detected than testing all specimens	Partial evaluation. No discussion or analysis of reinfection or infection of others or issue of false negatives

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Shafer, 1999[187] USA A(1) Pass	Screening (selective opportunistic) Adolescent females 15–19 years	Healthcare system	Literature	Government charges deflated to reflect cost US$, 1995	Decision analysis	LCR, PCR	Azithromycin (1 g single dose), ceftriaxone (1 g i.m.)	PID prevented	1283 cases of PID would be prevented at a mean cost of $5093	Model used takes no account of reinfection and population effects and therefore results may be misleading
Skjeldestad, 1988,[191] Norway A(1) Pass	**Screening** (selective opportunistic) Women seeking abortion Age not specified	Healthcare system	Own primary study	Local cost data US$ and NOK, 1985	No model	Culturing, but not specified	Lymecycline (7 days)	Salpingitis	Abortion-seeking women should be screened and treated for chlamydia	No model and no attempt to make policy decisions. Acceptable conclusion
Townshend, 2000[199] UK A(1)?	**Screening** (non-selective opportunistic) Men and women 12–40 years	NHS	Literature	Literature UK £, sterling no year stated	Dynamic: system dynamics model	Not specified	Not specified	PID and related sequelae for men, women and neonates	Suggests that proposed screening programme would prevent significant numbers of infertility cases annually. It could be paying for itself after about 4 years and recouping the initial outlay after about 12 years	Appropriate transmission dynamic model. Paper highlights use of model and suggests some conclusions. Economic quality of this paper is dubious
Trachtenberg, 1988[192] USA A(1) Pass	**Screening** (selective opportunistic) FP Women Age not specified	Healthcare system	Based on study Handsfield[128] in Seattle FP clinics	Based on data used by Washington[233] Not stated in this study but cites Washington[233]	Static: decision-analytic model	DFA	Doxycycline (7 days)	Sequelae avoided	Screening asymptomatic women was cost-effective	Model used takes no account of reinfection and population effects and therefore results may be misleading

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
van Valkengoed, 2001[92] Netherlands A(1) Pass	**Screening** (non-selective population) Women only 15–40 years	Societal	Amsterdam pilot study, own primary data	Cites Postma[256] US$, 1996	Static: decision-analytic model	LCR	Azithromycin (1 g single dose) (or erythromycin for pregnant women for 5 days)	Woman cured and MOA	Estimated cost of curing one woman $1210. Net cost of preventing one major outcome $15,800. Population screening of 15–40-year-olds was not cost-effective	Model used takes no account of reinfection and population effects and therefore results may be misleading
Wang, 2002[209] USA A(1) Pass	**Screening** (non-selective population) School pupils Chlamydia and gonorrhoea Men and women	Healthcare sector	Own primary study, literature	US$, 1997	Static: decision-analytic model	Urine: LCR for school-based testing. For non-school-based testing the test could vary	Azithromycin (1 g single dose)	Cost per case of PID prevented	School-based screening programme prevented an estimated 38 cases of PID as well as $119,866 in treatment costs. For PID and sequelae it resulted in savings of $1524 per case of PID prevented	Model used takes no account of reinfection and population effects and therefore results may be misleading
Washington, 1987[233] USA A(1) ?	**Treatment** (combined treatment for gonorrhoea and coinfection with chlamydia)	Healthcare system	Observational data, literature	Wholesale prices, hospital charges, literature, arbitrary US$, year not given	Static: decision-analytic model	NA	Three regimens: Ampicillin (3.5 g + probenecid, single dose); tetracycline (7 days 500 mg q.d.s.); combined treatment, same dosage and regimen	Cost per case treated	Combination treatment more than twice as cost-effective as tetracycline and seven times as cost-effective as ampicillin when the medical cost of managing PID was considered. When the costs of treating ectopic pregnancy and infertility were considered the cost-effectiveness increased further	Model takes no account of population effects and therefore results may be misleading. Old paper, pre-1987, also combined treatment for chlamydia and gonorrhea

continued

TABLE 69 *All studies included in the systematic review, in alphabetical order (cont'd)*

Study, country, quality[a]	Primary focus, (screening approach), gender, age	Viewpoint	Effectiveness data sources	Cost data, currency, year	Model used	Test	Treatment	Primary outcome	Results	Comment
Welte, 2000[198] Netherlands A(1) Pass	**Screening** (non-selective opportunistic); General practice Men and women 15–65 years	Societal	Amsterdam pilot study, literature	Short-term costs from Postma.[256] Long-term costs estimated from resource use US$, 1997	Dynamic: discrete event simulation	LCR	Azithromycin (1 g single dose)	MOA	Screening may save costs in the long, but not short term	Appropriate transmission dynamic model. High estimate of progression to PID. 50–75% effective screening rate

[a] Explanation for study categorisation in Appendix 3.
ELISA, enzyme-linked immunosorbent assay.

