WORK IN PROGRESS – NOT FOR CITATION

Economic Evaluation of home based screening for Chlamydia trachomatis: Results from the UK Chlamydia Screening Study (ClaSS)

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Abstract:

Chlamydia trachomatis is the most commonly sexually transmitted infection in developed countries. The asymptomatic nature of the disease means that treatment is often delayed leading to an increased risk of complications and transmission to partners. Different approaches to screening are currently being considered by policy makers internationally. A systematic review of economic evaluations of screening for Chlamydia trachomatis carried out in an earlier part of our study found that an inappropriate modelling approach had been used in the majority of these studies. This risks providing misleading results to policy makers and an inefficient use of resources.

Method:

We constructed a transmission dynamic model simulating the transmission of Chlamydia trachomatis based on primary data collected from the ClaSS study, which included a lab study evaluating alternative test and the first RCT of PN. WE colleted resource use and cost data for all aspect of the study.

Results

We compare the cost effectiveness of population screening with current practice and determine the most cost effective screening test and method of partner notification. Results will be presented in terms of cots per major outcome averted and will be finalised in July 2004.

Discussion:

This is the first economic evaluation of Chlamydia screening to have used a transmission dynamic modelling approach and individual level data from the UK. This provides a more realistic evaluation of cost effectiveness than most existing studies because it incorporates the effects of successful treatment, re-infection and false negative test results on the transmission of chlamydia.

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Introduction:

Chlamydia trachomatis is the most commonly sexually transmitted infection in developed countries and is the most common preventable cause of infertility. The asymptomatic nature of the disease means that treatment is often delayed leading to an increased risk of complications and transmission to partners. Screening for genital chlamydia infection has been assessed or implemented in Sweden, the USA, Denmark and the Netherlands (refs Study design paper). In 1998 the Chief Medical Officer's Expert Advisory Group on *Chlamydia trachomatis* recommended action to reduce the prevalence and morbidity associated with chlamydial infection in the UK (refs).

The Chlamydia Screening Studies (ClaSS) project was commissioned by the Health Technology Assessment Programme of the National Health Service to answer questions posed by the Chief Medical Officer's Expert Advisory Group.

The research questions from the Expert Advisory Group included the evaluation of chlamydia screening in non-genitourinary medicine clinic settings, the best test and specimen to use in men and women, the most effective methods of accessing partners of infected patients and the most cost-effective criteria and appropriate outcomes for targeted screening. In addition, the study aimed to estimate the population prevalence of chlamydia in men and women and to explore possible adverse effects of the screening process.

The broad range of the research brief led to a design of a series of linked studies, based around a core study assessing the feasibility and accessibility of chlamydia screening. Figure 1 shows the links between ClaSS project components.

The core study used a non-selective, active screening approach in the general population (*prevalence study*), with participants randomly selected from general practice lists being asked to send home-collected specimens to a laboratory for chlamydia testing. The population-based approach enabled us to estimate the population prevalence of chlamydia, which would provide a key component for the economic analyses. 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 would also be useful in the economic analysis. Partner notification in the United Kingdom is usually carried out by specialist health advisers based in genitourinary

medicine clinics. The partner notification workload in a national chlamydia screening programme would exceed the capacity of health advisers and genitourinary medicine clinics may be inaccessible or unacceptable to many people. A randomised controlled *partner notification trial* was carried out to evaluate a strategy in primary care, where most new chlamydia cases would be diagnosed.

In chlamydia screening a positive result is diagnostic and tests therefore must be both highly sensitive and specific. Diagnosis has been revolutionised by nucleic acid amplification techniques that allow identification of *C. trachomatis* on non-invasively collected specimens such as urine and vulval swabs. Self-collection at home and mailing of these specimen types makes it possible to screen large numbers of people without the need for genital examination and invasive sampling by a health professional. L*aboratory-based studies* were carried out to examine the performance of two nucleic acid amplification-based tests and a restructured amplified enzyme linked immunoassay on different specimen types.

The psychosocial, emotional and social effects of the screening and partner notification were assessed throughout the various stages of the study using both qualitative and quantitative approaches. The data collected in this subsection of the project were not used directly in the economic evaluation because the data collection instruments used was not validated for use in an economic evaluation.

Finally, we conducted an *economic evaluation* to analyse the relative cost effectiveness of population screening compared to no screening using a dynamic model populated as far as possible with cost and resource use data from ClaSS.

The economic evaluation carried out as part of the ClaSS project itself comprises of a number of subsections which include a systematic review of the economic evaluations on Chlamydia screening; the construction of a transmission dynamic model using a discrete event simulation approach; an economic evaluation comparing alternative tests (expand NAAt's vs EIA); and an economic evaluation of the two alternative strategies for partner notification. The private time and travel costs incurred by patients who participated in the screening programme were also collected. The economic evaluation attempted to adopt a societal perspective as far as possible and

was based on a principal outcome of 'cost per major outcome averted', where major outcome refers to experience of at least one of the following: Pelvic inflammatory disease (PID), ectopic pregnancy and infertility.

