THE COST-EFFECTIVENESS OF SCREENING FOR GENITAL CHLAMYDIAL INFECTION IN THE UK

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ABSTRACT

This PhD thesis explores the cost-effectiveness of *Chlamydia trachomatis* (CT) screening, in the context of the National Chlamydia Screening Programme (NCSP) currently being implemented in England. It uses statistical, mathematical and economic modelling techniques and methods. The epidemiology of CT in the UK is explored by identifying studies through a systematic literature review. The data from them are extracted and analysed using regression techniques and CT prevalence is estimated, indicating a high burden in young women in health care settings. The prevalence estimates are used along with data on past CT treatment and sexual mixing behaviour to parameterise an individual-based dynamic mathematical model of CT transmission. An extensive fitting process identified parameter values that generated realistic epidemiology and sexual behaviour, to optimise public health applicability of the model.

The cost of offering CT screening is estimated based on empirical data from a screening study. The flow of patients through a screening programme is modelled and the associated costs of testing and treatment of positives are estimated. Results from the sensitivity analyses indicate that the proportion of individuals accepting a screening offer has the biggest impact on the results, and highlight how costs could be minimised. In the final analysis, results of the parameterised dynamic model are combined with an economic model of disease progression and costs to estimate the cost-effectiveness of the NCSP strategy and alternatives. Results indicate that the current NCSP strategy (screen women and men aged under 25 years) may be cost-effective when compared to no screening, but that alternate, less inclusive strategies may be more acceptable on cost-effectiveness grounds. Assumptions about the progression from CT to pelvic inflammatory disease have the largest impact on the results.

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DECLARATION

"If you tell the truth you don't have to remember anything." **Mark Twain**

The work presented in this thesis is the result of original research carried out by the author, *Elisabeth Jane Adams*, unless otherwise stated. No part of this thesis has been submitted for a degree elsewhere.

Supervision

The research was carried out under the supervision of Dr Philippe Mayaud at the London School of Hygiene and Tropical Medicine and Dr W John Edmunds at the Health Protection Agency, Colindale, London. Additional supervision was provided by Dr Gwenda Hughes of the Health Protection Agency and Dr Kevin Fenton, of the Centers for Disease Control (formerly of the Health Protection Agency).

Publications

Publications arising from this thesis or from work related to this thesis are given below and reprints of the articles are included in Appendix 1. Where work included in this thesis has been published in joint names, the role of each author is outlined below.

Chapter 3

Adams EJ, Charlett A, Edmunds WJ, & Hughes G. 2004. *Chlamydia trachomatis* in the United Kingdom: a systematic review and analysis of prevalence studies. *Sex Transm Infect*

EJ Adams was the primary author, performed the systematic review and data extraction, and planned and conducted the statistical analysis with A Charlett; WJ Edmunds and G Hughes participated in planning and design of the study and supervised the work.

Chapter 4

Adams EJ, LaMontagne DS, Johnston AR, Pimenta JM, Fenton KA, & Edmunds WJ 2004. Modelling the healthcare costs of an opportunistic chlamydia screening programme. *Sex Transm Infect* **80**, 363-370.

EJ Adams was the primary author, designed and planned the study with WJ Edmunds, created the decision tree model, collected and analysed the costs and related data, conducted interviews with the research nurses, conducted the cost and sensitivity analyses and interpreted results; DS LaMontagne, AR Johnston, WJ Edmunds and JM Pimenta helped develop the decision tree model, and helped with interpretation of the data and results, DS LaMontagne and AR Johnston extracted and analysed the data from the pilot study; JM Pimenta was a primary investigator of the pilot study; KA Fenton contributed to the study development; WJ Edmunds conceived the study idea and supervised the project.

Chapter 5

Turner KME, **Adams EJ,** Gay NJ, Ghani AC, Mercer CH, & Edmunds WJ (2006a). Developing a realistic sexual network model of chlamydia transmission in Britain. *Theor Biol Med Model* **3**, 3.

KME Turner was the primary author and developed the dynamic model; EJ Adams conducted the model parameterisation and analysed results; NJ Gay advised on the analysis; AC Ghani provided the original model and advised on the model development and analysis, CH Mercer provided the data and assisted with data interpretation, WJ Edmunds supervised the work.

Chapter 6

Adams EJ, Turner KME, & Edmunds WJ. The cost-effectiveness of screening for chlamydia in England. *Sex Transm Infect* May 2007; doi:10.1136/sti.2006.024364.

EJ Adams was the primary author, constructed the cost-effectiveness model and analysed the results; KME Turner developed the original model and added PID to it and revised the manuscript; WJ Edmunds assisted with model development, interpretation of results, revised the manuscript and supervised the work.

Adams EJ & Turner KME (2006). Invited commentary. *Sex Transm Infect* **82**, 201.

EJ Adams was the primary author, KME Turner revised the manuscript.

Turner KME, **Adams EJ**, LaMontagne DS, Emmett L, Baster K, & Edmunds WJ (2006b). Modelling the effectiveness of chlamydia screening in England. *Sex Transm Infect* **82**, 496-502.

KME Turner was the primary author, developed the model and helped interpret the results; EJ Adams ran the model, analysed the results and revised the manuscript; DS LaMontagne, L Emmett and K Baster provided comments on the results and revised the manuscript; WJ Edmunds assisted with model development, revised the manuscript and supervised the work.

ACKNOWLEDGMENTS

"Energy and persistence conquer all things." **Benjamin Franklin**
"Never discourage anyone... who continually makes progress, no matter how slow." **Plato**
"Have no fear of perfection - you'll never reach it." **Salvador Dali**

This PhD was a jointly funded collaborative project between the Clinical Research Unit at the London School of Hygiene and Tropical Medicine and the Statistics, Modelling and Bioinformatics Department and the STD & HIV Department at the Health Protection Agency. I am very grateful to both organisations for the resources they have provided me over the years, without their ongoing financial support I would not have been able to complete this project.

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All of my scientific peers and colleagues at the HPA have been truly amazing. They have offered so much wisdom, knowledge and help with all sorts of things, including how to do clever things in Excel, where to go first when you don't know the answer to something (Google or Wikipedia), the basics of economic analysis and statistics, the finer points of C++ programming, where to get the best pint of bitter (London Pride at the Hollybush), and the rules of cricket, croquet, boules & other English sports. The members of the Modelling Unit (past and present) will always be remembered: John, Nigel, Andrew, Ruby, Caroline, Marianne, Marc, David, Angela, Saila, Katy, Alessia, Zia, Emilia, Andy, Ben, Richard, Sharon, Yoon, Georgios, Mark C & Mark J. Thanks also to other HPA colleagues over the past 6 years who have provided help, support and friendship: members of the Statistics Unit (special thanks to André for his tireless explanations of statistics), HIV/STI Department (especially Lynsey and Scott for their discussions on chlamydia), past CDSCers- Tony, Delphine, Jeanne & Amanda, my friends in the IT Department; and countless others.