Appendix 5

Probability at birth of surviving to a given exact age

Age (years)	M	F	Age (years)	M	F	Age (years)	M	F
0	1	1	34	0.9752	0.9861	68	0.7639	0.8495
1	0.9936	0.9949	35	0.9741	0.9856	69	0.7432	0.8359
2	0.9931	0.9945	36	0.9731	0.9849	70	0.7206	0.8208
3	0.9928	0.9942	37	0.9719	0.9842	71	0.6961	0.8041
4	0.9926	0.9941	38	0.9707	0.9835	72	0.6699	0.7858
5	0.9924	0.9940	39	0.9694	0.9826	73	0.6422	0.7657
6	0.9923	0.9938	40	0.9680	0.9817	74	0.6129	0.7441
7	0.9921	0.9937	41	0.9664	0.9807	75	0.5818	0.7210
8	0.9920	0.9936	42	0.9647	0.9796	76	0.5498	0.6966
9	0.9918	0.9935	43	0.9628	0.9783	77	0.5163	0.6701
10	0.9917	0.9934	44	0.9607	0.9769	78	0.4825	0.6426
11	0.9916	0.9933	45	0.9584	0.9753	79	0.4478	0.6130
12	0.9914	0.9932	46	0.9559	0.9736	80	0.4122	0.5822
13	0.9913	0.9931	47	0.9533	0.9719	81	0.3763	0.5489
14	0.9911	0.9929	48	0.9503	0.9698	82	0.3407	0.5144
15	0.9908	0.9928	49	0.9471	0.9676	83	0.3052	0.4782
16	0.9906	0.9926	50	0.9437	0.9652	84	0.2701	0.4411
17	0.9901	0.9923	51	0.9400	0.9626	85	0.2364	0.4030
18	0.9896	0.9920	52	0.9358	0.9597	86	0.2042	0.3640
19	0.9888	0.9917	53	0.9311	0.9566	87	0.1743	0.3248
20	0.9880	0.9914	54	0.9258	0.9532	88	0.1465	0.2864
21	0.9871	0.9911	55	0.9198	0.9494	89	0.1213	0.2493
22	0.9863	0.9908	56	0.9134	0.9452	90	0.0988	0.2139
23	0.9854	0.9905	57	0.9063	0.9408	91	0.0794	0.1816
24	0.9845	0.9902	58	0.8981	0.9357	92	0.0634	0.1526
25	0.9836	0.9898	59	0.8894	0.9302	93	0.0497	0.1258
26	0.9827	0.9895	60	0.8800	0.9242	94	0.0383	0.1018
27	0.9819	0.9892	61	0.8696	0.9175	95	0.0289	0.0806
28	0.9810	0.9888	62	0.8582	0.9102	96	0.0213	0.0625
29	0.9801	0.9885	63	0.8459	0.9022	97	0.0155	0.0472
30	0.9791	0.9880	64	0.8323	0.8937	98	0.0108	0.0348
31	0.9782	0.9876	65	0.8175	0.8842	99	0.0074	0.0251
32	0.9773	0.9871	66	0.8010	0.8737	100	0.0050	0.0177
33	0.9762	0.9867	67	0.7834	0.8622	101	0	0

Source: Government Actuary's Department.