In this paper we report the preliminary findings of the main economic evaluation carried out as part of this collaborative and multidisciplinary project. Throughout this paper we use the term chlamydia to mean genital *C. trachomatis* infection.

Methods for the Study

Prevalence study

18,000 individuals between the ages of 16 and 39 were selected at random from the registers of 11 general practices in the Avon and West Midlands areas. The study pack which included a self completion lifestyle questionnaire required for the Case control study was sent out to all identified individuals, preceded by a letter from the general practitioner. Reminder letters followed if the pack was not returned within a designated time frame (6 weeks after he first mailing. Those not responding to the second mailing were telephoned). Some individuals were identified as 'ghost' patients (patients on the GP register but not living at their registered address when the pack was sent out) by telephone call or visit to the address. Finally participants were contacted by letter once test results were available.

Case control study

All participants with a positive chlamydia test result were eligible for the case control study and a sample of participants with a negative result were selected as controls. All seleted participants were invited to the GP surgery to be informed of their result. Individuals were asked to bring with them the self-completed lifestyle questionnaire based on the interview used in the National survey of Sexual Attitudes and Lifestyles (ref: Natsal). At the surgery the practice nurse received the questionnaire and then gave the test result. Positive patients were treated and then invited to participate in the randomized trial of partner notification strategies.

Partner notification trial

All participants who received their positive chlamydia result at the general practice were eligible for the partner notification trial. The patients were treated with Azithromycin 1 gram or an alternative in the case of allergy or pregnancy. Consenting patient were randomized to receive partner notification advice at the General practice

with the nurse or asked to attend the genitourinary clinic for partner notification advice. Patients declining randomization were asked for their preference or advised to attend their local genitourinary clinic.

Laboratory study

All participants were asked to provide an early morning first void urine and women were also asked to collect a non-invasive vulval swab. Two nucleic acid amplification tests, the PCR (the cobas Amplicor CT polymerase chain reaction) test and the SDA (BT prob Tec ET strand displacement amplification) test were tested and compared against the EIA (enzyme linked immunoassay) test.

Full details of the prevalence, case control, partner notification and laboratory studies are reported elsewhere.

Method for the Economic Evaluation

Systematic Review of the Economic Literature

A systematic review of the economic studies on chlamydia screening was carried out. The full methods of the review are reported elsewhere (Roberts et al, HESG July 2003). Reviewed studies were also assessed in terms of quality. The first criteria used to assess the quality of the papers mainly in terms of their quality as economic evaluations but because the majority of economic evaluations of chlamydia screening used a modelling approach the second stage of our quality assessment assessed the studies in terms of the appropriateness and quality of the model used. Data were extracted then converted from their respective currencies to UK £ *Sterling*, using Purchasing Power Parities published by the Organisation for Economic Co-operation and Development. Once converted to UK *Sterling* the cost data were inflated to 2003 prices using the NHS Executive Hospital & Community Health Services Pay and Prices inflation index. Some effectiveness data were extracted for use in our model and sensitivity analyses although these effectiveness data were not subject to quality checks.

Construction of the patient level simulation model

The ClaSS model is a new model based on the framework by Kretzschmar and colleagues (1996), a paper, which was identified by our review of economic studies and was singled out as the modelling method most appropriate for the ClaSS study.

A population is simulated over time with individual characteristics changing as necessary on a daily basis. The initial population consists of a number of virtual individuals with ages drawn from a uniform distribution between lower and upper limits. By default the ages range from 15 to 65 and individuals are equally likely to be male or female. As with previous models only heterosexual partnerships are considered. The initial population does not contain any partnerships but during the running of the model new partnerships form and are dissolved. Individuals are divided into two risk groups, a "core group" of highly promiscuous individuals and the rest. An individuals' propensity to form new partnerships is determined in part by their risk group, existing partner status and the age difference between the prospective partners. Frequency of sexual contact is also a key characteristic of the model. An individuals Chlamydia status can be represented by one of the four following options: no Chlamydia, latent chlamydia, asymptomatic chlamydia or symptomatic chlamydia. Initially a small proportion of the population is infected with Chlamydia and it spreads.

Three screening policies were programmed for comparison with no screening:

- Single pulse screening. Screening is assumed to start on a given date after the start of the running of the model. Once screening has started females within a certain age range (by default 16 to 24 inclusive) are eligible for selection as index cases. Women previously involved with the screening programme are not eligible
- Screen by ages (female only). Women are selected for screening on reaching any given set of ages (by default these run from 16 to 27 inclusive)
- Screen by Ages (all). Men and women are selected for screening on reaching any of a given set of ages.