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Finally, I want to dedicate this thesis to my wonderful friend and colleague Dr KT. You are the reason why the modelling work was ever finished and why this thesis has Chapters 5 & 6. Thanks for all of your help, encouragement, friendship, endless comments on papers and technical skills in all things mathematical, programming and numbers related.

ABBREVIATIONS & ACRONYMS

BNF	British National Formulary
CDSC	Communicable Disease Surveillance Centre
CI	Confidence/credibility interval
CMO	Chief Medical Officer
CT	Chlamydia trachomatis
DoH	Department of Health
EP	Ectopic pregnancy
FPC	Family planning clinic
GP	General Practitioner
GUM	Genitourinary Medicine
HES	Hospital Episode Statistics
HPA	Health Protection Agency
ICD	International Classification of Disease
LCR	Ligase chain reaction
LS	Least squares
ML	Maximum likelihood
MSGP4	Morbidity Survey of General Practice - Fourth Edition
NAAT	Nucleic acid amplification test
Natsal 2000	National Survey of Sexual Attitudes and Lifestyles (2000)
NCSP	National Chlamydia Screening Programme
NGU	Non-gonococcal urethritis
NHS	National Health Service
ONS	Office for National Statistics
OR	Odds ratio
QALY	Quality adjusted life-years
PCR	Polymerase chain reaction
PID	Pelvic inflammatory disease
PN	Partner notification
RCGP	Royal College of General Practitioners
SS	Sum of squares
STD	Sexually transmitted disease
STI	Sexually transmitted infection
TOP	Termination of pregnancy
UK	United Kingdom

CHAPTER 1 - INTRODUCTION

"THE SEXUAL EPIDEMIC"

The Daily Mail, September 30, 2004

Chlamydia trachomatis (CT) is a common curable bacterial infection found throughout the world and is the most commonly diagnosed STI in the UK. Acute infection can be asymptomatic, so men and women can have CT without realising they are infected. Acute and chronic complications may occur in women and men following acute infection and vertical transmission during birth may cause disease in neonates. Diagnosis and treatment of CT is simple, effective and readily available. Data are available to explore the epidemiology of CT, including acute infections and complications in England. Chlamydia screening has been implemented in England based on preliminary estimates of its effectiveness and cost-effectiveness, and it is thought that early detection and treatment of infection may prevent complications, reduce costs and improve health. However, recently some of this early work has been called into question and further work is needed to explore aspects of chlamydial infection and screening and ensure that the evidence base for the National Chlamydia Screening Programme (NCSP) is sound.

The work presented in this thesis is the culmination of six years of research, during which time the context of CT screening in England has changed dramatically. When this project

commenced, a national screening programme did not yet exist. The Department of Health's National Strategy for Sexual Health and HIV identified CT screening as a priority for improving sexual health in England (Department of Health, 2001), and work was being completed to assess the feasibility and acceptability of screening (Pimenta JM, *et al.*, 2003b). In 2002 the NCSP began a phased implementation of screening and results of the first three years of screening have been published (Department of Health, 2004b; National Chlamydia Screening Steering Group., 2005; National Chlamydia Screening Steering Group., 2006). Each chapter of this thesis fits into the context of developing and implementing the NCSP.

Mathematical modelling has been used in other countries to help estimate the cost-effectiveness of screening (Roberts TE, *et al.*, 2006). Differences in infection epidemiology and in the structure of the services delivering health care mean that these models may not be directly applicable in England. Preliminary work on the cost-effectiveness of screening in England and Wales was undertaken for the Chief Medical Officer's (CMO) Expert Advisory Group (Townshend JRP, *et al.*, 2000) before implementing the NCSP. However, new data on screening costs, sexual behaviour, CT prevalence and natural history are now available and can be used to update and improve the previous estimates of cost-effectiveness, thereby making the results directly applicable to the current situation in England.

Aim

The aim of this thesis is to estimate the cost-effectiveness of the NCSP and alternate screening strategies in England. This comprises preliminary work to analyse the prevalence of infection, estimate the costs of screening and parameterise a dynamic mathematical model of sexual behaviour, CT transmission and screening. Mathematical, statistical and economic modelling techniques will be used, and parameters for the model will be estimated from empirical studies, health surveillance data and published literature.

Objectives

1. To estimate the prevalence of CT infection in the UK, based on data from the published and unpublished literature, and to explore which factors have the biggest impact on prevalence estimates;

2. To estimate the costs of an opportunistic CT screening programme and explore which factors are most important to the costs;

3. To estimate the parameter values for an individual-based dynamic model that give the best fit to data on the current sexual behaviour and CT epidemiology;

4. To estimate the costs of infection and complications and the probability of developing complications to assess the cost-effectiveness of the NCSP and alternative screening strategies.

Overview of the thesis

The thesis begins with the background for this project (Chapter 2). It describes the natural history of genital CT infection, the epidemiology of infection and CT complications in England, an overview of CT screening in the UK and abroad, and the health economics of screening for CT infection. A systematic review of CT prevalence in the UK and analyses to estimate the prevalence of CT and explore the factors associated with infection are performed (Chapter 3).

The costs of CT screening are estimated in Chapter 4. Data on the flow of individuals through a screening programme and the costs come directly from an empirical study and other sources. The cost per screening offer, cost per testing episode and the cost per positive episode are estimated, and a detailed sensitivity analysis performed to explore the factors driving the costs of screening.

In Chapter 5, an individual-based dynamic model is parameterised to simulate the current sexual behaviour and CT epidemiology in the UK. The parameters for the model are estimated by fitting to from the second National Survey of Sexual Attitudes and Lifestyles (Natsal 2000) study, results from Chapter 3, and other studies taken from the literature.

Chapter 6 uses the results from previous chapters to estimate the cost-effectiveness of the NCSP and alternate screening strategies. The fully parameterised dynamic model (Chapter 5) is combined with an economic model incorporating the costs of acute infection, complications and screening (Chapter 4) and estimates of the progression to CT complications.

Chapter 7 presents a discussion of the main findings and themes of the thesis, and places the thesis in the context of the current national screening policy and broader international public health context.

CHAPTER 2 - BACKGROUND

"THE SILENT DANGER TO PUBLIC HEALTH"

The Telegraph, October 14, 2005

2.1 Introduction

This chapter will give an overview of the clinical aspects of chlamydial infection and management, evidence for the epidemiology of CT in England, the rationale for screening, and a summary of existing research and policies nationally and internationally.