Appendix 6

Daily propensity to form a new partnership

Males					Females				
	Activity group 1: current partners					Activity group 1: current partners			
Age (years)	0	1	2	3+	Age (years)	0	1	2	3+
14	0	0	0	0	12	0	0	0	0
16	0	0	0	0	14	0	0	0	0
18	0.002	0	0	0	15	0.0003	0	0	0
20	0.002	0.0002	0	0	17	0.0007	0	0	0
22	0.001	0.0002	0	0	20	0.0015	0.0002	0	0
25	0.0005	0.0001	0	0	25	0.0015	0.0004	0	0
30	0.0005	0	0	0	30	0.0015	0.0001	0	0
35	0.0005	0	0	0	40	0.0005	0	0	0
70	0.0005	0	0	0	70	0.001	0	0	0
	Activity group 2: current partners					Activity group 2: current partners			
Age (years)	0	1	2	3+	Age (years)	0	1	2	3+
14	0	0	0	0	12	0	0	0	0
16	0.002	0	0	0	14	0	0	0	0
18	0.005	0.002	0	0	15	0.002	0	0	0
20	0.005	0.002	0	0	17	0.002	0	0	0
22	0.01	0.002	0	0	20	0.003	0.001	0	0
25	0.002	0.002	0	0	25	0.003	0.001	0	0
30	0.001	0	0	0	30	0.003	0.0005	0	0
35	0.001	0	0	0	40	0.002	0	0	0
70	0.001	0	0	0	70	0.001	0	0	0
	Activity group 3: current partners					Activity group 3: current partners			
Age	0	1	2	3+	Age	0	1	2	3+
14	0	0	0	0	12	0	0	0	0
16	0.005	0.001	0	0	14	0.03	0.005	0	0
18	0.05	0.02	0.002	0	15	0.03	0.01	0.001	0
20	0.1	0.05	0.005	0.001	17	0.04	0.02	0.002	0.001
22	0.1	0.05	0.005	0.001	20	0.06	0.03	0.005	0.002
25	0.02	0.005	0.001	0	25	0.06	0.03	0.003	0.001
30	0.01	0.002	0	0	30	0.04	0.02	0	0
35	0.005	0.001	0	0	40	0.002	0	0	0
70	0.002	0	0	0	70	0.001	0	0	0

Appendix 7

Sensitivity analysis of incremental cost-effectiveness ratios for scenarios of chlamydia screening