A partner notification strategy is included in the model. To compare the effects of two alternative partner notification strategies the model is run twice with the data for each strategy used respectively.

The ClaSS model is coded in Borland Delphi, which is based on Pascal. Full details of the ClaSS model are presented elsewhere (refs Barton et al, HESG July 2003)

Data collection

Effectiveness data

Where possible the effectiveness data required for the model was determined from the ClaSS study. The number of positive cases of chlamydia as a proportion of the total response rate was used to provide an estimate of the population prevalence of the disease (for details see prevalence study paper) and used in the calibration of the model. The case control study questionnaire provided the required information sexual behaviour used to determine the 'core' group and the transmission probabilities of the disease. The laboratory study provided estimates of the sensitivity and specificity of each test appropriate for each specimen type (female swab, male or female urine). The partner notification trial provided the data on the relative success of the alternative methods of partner notification. Other clinical data required for use in the model include data on the probability of suffering a major outcome as a result of Chlamydia. The probability estimates for the chances of developing PID, ectopic pregnancy or infertility as a result of Chlamydia were estimated from a parallel study carried out by some of the same authors which examined a cohort of Swedish women for a period of 10 years or more (refs: Swedish cohort study). These estimates for the long term sequelae were compared with those used in the published economic evaluations in the literature.

Cost Data

We collected cost and resource data from all the study components presented in Figure 1. Many of these data were available directly from the project manager (AM). For the prevalence study we collected all the NHS costs which included cost per study pack, postage, cost of reminder, follow up telephone call (if reminder not successful). For the Case Control study, data on cost of treatment and staff time for a session in the surgery, the cost of counselling if positive and time to receive partner notification advice, training counsellors and other staff were collected. In addition to the NHS costs, individuals who turned up at the General practice to obtain their results were asked to complete a patient cost questionnaire in order to collect the private costs of time and travel experiences by participating patients (Refs: Robinson et al, HESG Jan 2003). The relevant Pharmaceutical Companies provided the cost data for all the tests used in the study. A time and motion study was carried out at the laboratories to estimate the resource use and costs in terms of time taken by staff and use of equipment for each individual test on each specimen type and this provided a cost per

test for each sample type (This time and motion study is reported in detail elsewhere refs: Robinson et al forthcoming.)

Results

Prevalence Study:

Mailing of study packs started on Valentine's day 2001 (14th February). Table 1 shows response rates in the first four practices by age group and sex. The overall response rate was 34% with men being least likely and women aged 26-39 years most likely to provide a specimen. Overall in the study there were 219 positive results. Based on the first four practices only, the prevalence of chlamydia was 2.8% (95% confidence interval 2.0 to 4.0%), with similar rates in men and women in both age groups (Figure 2). Prevalence was highest in the younger age group with a sharp drop above 25 years of age. This is not expected change when the prevalence results are finalised. The prevalence results are an important input for the model and required for calibration.

Case Control Study:

The case control study provides information on the sexual behaviour of the individuals and includes data on age balance of partners, number of new partnerships in a year, condom use and duration of partnerships. These data can be used to estimate the likely mixing patterns of individuals determined by a mixing matrix, which helps to define the likely characteristics of the "core" group. We have not yet used these data to compile the mixing matrix and for the purpose of the current paper we use existing data used by a previous dynamic model of Chlamydia screening (Townshend). Those data are based on the sexual behaviour survey published by Natsal (Survey of National Attitudes of Sexual Behaviour and Lifestyle) in 1990 and will not reflect accurately current sexual behaviour patterns. The numbers of new sexual partnerships in the past year is a critical measure of sexual behaviour.

Laboratory Study:

Table 2 presents range of alternative tests carried out for each specimen type and the comparator specimen and test against which each was compared. In Table 3 the

estimated sensitivity and specificity for each test and specimen is presented against its respective comparator. Table 4 presents the average cost per test for each specimen estimated by the time and motion study. Full details of the economic evaluation of the laboratory study are presented elsewhere (refs: Robinson et al, forthcoming). Only the baseline results of the most cost effective test and specimen type will be used in the final analysis. These data have not been finalised and the most cost effective test requires evaluation using the dynamic model.

Partner Notification Trial:

The preliminary results of the partner notification trial revealed that of the 219 Chlamydia positive individuals, 178 were eligible for randomisation and 133 of these individuals consented (44 declined and 1 was not asked). Of the 133 agreeing to randomisation, 67 were referred to the GUM clinic for randomisation and 66 received partner notification advice from the Practice Nurse. Consequently all those randomised to the practice nurse received partner notification advice. The study records reported that only 35 of the 67 randomised to GUM clinic for advice actually turned up. The preliminary results also show that all those index cases that received Partner notification in either arm of the trial did inform their partners. In this trial it was obviously more efficient to receive it from the Nurse at the time of treatment and there seems to be no incentive to turn up and receive advice at the GUM clinic. It is also possible that those randomised to receiving partner advice at the GUM clinic but did not turn up may have informed their partners anyhow. However, for the purpose of sensitivity analysis in our model we have used the results that Partner notification was twice as effective at the Practice compared to the GUM clinic.