2.2 Natural history of chlamydial infection

This thesis will focus specifically on *C. trachomatis* (CT) associated with sexually transmitted genital infection, and will henceforth be referred to as chlamydia or CT unless otherwise stated.

2.2.1 Acute chlamydial infection

Chlamydia can enter the genital tract through sexual intercourse, and may enter the epithelial cells lining the internal organs. In women, CT enters through the vagina, and may remain in the lower reproductive tract, causing inflammation in the urethra (urethritis) and cervix (cervicitis) (Stamm WE, 1999). In men, entry is through the urethra and inflammation (urethritis) may occur.

Cell and tissue damage from chlamydial infection may occur including acute inflammation. After initial infection, the immune system produces antibodies to chlamydia, which might offer some protection against future infection, although re-infection is common (Burstein G, *et al.*, 1998). There is evidence that older women often have higher levels of antibody, supporting the immune system's role in reducing re-infection (Schachter J, 1999; Brunham RC, *et al.*, 1994), although sexual behaviour (i.e. fewer partners in older ages) probably plays a large role. While there is evidence for some level of immunity developing after a CT infection and the consequent protection from re-infection, it is difficult to quantify. Therefore, immunity will be ignored in the modelling work for this thesis since there is no evidence on how to quantify the reduction in the transmission probability from acquired immunity, given a prior infection, although immunity will be discussed in future chapters.

2.2.1.1 Symptoms

During the course of infection, symptoms may prompt infected individuals to seek treatment. Symptoms are self-reported indicators of infection (therefore measured subjectively) and are different from clinical signs, which can be objectively and directly observed on clinical examination. The presence or absence of symptoms may vary depending on differences in what is perceived as "normal". Symptoms of acute lower genital tract infection in women include abnormal bleeding, abnormal vaginal discharge, painful urination, post-coital pain or cervical contact bleeding (Horner PJ, *et al.*, 2006). Many other pathogens or non-infectious agents may cause the same symptoms in women. In men, acute CT infection may cause

urethritis, symptoms of which can include discharge or painful urination (Hicks D, 2006). Other infectious pathogens (e.g. gonorrhoea) and non-infectious agents may also cause urethritis. Chlamydia has been identified in about 10-40% of urethritis, although the majority of cases (~60-80%) are of unknown aetiology (Stamm WE, 1999; Horner PJ, *et al.*, 2007; Keane FEA, *et al.*, 2000; Hay PE, *et al.*, 1992; Dixon L, *et al.*, 2002).

Researchers have measured the frequency of self-reported symptoms in CT patients in clinics. A high proportion of men and women diagnosed in GUM clinics report symptoms (roughly 40-90%, slightly higher in men) (Zelin JM, *et al.*, 1995; Butt A, *et al.*, 2001; Hunter JM, *et al.*, 1981; Paul I, *et al.*, 1990; Crowley T, *et al.*, 1992; Harry T, *et al.*, 1994; Oriel J, *et al.*, 1978; Opaneye A, *et al.*, 1994). However, the GUM clinic attenders may be different from those of the general population, probably representing a higher risk group, with a higher probability of co-infection with another STI, who have actively sought care because of symptoms or their perceived risk of an STI. Fewer than 10% of men and women report symptoms when screened opportunistically or routinely (McKay L, *et al.*, 2003; van Den Brule AJ, *et al.*, 2002; Cohen DA, *et al.*, 1999; Miller WC, *et al.*, 2004), suggesting that asymptomatic infection is very common. A study by Korenromp *et al* (2002) found that symptoms may be intermittent and not present throughout the infection, therefore infected individuals may not seek treatment if their symptoms disappear. Therefore, the proportion of infected individuals that actively seek care is expected to be low compared to the proportion of CT patients in GUM clinics reporting symptoms. In this thesis, it will be assumed that a proportion of people will actively seek treatment for infection, which is linked to having symptoms but may also be due to perception of risk or knowledge of partner infection status. The proportion of newly infected individuals who will seek treatment is unknown and will be further explored in Chapter 5.

2.2.1.2 Duration

The duration of CT infection is difficult to measure accurately since it depends on symptoms, treatment seeking behaviour, contact tracing and screening, and may be highly variable. A review by Golden *et al* (2000) concluded that untreated infection may last longer than three weeks in men and two months in women, although it is difficult to determine the median duration of infection. Korenromp *et al* (2002) also reviewed the literature and estimated the mean duration of infection was between 26 and 320 days for males (pooled estimate over the individual studies of 132 days), and between 28 and 1112 days for females (pooled estimate of 499 days). Another study by Morré *et al* (2002) studied the natural course of asymptomatic infection in females, and at the end of one year, 45% of the initially positive women had cleared their infection. Positivity at the end of the year may have been due to persistent infection, re-infection from a partner, or a new infection from a new partner. Based on the inconclusive evidence from these and other studies, it is clear that the duration varies greatly and is difficult to measure. For simplicity it will be assumed later in Chapter 5 when the model is parameterised that the average duration of infection in those seeking treatment is 30 days and in those not seeking treatment is 180 days.

2.2.1.3 Transmission

Quantifying the risk of CT transmission within a partnership is difficult to estimate as it depends on the number of sexual acts, type of sexual acts, infection status, susceptibility of the partner or the use of barrier protection (Garnett G, *et al.*, 1999). Estimates of the transmission probability per partnership from studies of the infection status of partners of positive men and women vary between 22% - 70% for female to male transmission and 46% - 70% for male-female transmission (Lycke E, *et al.*, 1980; Quinn T, *et al.*, 1996; Lin JS, *et al.*, 1998). In other mathematical modelling studies, this has been extrapolated to a transmission probability per contact following vaginal intercourse of 11% (both male-female

and female-male) (Kretzschmar M, *et al.*, 2001; Welte R, *et al.*, 2000). This will be re-examined in Chapter 5 when it will be fitted to data using a transmission dynamic model.