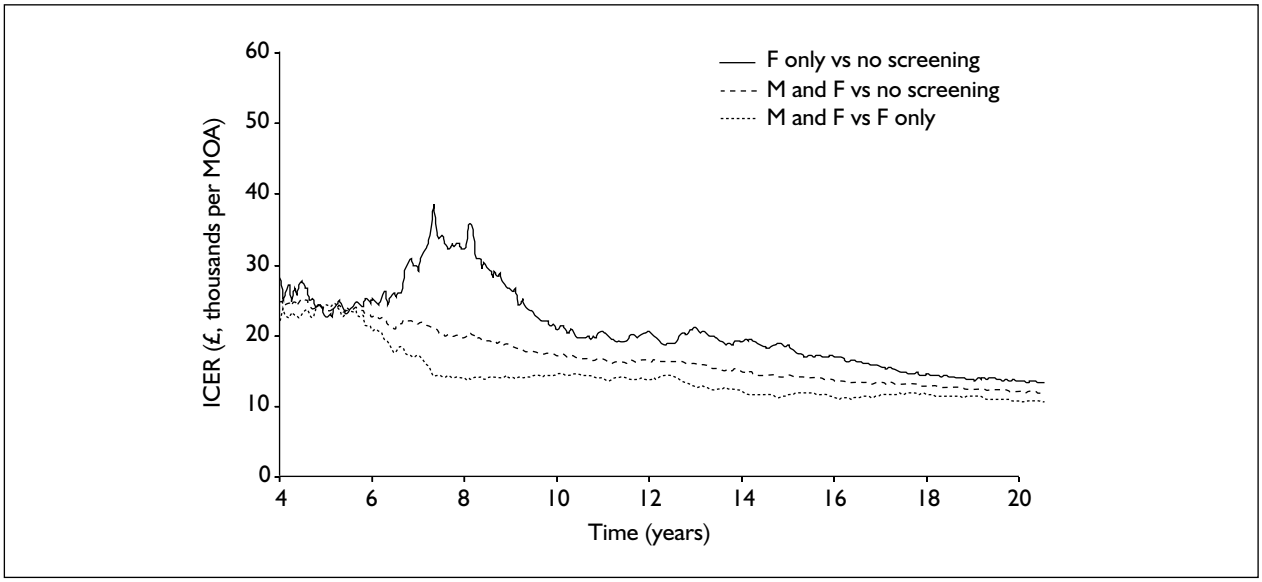

FIGURE 23 *Equal response rates, 39% women and men*

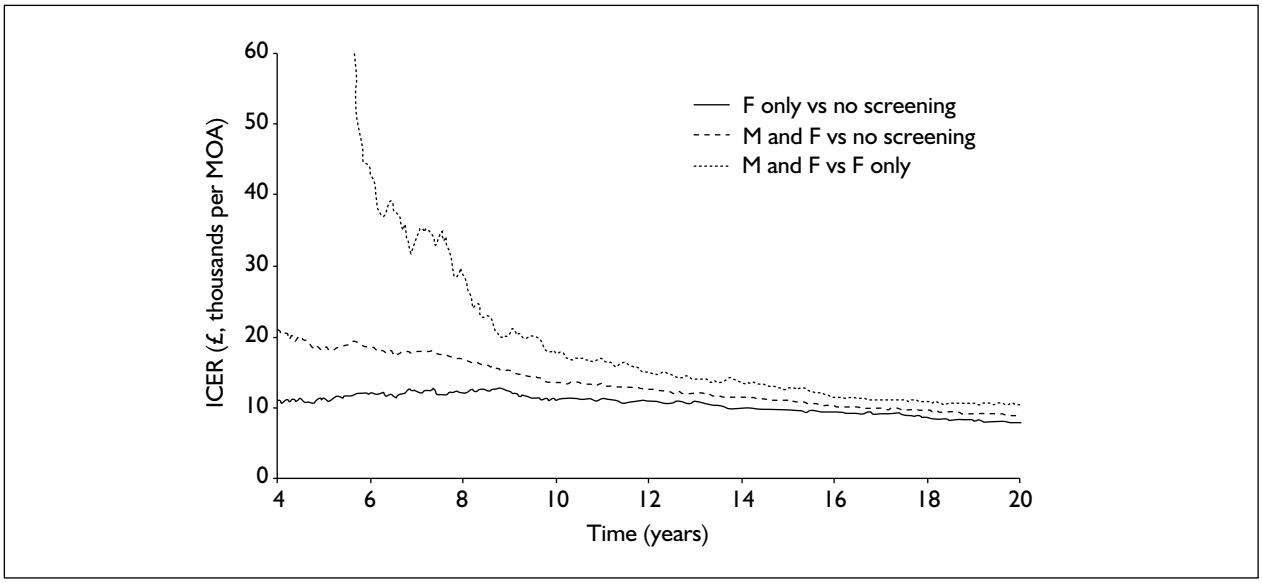

FIGURE 24 *Response rates, 60% women, 40% men*