Cost data:

The cost data currently used in the model is preliminary and presented in Table 5. The simulated population used in the ClaSS study model is a greater number than the population screened in the ClaSS study and so for most items only the unit cost is used. (For example the cost of a pack is relevant but the number of packs sent out as part of the ClaSS study is not). All the costs presented in Table 5 are based on the primary data collected in the ClaSS study. The cost of the long-term sequelae such as PID and Ectopic Pregnancy are taken from the literature.

Analysis

Some illustrative results from our model are presented in Graphs 1 to 5. These results are based on inputs calibrated approximately to prevalence data from ClaSS study and some (as yet) arbitrary data. The results are a consequence of an average of 10 runs. The warm-up period 5000 days and screening is initiated after the after warm-up period.

For all 5 graphs, the black and white print out conceals the distinction of gender (better in colour). For all five graphs the female prevalence is higher than the male prevalence with the exception of the age group of 30 years plus *or* where the two prevalence rates converge as they do in the age group 20years to 25 years.

In Graph 1 the situation of 'No screening' is presented. The graph rapidly reaches a steady-state equilibrium (at the line) and this equilibrium does not depend on initial state of Chlamydia in any way.

Graph 2 presents the situation if females only were screened. The graph shows a clear drop in prevalence of Chlamydia (after the line) due to screening females.

Graph 3 presents the situation for screening both Males and Females. The drop in the prevalence (after the line) due to screening males and females is greater than the drop incurred when females only are screened. Graphs 4 and 5 represent our preliminary sensitivity analysis as they are directly comparable with Graphs 2 and 3 respectively except they represent the situation where Partner notification advice is only half as effective (as could be the case with the advice at the GUM clinic).

Finally, in Figure 4 we show the preliminary estimated cost saving due to the screening programme. It shows that the initial outlays for screening men and women are greater than for women only. But after a few years the costs of screening are offset by the savings and the cumulative savings as a result of screening are greater and earlier for screening programmes aimed at both men and women.

Sensitivity Analysis:

A comprehensive sensitivity analysis will be carried out. Initially one-way sensitivity analysis will be performed. Multi way sensitivity analysis will follow concentrating on the significant variables.

Discussion

The results from the different Work-Streams of the ClaSS study are still being finalised. As a result preliminary data, and some arbitrary data have been used in the current version of the model to ensure appropriate working of the model and assess whether or not the output is plausible. As the data are finalised the model is likely to require re-structuring and re-calibration.

The systematic review of the economic literature was a crucial element in our study. The key issues identified in the literature review will be explored in depth in our model and the sensitivity analysis.

- *Modelling approach used:* the use of an appropriate transmission dynamic model is crucial in the economic evaluation of Chlamydia screening. Static models will lead to a bias in the results. We aim to prove this.
- *Partner notification:* The dynamic impact of effective partner notification can only be adequately evaluated using a transmission dynamic model. The ClaSS study model will explicitly evaluate the alternative partner notification strategies using a transmission dynamic approach.
- *Women only*: The majority of economic evaluations focussed on women only. This highlights the point that the transmission dynamic nature of the disease tends to be overlooked. In our evaluation as part of the ClaSS study we aim to present the case illustrating the improved effectiveness of the screening programme if both men and women are included.
- *Sexual activity data:* In order to adequately represent the population impact of the screening, information on the population risk groups is required, an obvious risk group is one categorised by age. The case control study data will provide help us define the critical risk groups which is vital information for our model
- *Data on long term sequelae***:** The probability of developing PID as a result of Chlamydia and the subsequent probability of having an ectopic pregnancy or fertility problems as a result of the PID are data which will exert a significant influence on the cost effectiveness of Chlamydia screening. In the ClaSS study

model, in addition to he widely used published probabilities of developing long term sequelae we will use new data for these probability values which have been estimated from a cohort study carried out in Sweden by some ClaSS study colleagues and others (refs: Swedish study).

- *Diagnostic tests:* The issues regarding the correct modelling approach and the use of an appropriate outcome are both applicable to the evaluation of alternative diagnostic tests. For instance a false negative would mean the individual remains infectious and consequences will arise for other potential partners who may become infected and the effect of this can only be adequately represented by a transmission dynamic model as discussed above.

This ClaSS economic evaluation is the first evaluation of Chlamydia screening to have used a transmission dynamic modelling approach and individual level data from the UK. This provides a more realistic evaluation of cost effectiveness than most existing studies because it incorporates the effects of successful treatment, re-infection and false negative test results on the transmission of chlamydia.