2.2.2 Complications of chlamydial infection

2.2.2.1 Women

CT infection may ascend through the cervix to the upper genital tract and surrounding tissues, causing pelvic inflammatory disease (PID). This may include inflammation of the uterus (endometritis), fallopian tubes (salpingitis), lining of the liver (perihepatitis) and lining of the abdomen (peritonitis) (Rogstad KE, 2006). The clinical presentation of PID can include signs and symptoms of acute chlamydial infection and also lower abdominal pain, fever and abnormal bleeding (Ross JDC, 2006; Stokes T, 1997b). PID is also associated with disturbances in the endogenous vaginal flora (such as found in bacterial vaginosis), *Mycoplasma genitalium*, *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* (Ross JDC, 2006; Simms I, *et al.*, 2000b). Results from two studies by Simms *et al* (a literature review and a study of women in three sites in England) reported that CT could be detected in 14% to 65% of laparoscopically proven PID (an invasive procedure to view the pelvic regions) and 30% (42/140) of clinically diagnosed PID (Simms I, *et al.*, 2000b; Simms I, *et al.*, 2006b). Clinical diagnosis of PID diagnosis can be problematic due to low awareness of signs of PID especially among general practitioners (GP). Clinical diagnosis depends on a set of signs of varied aetiology and no gold standard test with high sensitivity and specificity exists. Therefore, women may remain mis- or undiagnosed (Kahn J, *et al.*, 1991). Additionally, PID may be asymptomatic, although as such it would not normally be clinically diagnosed, although it could be laparoscopically diagnosed (Ross JDC, 2006). There is evidence that asymptomatic or mild PID does not have an increased risk of further complications (Weström L, *et al.*, 1992). However, asymptomatic or subclinical PID is often used to retroactively explain ectopic pregnancy (EP) or tubal factor infertility (TFI), although its links with past CT and these future severe complications are not well established. As

such, only symptomatic PID will be included as a complication considered in further analyses and asymptomatic PID will be ignored (Chapter 6).

The proportion of women with acute untreated CT infection who will develop PID is not well understood, nor is the impact of early treatment. It will be assumed in this thesis, that women who seek treatment for their infection will not develop further complications such as PID, EP or TFI, although they may transmit infection to neonates. A review by Roberts *et al* (2006) found that cost-effectiveness studies cite 25-30% progression to PID following CT infection, which may include symptomatic or asymptomatic PID. This estimate is based on a study by Stamm *et al* (1984) of women identified through an STD clinic with dual gonococcal and chlamydial infections, correctly treated for only gonorrhoea. Two to seven weeks after initial treatment, 30% (6 of 20) of women developed PID. Although commonly cited, this study had many flaws: the sample size was very small, it may not have been generalisable since it only included a high risk group of women (STD clinic attenders), and the main outcomes were potentially confounded by concurrent gonococcal infection, which may have indicated a higher degree of previous pathological damage.

Newer studies investigating the progression from CT infection to PID have found very different results from Stamm *et al.* Morré *et al* (2002) tested 744 women attending for a health check prior to new employment (not a high risk group), and identified women asymptomatically infected with chlamydia using PCR on a urine sample. These women were left untreated and followed up for a year, and retested after one, six and 12 months to explore the clearance of infection and development of symptoms or complications. At the end of one year, none of the 30 positive women developed any clinical symptoms of either acute infection, clinical PID or other complications. While withholding treatment from infected women may be ethically questionable, none of the women developed adverse complications from acute asymptomatic infection. Van Valkengoed *et al* (2004) estimated the probability of complications for a current CT infection based on Dutch GP registration data. They concluded that the risk of PID from a current CT infection is likely to be less than 1%. There

is also evidence for chlamydia's role in PID development from a screening study. A randomised controlled screening programme in Washington, USA found that women at high-risk who were selectively screened for chlamydia were less likely to develop PID and had a relative risk of developing PID of 0.44 (95% CI 0.2-.0.9) compared to those not screened (Scholes D, *et al.*, 1996).

Inflammation from PID can cause scarring, separation or detachment of the fallopian tube. This may lead to pregnancy complications such as EP or TFI when a woman decides to conceive. Ectopic pregnancy occurs when a fertilised egg implants in the fallopian tube or contiguous structure, resulting from a blocked or damaged fallopian tube (Abou-Zahr C, *et al.*, 1998). The continued growth of the fertilised egg can cause the tubes to rupture around eight weeks of gestation, putting the woman at risk of potentially fatal internal bleeding (Rice P, *et al.*, 1991; Abou-Zahr C, *et al.*, 1998). While 69% of ectopic pregnancies may resolve spontaneously (Scientific Advisory Committee of the Royal College of Obstetricians and Gynaecologists, 2002), the remainder will require medical or surgical termination.

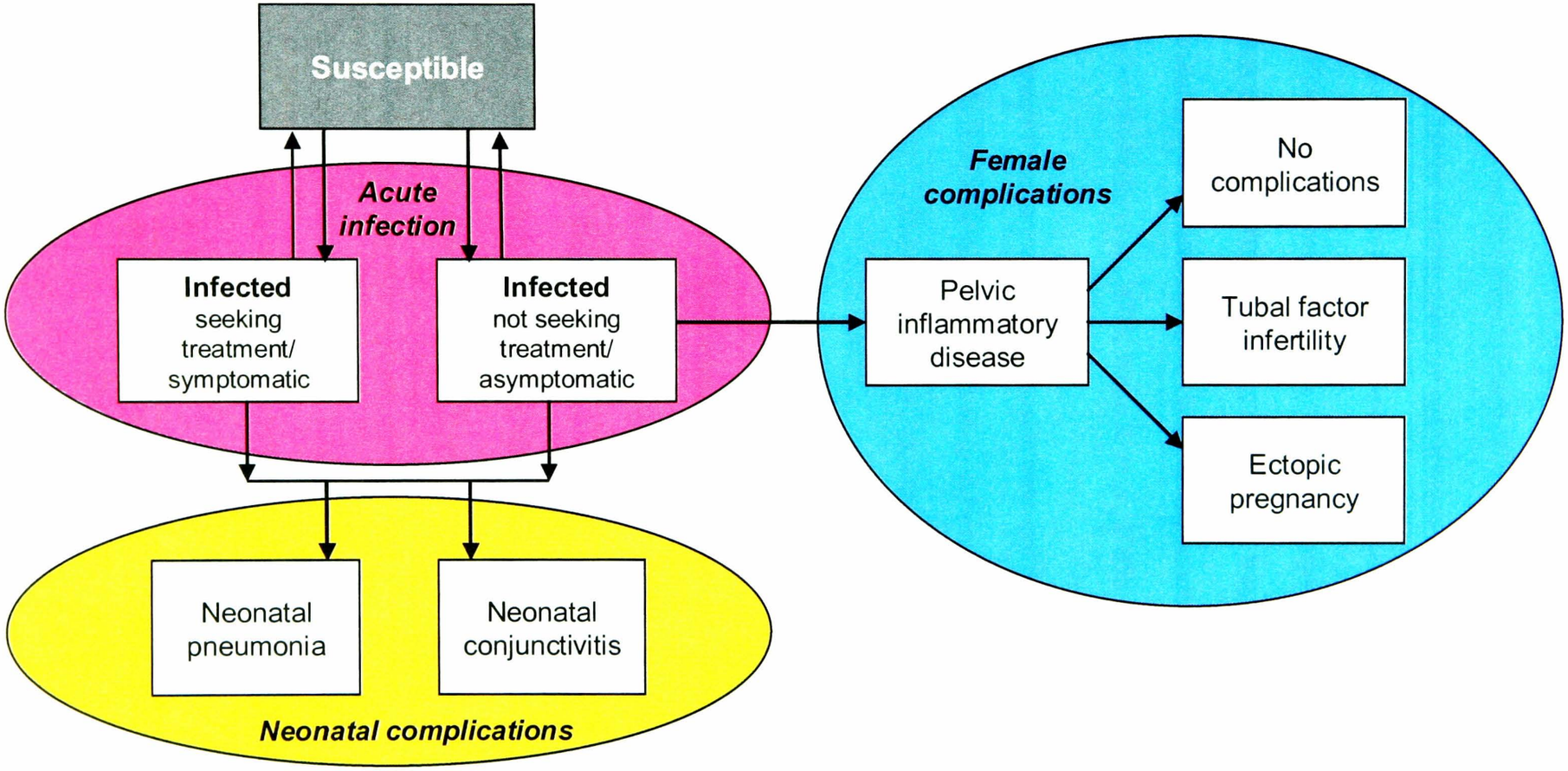
Tubal damage might also make conception difficult, resulting in TFI or sub-fertility (difficulty in conceiving). It has been estimated that roughly 20-30% of women who suffer from infertility and who are seen in clinics have partially or fully blocked fallopian tubes (Cahill DJ, *et al.*, 2002). This may result from scarring due to prior CT infection, associated with high levels of chlamydial antibody suggestive of prior infection (Human Fertilisation and Embryology Authority, 2000). The flow of possible complications following CT infection is given in Figure 2.1.