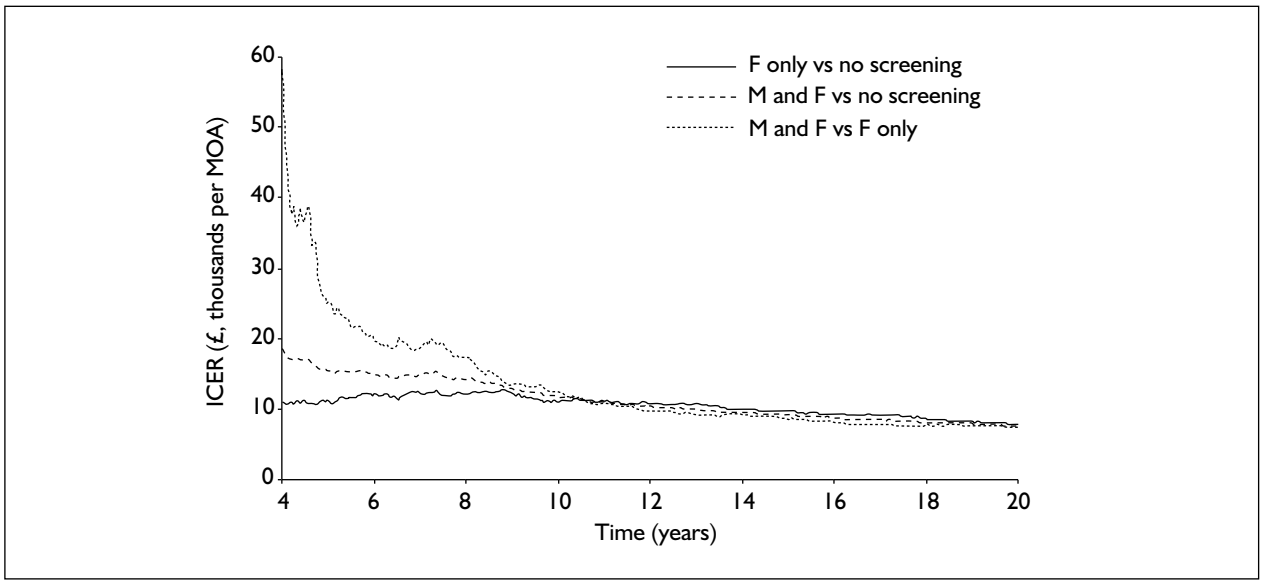

FIGURE 25 *Equal response rates, 60% women and men*

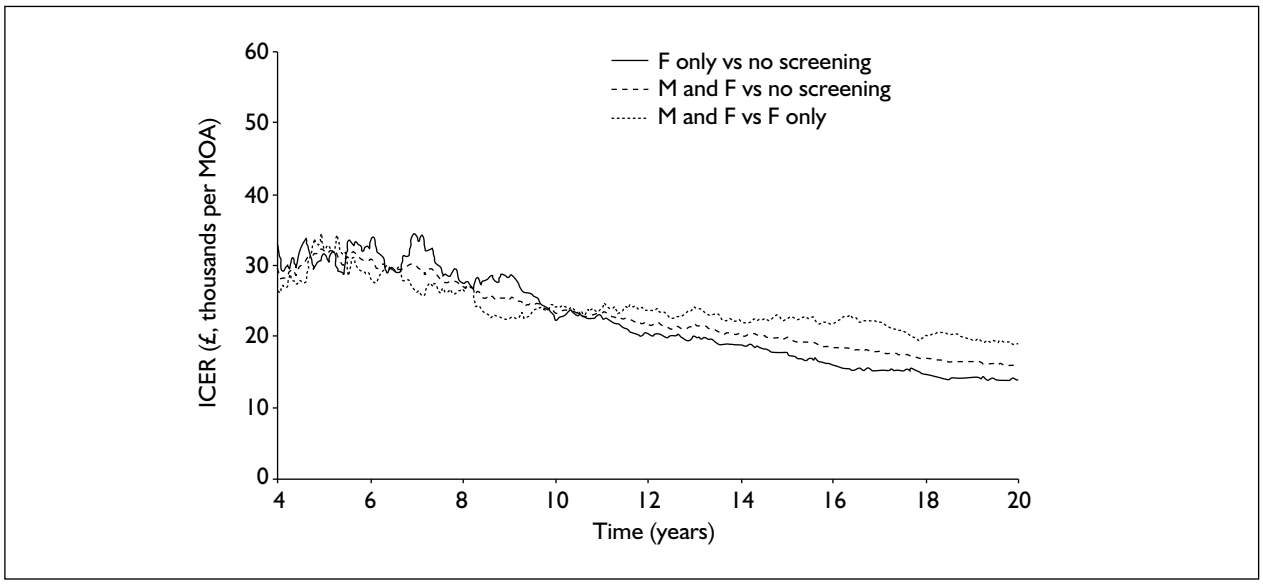

FIGURE 26 *Six-monthly screening*