KEY Questions for the Discussant/discussion:

This is a huge project both in terms of the clinical aspect and the economic aspects. A number of economic papers are planned in order to report in detail sections such as the systematic review and the lab economic study etc. Obviously there will also be a number of clinical papers. How much can they be simply refereed to in order that this overview of the whole economic evaluation and the report of the main baseline results can be a stand alone paper for a broad spectrum journal?

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Ref Type: Report

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Figure 1

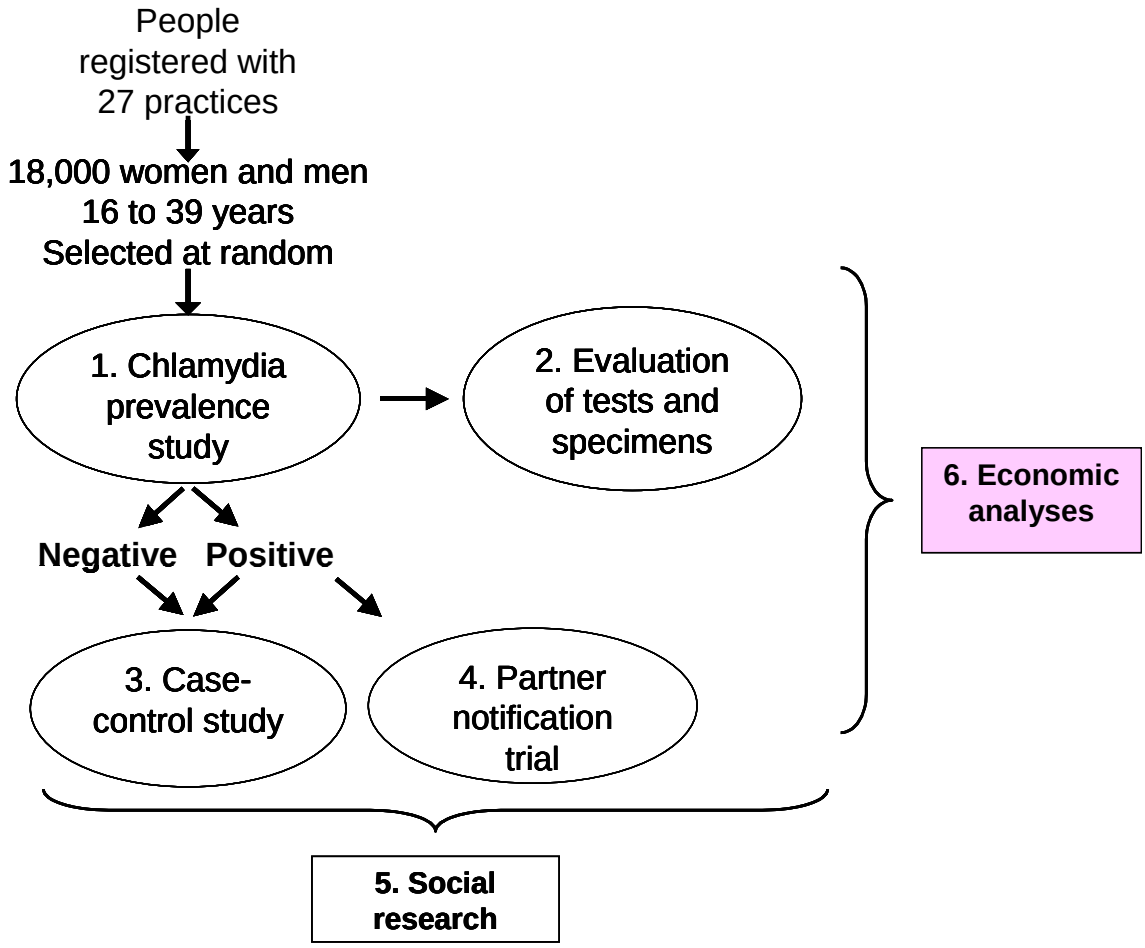


Figure 2

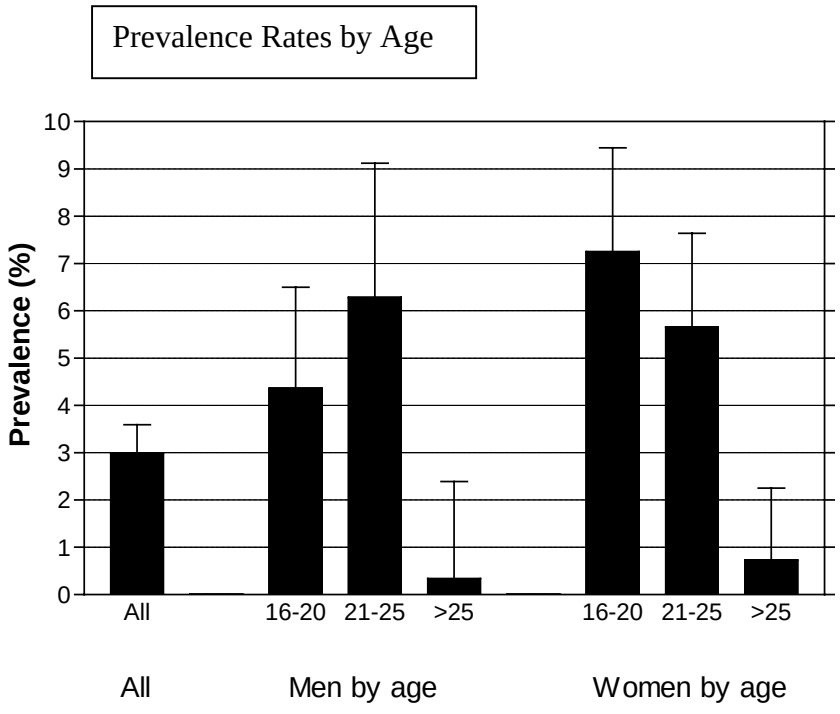


Table 1: Prevalence of Chlamydia in specimens from study participants in first four practices

Characteristic	*No of specimens*	*Positive*	*Prevalence %*	***(95% CI)***
Men				
16-25 yrs	219	11	5.0	(2.8 to 8.9)
26-39 yrs	82	0	0	
All men*	301	11	2.1	(1.2 to 3.8)
Women				
16-25 yrs	309	22	7.2	(4.8 to 10.7)
26-39 yrs	130	1	0.8	(0.1 to 5.2)
All women*	439	23	3.2	(2.2 to 5.1)
Age group				
16-25 yrs	528	33	6.3	(4.5 to 8.7)
26-39 yrs	212	1	0.5	(0.1 to 3.2)
Total	740	34	2.8	(2.0 to 4.0)

Prevalence estimates weighted to take into account 2:1 sampling of 16-25 and 26-39 year olds and clustered nature of data

Table 2: Number of new partnerships in a year

	Number	Number of new partners, mean (SD)	Natsal 2000 comparison (16-24 years)
Men			