Van Valkengoed (2004) estimated the proportion of current CT infections that result in EP or TFI to be 0.07% and 0.02% respectively, based on epidemiological data from Holland. Most other studies however, have estimated only the probability of progression from PID (not acute CT infection) to EP and TFI. The most robust data on outcomes of PID is from Weström and colleagues (Weström L, *et al.*, 1981; Weström L, *et al.*, 1992; Weström L,

1994). A 24-year longitudinal study in Sweden followed women with a diagnosis of laparoscopically proven PID. They reported the probability of EP and confirmed TFI for the first pregnancy following PID among those women attempting pregnancy to be 7.6% (EP) and 10.8% (TFI), respectively (Weström L, *et al.*, 1992). Another study using hospital discharge data from selected hospitals in England estimated that women with a diagnosis of PID were 10 times more likely to be subsequently admitted for EP than women without a PID diagnosis (Buchan H, *et al.*, 1993). There is also evidence that the risk of developing EP and TFI increases with each subsequent infection with CT (Weström L, *et al.*, 1992).

There are other complications associated with CT infection including Reiter's syndrome (a combination of urethritis, conjunctivitis, arthritis and mucocutaneous lesions) and chronic pelvic pain (Rogstad KE, 2006). However, as the evidence for progression to these conditions is weak they will not be addressed further in this thesis or included in the cost-effectiveness analysis (Chapter 6).

Figure 2.1 – Progression in women from acute chlamydial infection to complications.



2.2.2.2 Men

Chlamydia may cause epididymitis in men, which is unilateral testicular pain, swelling, tenderness and fever resulting from inflammation in the spermatic cord (Hicks D, 2006; Walker PP, *et al.*, 2001). This can be a serious condition that may require surgical operation. Chlamydia is thought to be the leading cause of epididymitis in men aged under 35 years (Berger RE, 1999; Eley A, *et al.*, 1992) and accounts for between 30% to 80% of cases in heterosexually active males, and is rarely associated with chlamydial infection in males aged over 35 years (Walker PP, *et al.*, 2001). The risk of epididymitis following acute infection is thought to be low, and it will be assumed that 1% progress, similar to assumptions from other modelling studies (Welte R, *et al.*, 2000; Welte R, *et al.*, 2005).

Prostatitis (inflammation of the prostate gland, causing pain and swelling), proctitis (rectal inflammation), and male infertility have been linked to chlamydial infection, although the role of CT is unclear (Hicks D, 2006), and will not be considered in this thesis.

2.2.2.3 Neonates

Genital CT infection in women can be transmitted vertically to neonates during birth. The most common site of neonatal infection is the conjunctiva, and results in inflammation of the eyes (Hammerschlag MR, 1999). Symptoms of conjunctivitis occur within the first week or two after birth (Rogstad KE, 2006) and infection is easily treated with antibiotic eye drops (CDC guidelines). An infant who is infected with CT infection may also develop pneumonia (Hammerschlag MR, 1999) which develops a few weeks after birth (Rogstad KE, 2006). There is good evidence from a systematic review by Rosenman *et al* (2003) that if a pregnant woman with CT infection exposes her infant to infection during birth, the probability of transmission resulting in neonatal pneumonia is 7.0% and neonatal conjunctivitis is 14.8%, and that pneumonia may require hospitalisation in a fifth of cases.

2.2.3 Risk factors for infection and disease

There are three categories of risk factors for infection and complications: 1) demographic, 2) behavioural, and 3) biological. Demographic risk factors include young age, single marital status and ethnic group (Radcliffe KW, *et al.*, 2001). Behavioural risk factors include recent partner change, use of oral contraceptives or no condom use (Fenton KA, *et al.*, 2001b; LaMontagne DS, *et al.*, 2006). Biological risk factors such as immunity to infection or cervical ectopy (in which the cells that CT attacks are exposed) (Lee V, *et al.*, 2006) may also contribute to the chance of acquiring infection. Other groups might be at particular risk of developing an upper genital tract infection (such as females undergoing invasive procedures such as infertility treatment, termination of pregnancy or intra-uterine device insertion). The risk factors are quite broad, and infection is in fact widespread. These will be examined in more detail in Chapter 3 when CT prevalence is analysed.

2.2.4 Diagnostic tests

There have been rapid advances in diagnostic tests for CT infection in recent years. The current UK guidelines recommend that nucleic acid amplification tests (NAAT) are used for diagnosis and screening (Carder C, *et al.*, 2006; National Chlamydia Screening Programme, 2006). NAATs such as ligase chain reaction (LCR) have a high specificity (few false positives) and high sensitivity (few false negatives), meaning that low-level infections common with CT can be detected (Watson EJ, *et al.*, 2002). NAATs can be done on non-invasive samples (urine or vulvo-vaginal swab) and can be self-collected outside of a clinic setting. Their use as a screening test has been reported as highly acceptable (that is, worthy of acceptance), to a population surveyed about their use; over 90% of respondents from two studies agreed that CT screening should be offered and would be willing to participate (Department of Health, 2002a; McMillan LE, *et al.*, 2006). NAATs are also cheap, fast and can be performed at high volumes. While in theory the tests are acceptable, in practice the actual range of test offer acceptance (that is, the act of actually taking the test) in screening

studies is much wider (30-85%) (Department of Health, 2002a; Fenton KA, *et al.*, 2001a; Pimenta JM, *et al.*, 2003b).