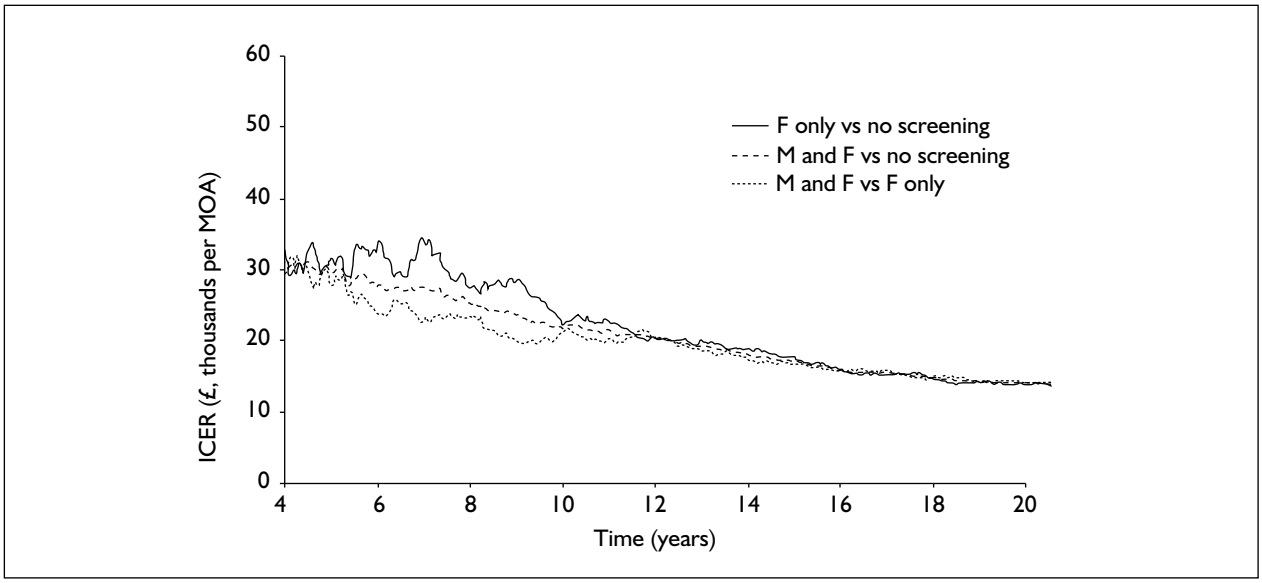

FIGURE 27 *Six-monthly screening, equal response rates 39%*

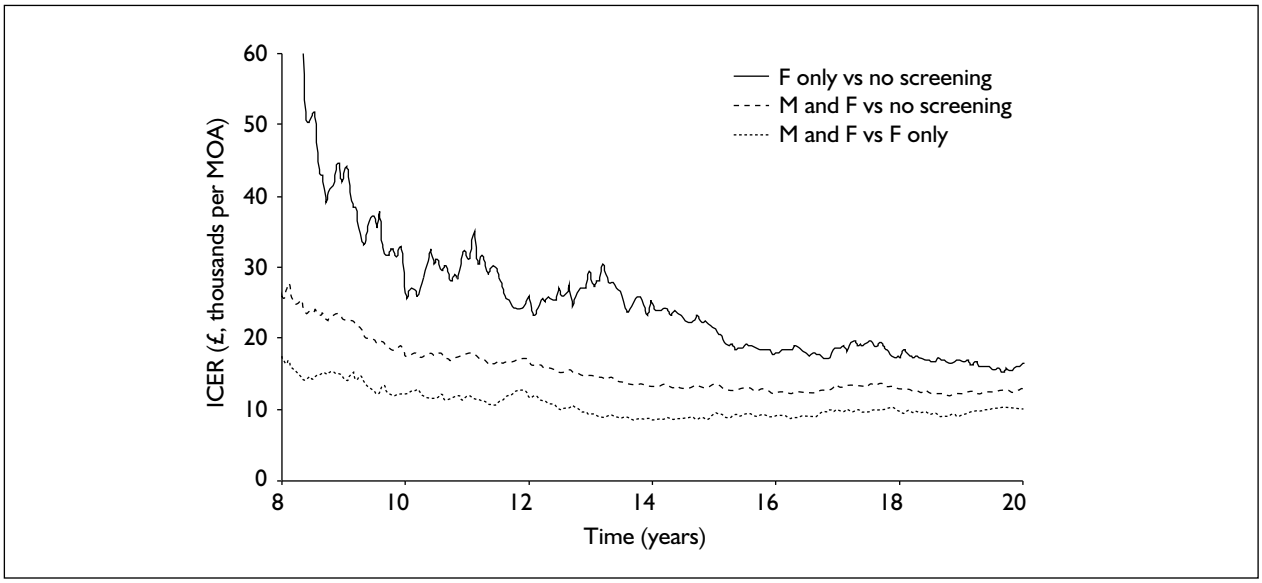

FIGURE 28 *Screening every 2 years*