Cases	47	2.45 (3.75)	
Controls	60	1.05 (1.40)	
All	107	1.15 (1.66)	1.45 (3.2)
Women			
Cases	112	1.50 (1.84)	
Controls	169	0.67 (1.15)	
All	281	0.74 (1.24)	0.75 (1.7)

Table 3: Duration of partnership

Sex	Duration of most recent sexual relationship in months, mean (SD)					
	16-20 year olds		21-25 year olds		16-25 year olds	
Men	n		n		n	
Cases	16	11.91 (19.48)	17	18.98 (29.47)	33	15.6 (19.7)
Controls	17	12.70 (11.63)	30	21.16 (27.53)	47	18.1 (23.3)
All	33	12.63 (11.67)	47	21.04 (27.14)	80	17.9 (22.9)
Women						
Cases	46	12.87 (16.29)	44	27.2 (27.28)	90	19.9 (22.6)
Controls	54	11.85 (11.16)	94	42.09 (29.63)	148	31.1 (28.5)
All	100	11.96 (11.60)	138	41.24 (29.58)	238	30.2 (28.2)

Table 4: Study comparators for individual specimen testing

Specimen type	**Tests**	**Specimen type**	**Tests**
Male urine	EIA	Male urine	PCR
Female swab	EIA	Female swab	PCR
Female swab	EIA	Female swab	SDA
Female urine	SDA	Female swab	SDA
Female urine	PCR	Female swab	PCR

Table 5: Sensitivity and specificity of the tests by sample type

Specimen type	**Tests**	**Sensitivity**	**Specificity**	**Specimen type**	**Tests**	**Sensitivity**	**Specificity**
Male urine	EIA	73%	99%	Male urine	PCR	99%	99%
Female swab	EIA	65%	99%	Female swab	PCR	97%	99%
Female swab	EIA	65%	99%	Female swab	SDA	97%	99%
Female urine	SDA	93%	99%	Female swab	SDA	97%	99%
Female urine	PCR	90%	100%	Female swab	PCR	97%	100%

Table 6: Costs per specimen

Test	Cost per individual specimen tested	
	Urine	Swab
EIA	£3.10	£3.41
PCR	£7.64	£7.32
SDA	£7.34	£7.53