In the past, other tests have been used for CT diagnosis. These primarily included antigen tests (including enzyme immunoassay (EIA), direct fluorescent antibody (DFA), and others) and culture tests. These tests are mentioned here because in Chapter 3 they are included in a regression analysis of possible factors influencing CT prevalence. These tests are no longer recommended for routine diagnosis and screening and are not considered further here. For a thorough review of all tests, see Van der Pol (2006) and www.chlamydiae.com.

Since no test is 100% accurate, there will be false positives and false negatives in the population tested. A positive test may have a negative impact on psychosocial functioning (Duncan B, *et al.*, 2001), and false positives have no associated benefits of treatment for infection. Given a positive test, the positive predictive value (PPV) estimates the probability that an individual actually has infection. The negative predictive value (NPV) is the probability that an individual does not have infection given a negative test. Both the PPV and NPV are linked to the prevalence in a population and the sensitivity and specificity of the screening test (Table 2.1). In a population with a chlamydia prevalence ranging from 1-15%, and a test with sensitivity and specificity ranging from 85-95% and 95-99% respectively (such as LCR), the PPV and NPV are given in Figure 2.2, see also Zenilman *et al* (2003). The specificity and the prevalence have a large impact on the PPV and when the prevalence is low the PPV drops rapidly. Implications are that if a test (assuming an LCR with 90% sensitivity and 99% specificity) are used in a screening programme, when the CT prevalence is 10%, then 91% of individuals with a positive test result would actually have infection. However if the prevalence drops to 2% because of screening, then the PPV would fall to 65%, meaning that 35% would be falsely identified as being positive. Recognising a potentially high rate of false positives in low prevalence populations is important for those providing counselling and partner notification, especially if opportunistic screening does reduce the population prevalence of CT. The NPV changes little for the sensitivity,

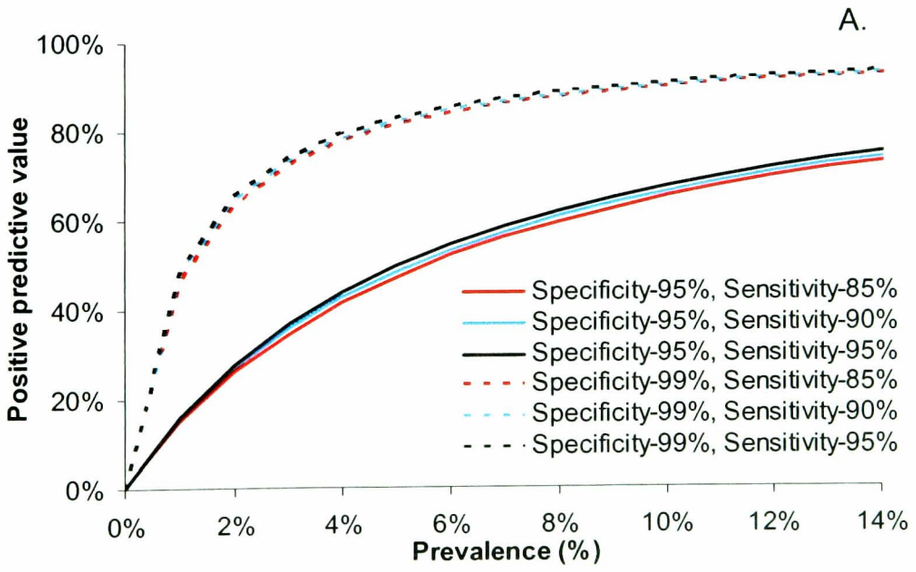
specificity and prevalence in the range given above (Figure 2.2B), although it does drop slightly as the prevalence increases. This means that a small proportion (less than 2 percent) of those told they have a negative test are actually positive, given a prevalence of 10%.

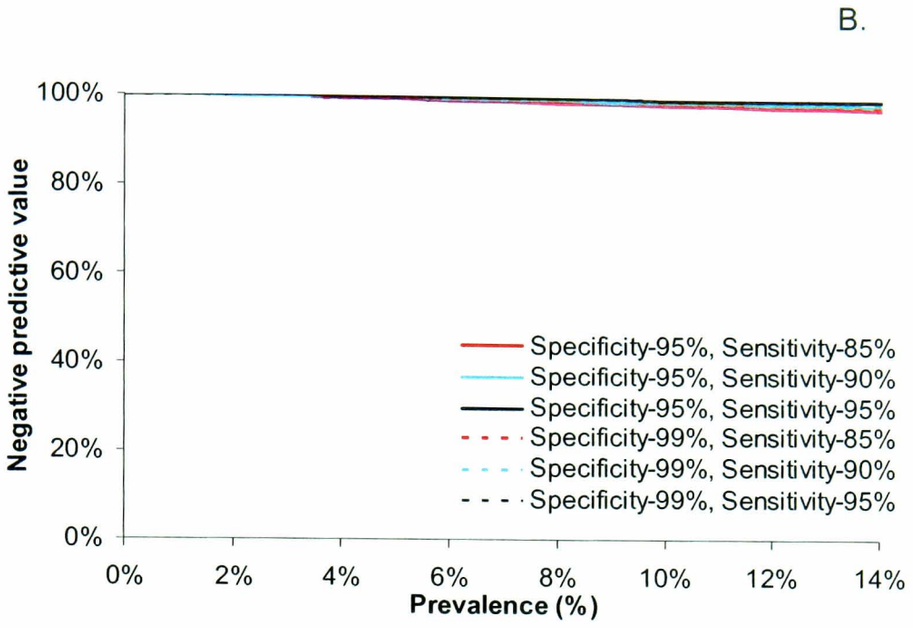
Table 2.1 – Calculations of the positive predictive value, negative predictive value, and test sensitivity and specificity.

		Disease status		**Total**
		Present	Absent	
Results of screening test	Positive	a	b	**a+b**
	Negative	c	d	**c+d**
	Total	**a+c**	**b+d**	

Sensitivity = a/(a+c)
Specificity = d/(b+d)
Positive predictive value = a/(a+b)
Negative predictive value = d/(c+d)

Figure 2.2 – Range of positive predictive values (A) and negative predictive values (B) for a given prevalence and test sensitivity and specificity.





2.2.5 Clinical management

There are two parts to clinical management, both of which are essential to curing infection and preventing re-infection and onward transmission: treatment and partner notification. Treatment of CT with antibiotics is simple and effective (over 95% cure rate for both men and women (Clarke J, 2006; Horner PJ, *et al.*, 2006)). Recommended drug choices include a single dose of Azithromycin or a seven-day course of Doxycycline in most cases, although alternate therapies exist for pregnant women or when contraindicated (Horner PJ, *et al.*, 2006). Their usage and costs of drug treatment are explored in Chapter 4.