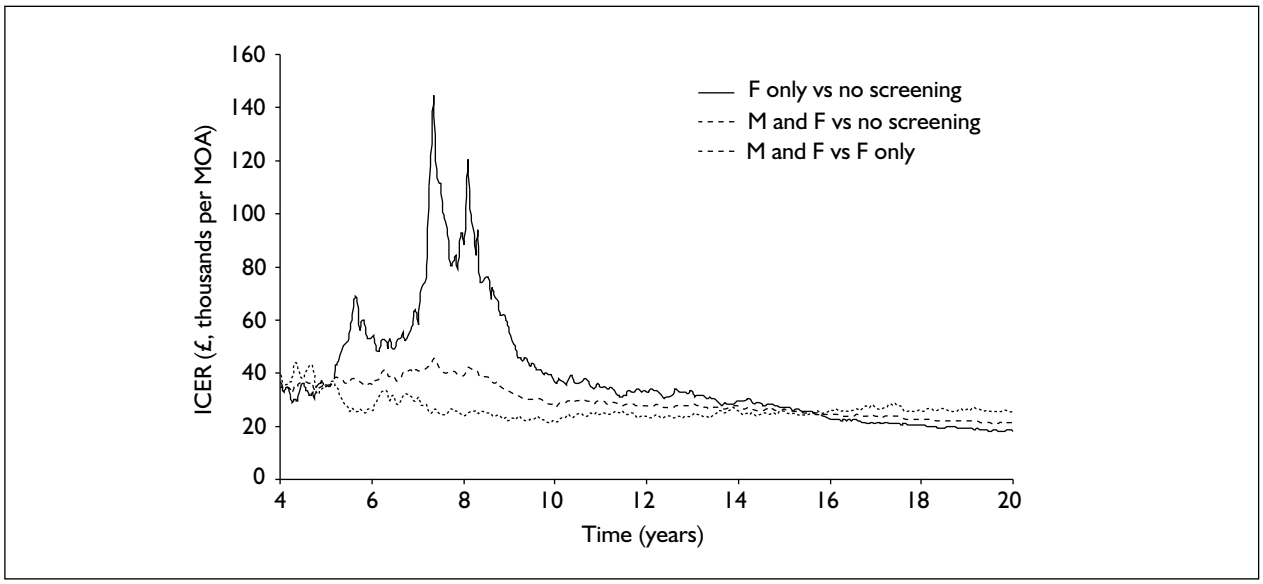

FIGURE 29 *EIA as a diagnostic test for population screening*

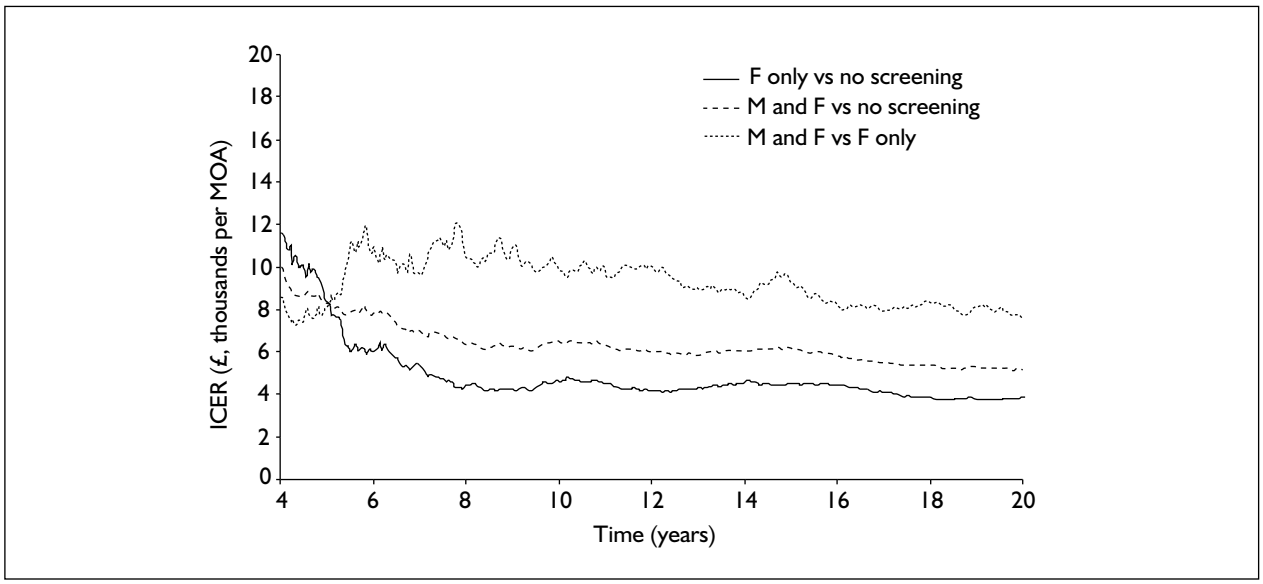

FIGURE 30 *Incidence of PID equivalent to Welte*[198]