Figure 3: Cumulative cost saving due to screening

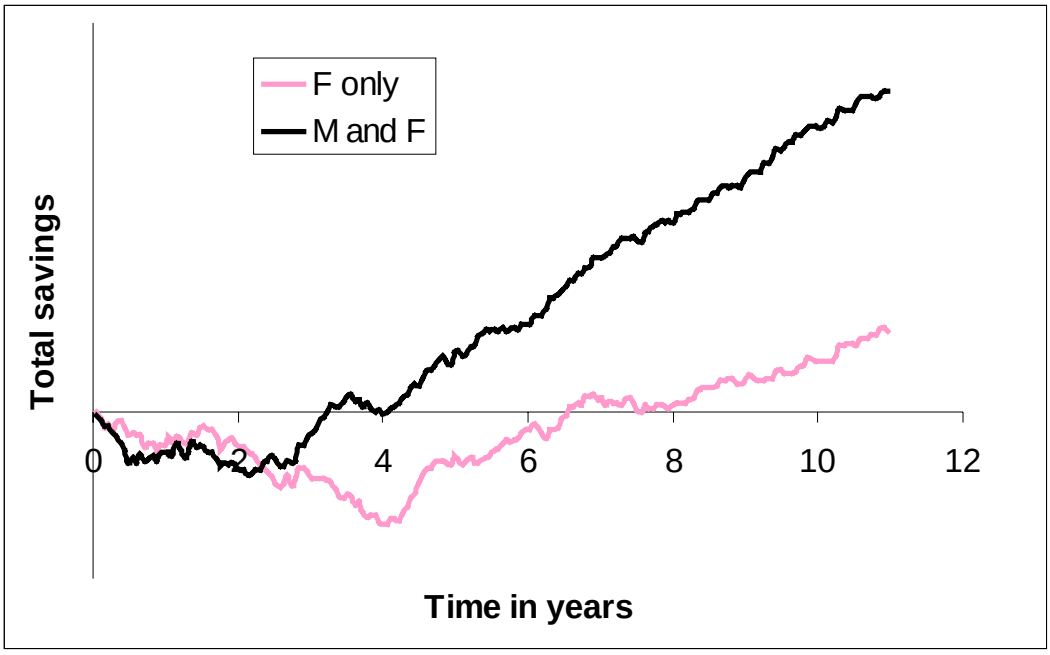


Table 7: Cost Data HESG - Draft main paper)

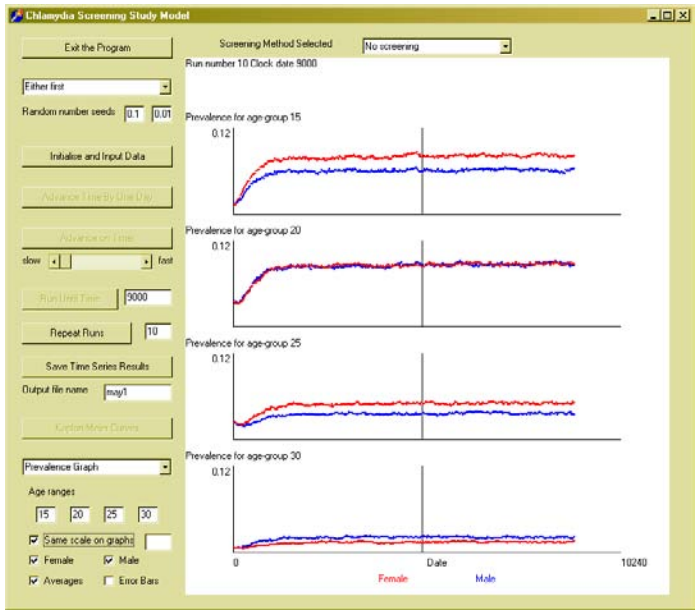
All provisional data: all needs to be re- checked

Cost required	Unit costs for model	Resources used	**Cost estimate**
Prepare pack and send out	**Cost of Pack including postage = *£4.22***	No of Packs = 19772	= £83,437.84
Reminders – first round		*(reminder not included at present)*	
Compliance: returned pack	**Cost of return post = £0.63**	No. of Returned packs = 4740	=£2,986.20
Cost per follow up of non attending positives		Not included at present	
Average cost per test	**Male urine = £7.07** **Female Urine= £5.64** **Female swab =£5.64**	NB. Cost of these tests includes labour Refer to time and motion study (refs: Laboratory paper by Robinson et al)	
Treatment: Cost per drug	**Cost of Azithromycin = £12.00**		
Consultation time: GP/Nurse Result, treat & PN	Cost of session = £0.28 per minute	Average time of session 41.87 mins	**£11.72**
Consultation Time: GP/Nurse Result and treat (excluding PN advice)	Cost of session = £0.28 per minute	Average time of session x cost of session 40.3 mins	**=£11.28**
Consultation time: GUM clinic (PN only)	Cost of session with Health advisor = £0.33 p per minute	Average time of session 12.6 mins[2]	**=£4.16**
Cost of PID	**Severe PID = £3,389** **Mild = ?£709**	Upper genital tract complex major procedures: Severe PID Mild PID (NHS ref cost 2002)	