Partner notification (PN) refers to the notification of an index case's recent sexual partners of their potential infection, and the recommendation to attend a clinic for epidemiological (i.e. presumptive) treatment of CT and/or testing (Horner PJ, *et al.*, 2006). PN identifies asymptomatic cases, can prevent re-infection by an untreated partner, and during PN positive patients and their partners can be counselled on the risks of re-infection and the use of condoms. PN can be done in GUM clinics, but other clinicians can be trained to initiate it, and either the positive individual or a health care worker can contact partners, although one

study found that 98% of women chose to notify their partners themselves (Pimenta JM, *et al.*, 2003a). The guidelines for the "look back" period in which to identify and treat sexual partners for infection range between four weeks for symptomatic infection to six months for asymptomatic infection (Horner PJ, *et al.*, 2006). The Chlamydia Pilot Study chose three months for the look back period (Pimenta JM, *et al.*, 2003a), and this assumption will be used in Chapter 4 when estimating the costs of screening. The target for PN for the NCSP is:

> "*at least 0.4 contacts per case within London or a large city or 0.6 contacts per case elsewhere will be verified as having attended a health care site for epidemiological treatment for chlamydia.*" Page 51. (National Chlamydia Screening Programme, 2006)

In this thesis, PN will refer to partners notified and effectively treated, unless otherwise stated.

2.3 Epidemiology of chlamydial infection and its complications in England

This section will give an overview of the data sources available in the routine surveillance of CT (including NCSP results) and its complications in England. The published data are summarised here, and further data will be presented in other sections of this thesis (Chapter 3 – prevalence, Chapter 6 – complications).

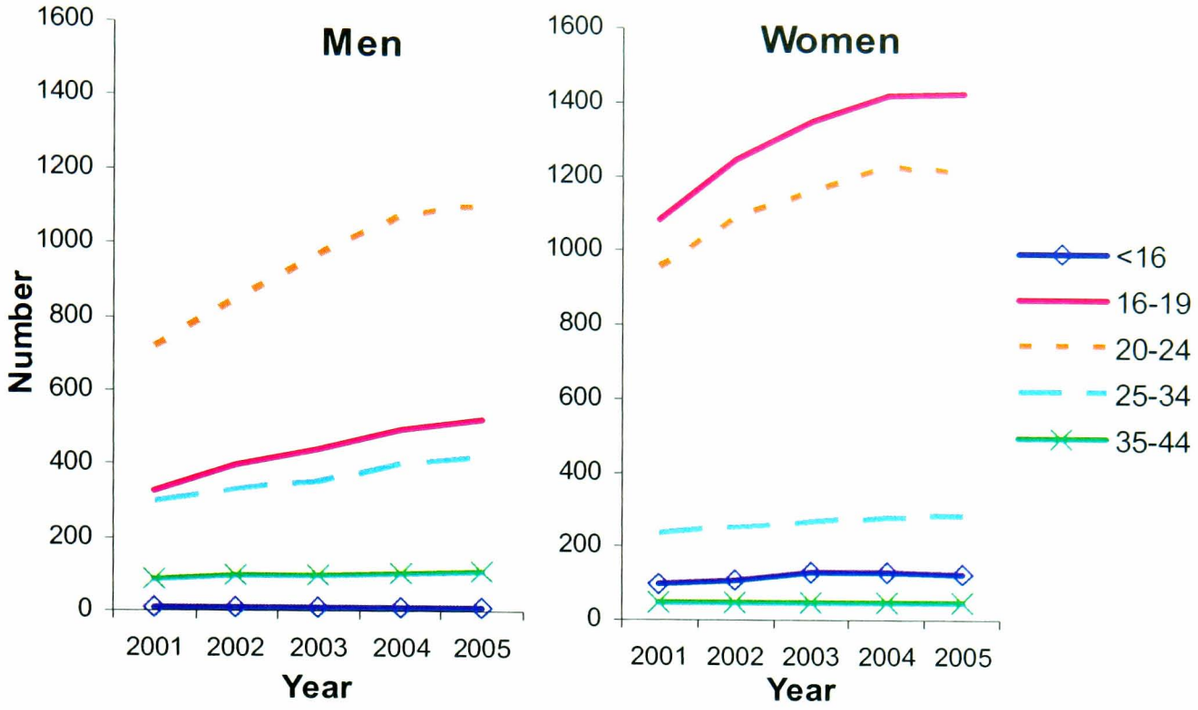
2.3.1 Genitourinary medicine clinics

GUM clinics provide free and anonymous CT testing and treatment and there is mandatory reporting of all STI diagnoses to the Health Protection Agency (HPA) (Health Protection Agency, 2006a). The results are aggregated, so individual level data analysis is not possible. GUM data highlight trends in chlamydia diagnoses in England. However, the total number of

diagnoses is thought to be an underestimate of the actual number of cases in the population for several reasons: 1) most asymptomatic CT cases will not seek testing or treatment and remain undiagnosed, 2) some people are diagnosed in other settings especially as CT screening is implemented in other clinical settings (National Chlamydia Screening Steering Group., 2006), and 3) GUM service provision and access across England are not uniform (Foley E, *et al.*, 2001).

In 2005, there were 45,338 diagnoses of uncomplicated (i.e. acute) CT infection in men and 51,013 in women made in GUM clinics in England (Health Protection Agency, 2006a). Diagnoses have increased over the past five years (2001-2005) particularly in those aged under 25 years (Figure 2.3). Rates are highest in men aged 20-24 and in women aged 16-19. Recent increases in diagnoses may reflect improved ascertainment from an increase in clinic attendance and screening as well as a possible rise in incidence (Health Protection Agency, 2006a). Increases in the reported epidemiological treatment of suspected genital chlamydial infection (i.e. partner treatment of a confirmed case) have also increased in line with acute infection (Health Protection Agency, 2006a). Increases in partner referred cases may be a marker of more index cases, as well as better partner management.

Figure 2.3 – Annual rates of uncomplicated genital chlamydial infection diagnoses in GUM clinics by sex and age group, England.



Note: Data from the HIV/STI Department, Health Protection Agency (2006a)

2.3.2 General Practice

It is estimated that around 75%-85% of individuals attend a GP annually for any reason (Salisbury C, *et al.*, 2006; Chlamydia Recall Study Advisory Group, 2004). Having GPs take a more active role in the sexual health of patients was set as a priority in the National Strategy for Sexual Health and HIV (Department of Health, 2002b), whereas in the past GPs may have referred suspected STI cases to GUM clinics.