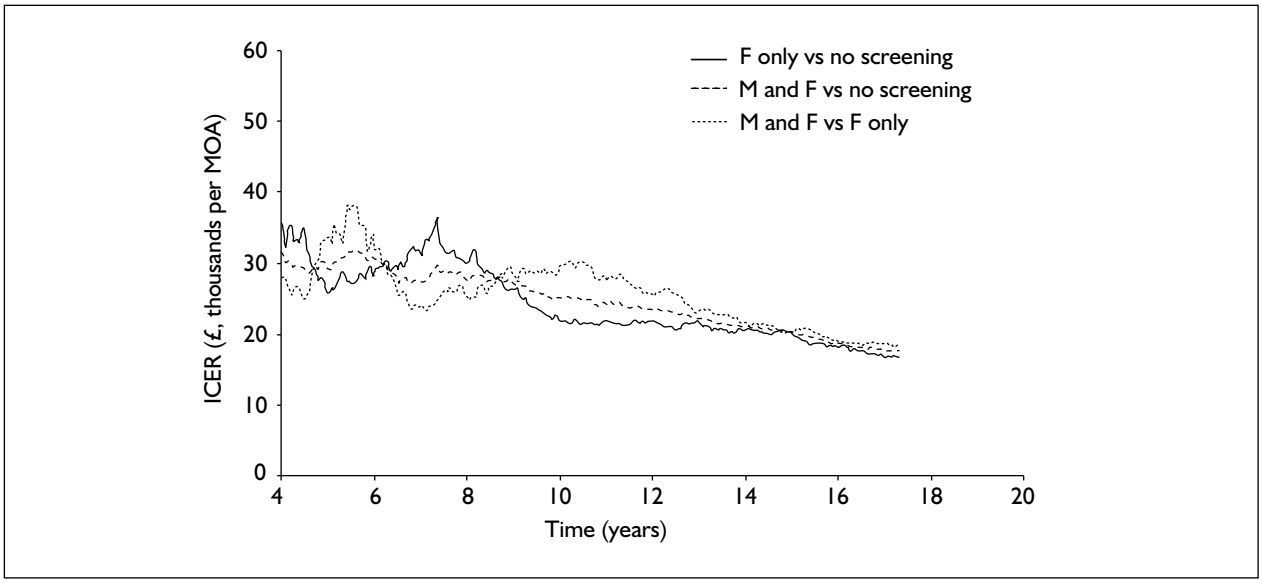

FIGURE 31 *Base case, outcomes discounted at 1.5%*

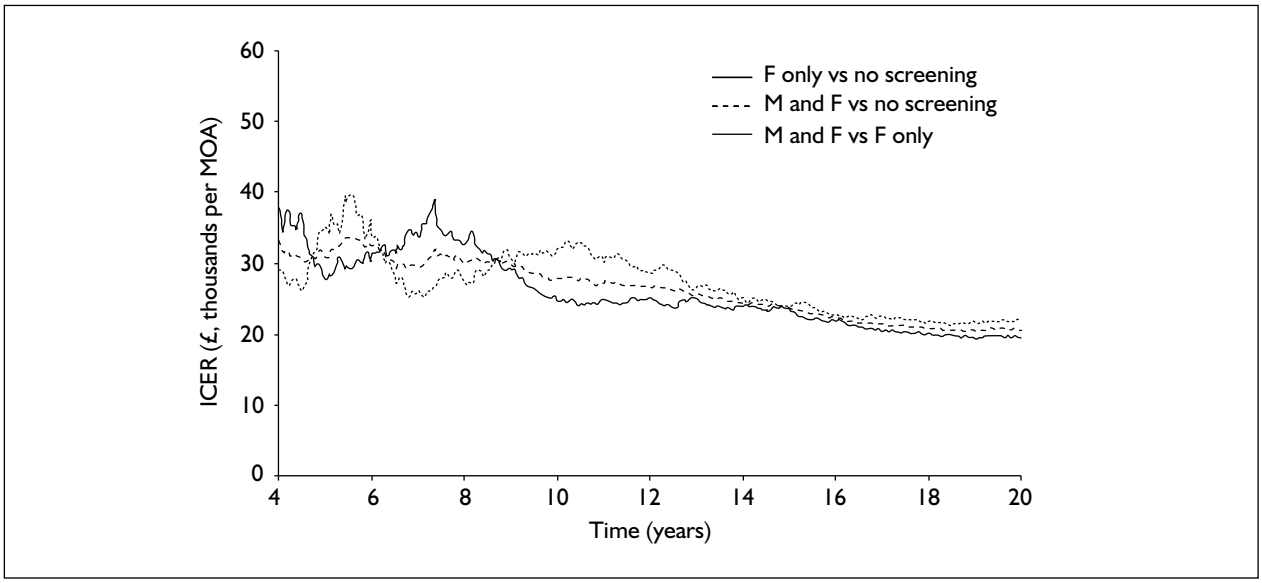

FIGURE 32 *Base case, outcomes discounted at 3.5%*

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We look forward to hearing from you.

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ISSN 1366-5278