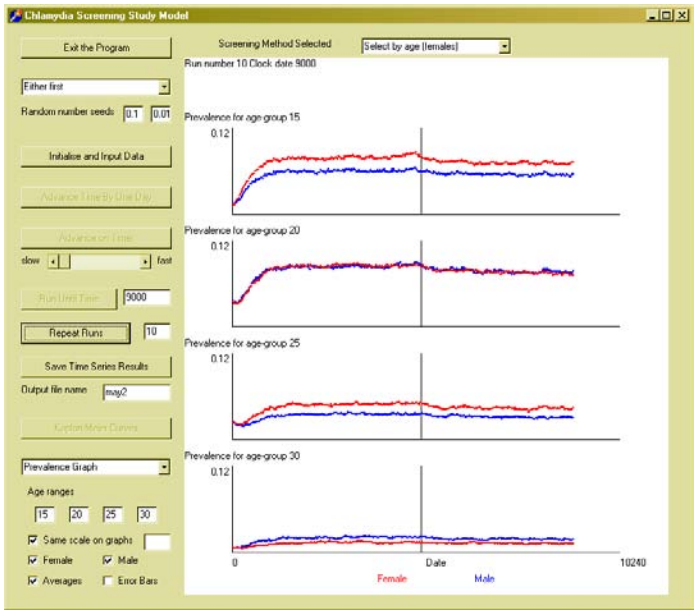
Cost of Infertility	**Cost per case of infertility** **= £2,771**	*Baseline (NICE) = £2,771 (includes costs associated with Health services use, counselling and drugs* *NB. Refer to NICE report for more cost data and ranges and age specific costs of infertility*	
Cost of ectopic	Cost per case of ectopic (NHS ref cost 2002 refs NICE report) **=£769.00**	*Cost per case of ectopic (Source:NHS ref cost 2002 refs NICE report)*	
Male complications	**Epididimytis = £28**	Source : Welte et al	=
Neonatal complications	**Conjunctivitis = £392** **Pneumonia - £1,341**	Conjunctivitis (minor disorders) Pneumonia (major lower respiratory tract complications) (source: NHS ref cost 2002)	

1: this is a arbitary cost of letter
2 : pssru clinic consultation
These costs are preliniary and exclude training costs

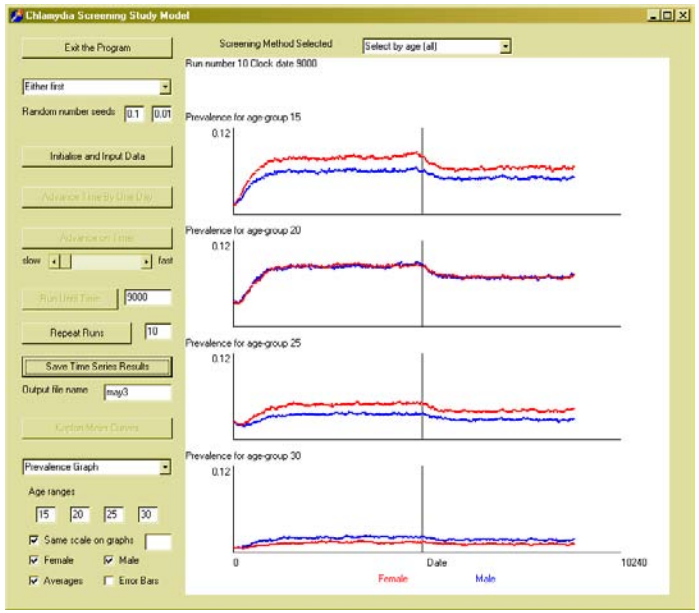
Graph 1



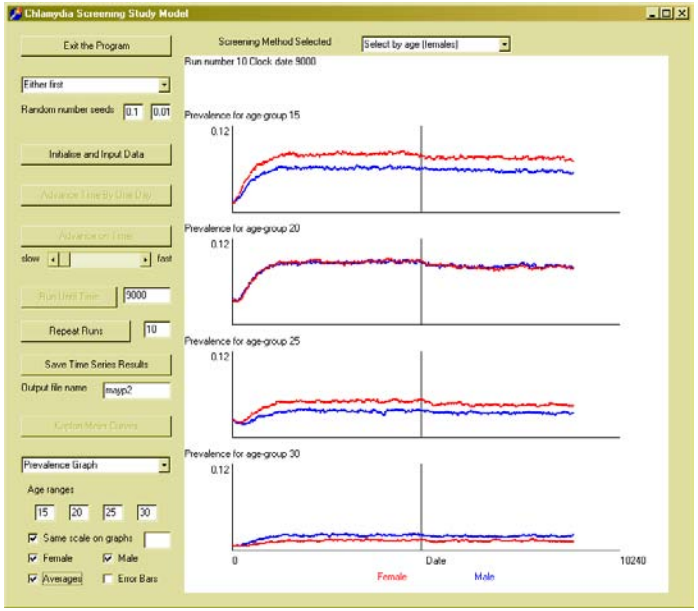
Graph 2



Graph 3



Graph 4



Graph 5