The Royal College of General Practitioners Weekly Returns Service contains data from select GP surgeries across England and Wales, with approximately 79 participating GPs in 2005 (Birmingham Research Unit of the Royal College of General Practitioners, 2006). A study using these data found a mean annual incidence of clinical diagnosis PID of 1.1% across all ages (Simms I, *et al.*, 2006a). However, the results stratified by age indicated a high prevalence in women aged less than 15 years and over 45 years, which are unlikely to

be caused by CT infection, or in fact be true PID. Therefore these results should be interpreted with caution and will not be considered further in this thesis.

Another large dataset, the General Practice Research Database (GPRD), covers about 5% of the UK population (Medicines and Healthcare Regulatory Agency, 2005). An analysis of this dataset by Cassel *et al* (2006) estimated the reported annual incidence of CT infection from 1998-2000 to be 5.0 in men (95% CI 4.4 to 5.8) and 34.7 in women (95% CI 33.0 to 36.5) per 100,000 population. They also compared the incidence from the GPRD and GUM surveillance data (Health Protection Agency, 2006a), and it was estimated that 5% and 23% of infections in men and women were diagnosed in GP clinics compared to GUM clinics from 1998-2000.

2.3.3 Hospital Episode Statistics

Patients with PID or EP may be admitted to a hospital. The Hospital Episodes Statistics (HES) dataset covers all inpatient admissions in NHS hospitals in England. It contains individual level data for all patients including the number of admissions, the length of admission and demographic information such as age and gender (www.hesonline.org.uk). These data can be used to explore the burden on the health care system and also to compute the average cost per episode of the selected diagnoses (Chapter 6).

Data from the HES dataset were examined for chlamydia related sequelae (The Information Centre, 2006). The specific ICD 10 codes for ectopic pregnancy (O00), pelvic inflammatory disease and salpingitis (N70-73), infertility of tubal origin (N97), epididymitis (N45), neonatal conjunctivitis (P39.1), neonatal pneumonia (P23.1) and others were extracted. The total number of patients (count of `hesid`) and the total number of bed days for each code were extracted by age group. The average incidence of inpatient episodes per 100,000 population, and average length of stay were estimated from the HES data and ONS 2003 mid-year population estimates (www.statistics.gov.uk). PID, EP, TFI and epididymitis were

estimated for individuals aged 16-44 years, and neonatal conjunctivitis and pneumonia for those aged less than one year (Table 2.2). For neonatal pneumonia, 90% of admissions were for pneumonia of an unspecified cause (only one admission for pneumonia caused by CT); therefore all causes of neonatal pneumonia were included in the estimate for incidence and length of stay. The complications listed below are all clinical cases recorded in HES, which may or may not be associated with chlamydial infection, and therefore represent an upper bound on the incidence.

Table 2.2 – Annual incidence and length of inpatient stay of CT complications from HES data (2002-2003)

	Incidence per 100,000	**Average length of stay**
PID	126.0	1.7
EP	80.8	2.9
TFI	16.4	0.4
Epididymitis	31.0	1.6
Neonatal conjunctivitis	7.7	1.8
Neonatal pneumonia* (<1yr)	12.0	7.8

*All causes of pneumonia (P23)

2.3.4 Mortality estimates

The Office for National Statistics (ONS) publishes mortality estimates for England (www.statistics.gov.uk). There was an annual mortality rate for 2001-2005 of less than 1 per million population for PID and EP in women aged 25-44 (Office for National Statistics, 2005b). The proportion attributable to CT is unknown. There were no deaths reported for neonatal conjunctivitis, neonatal pneumonia, TFI or epididymitis in those aged <45 years. Therefore mortality from CT will not be included in this thesis.

2.3.5 Additional data sources

Various studies have reported on acute CT prevalence in the UK, and a systematic review and analysis of these studies is presented in Chapter 3. Three key studies are highlighted here as they are important to understanding the context of chlamydia screening. Results of the first three years of the NCSP (total numbers tested and positivity) are also presented.

In 1998 the CMO's expert advisory group issued a report on chlamydia screening (Chief Medical Officer's Expert Advisory Group, 1998), and in 1999 the Department of Health for England initiated a chlamydia screening pilot study to explore the feasibility, acceptability and logistical issues around chlamydia screening, and to assess the prevalence in different health care settings in Portsmouth and the Wirral (Pimenta J, *et al.*, 2000; Pimenta JM, *et al.*, 2003b; Pimenta JM, *et al.*, 2003a). Opportunistic screening was offered to over 33,000 sexually active women aged 16-24 in various healthcare settings (urine sample tested using LCR) (Pimenta JM, *et al.*, 2003a). Screening was acceptable (Pimenta JM, *et al.*, 2003b; Department of Health, 2002a), and approximately 18,000 tests were performed. There was a high prevalence (8-10%) in health care settings (Pimenta JM, *et al.*, 2003a). This pilot study will contribute to the analyses of CT prevalence (Chapter 3) and screening costs (Chapter 4). Henceforth, this study will be referred to as the Chlamydia Pilot Study, and a summary of results is given in Appendix 2.

Concurrent with the Chlamydia Pilot Study, the Chlamydia Screening Study (ClaSS) was conducted in Bristol and Birmingham, to evaluate postal screening of women and men recruited from GP registration lists (ClaSS Study Group, 2001). Individuals aged 16-39 were sent screening packs, and asked to return by post a urine sample for men and women and an additional vaginal swab for women. This study included a case-controlled study to improve the targeting of screening, a trial on PN in general practice, laboratory studies to assess diagnostic tests, cost analysis, qualitative work on the psychosocial aspects of screening and modelling work to investigate its cost-effectiveness (Low N, *et al.*, 2004; Macleod J, *et al.*,

2005b; Horner P, *et al.*, 2005; Salisbury C, *et al.*, 2006; Roberts TE, *et al.*, 2006; Low N, *et al.*, 2006; Campbell R, *et al.*, 2006; Skidmore S, *et al.*, 2006; Robinson SM, *et al.*, 2007) (www.chlamydia.ac.uk). The acceptance rate was 30% (Macleod J, *et al.*, 2005b), which was lower than that achieved in the Chlamydia Pilot Study. The positivity was 5% in men and 6% in women for those aged under 25 years (Macleod J, *et al.*, 2005b).

The second National Survey of Sexual Attitudes and Lifestyles (Natsal 2000) (Fenton KA, *et al.*, 2001b; Wellings K, *et al.*, 2001; Johnson AM, *et al.*, 2001), was undertaken in 1999-2000 in Great Britain. This was a large (11,161 men and women interviewed) stratified probability sample survey, with a semi-structured in-depth interview about sexual behaviour, as a follow-up to a similar study done in 1990 (Johnson A, *et al.*, 1994). As part of this survey, 5026 individuals were asked to submit a urine sample for chlamydia testing using NAAT, of which 71% provided a sample (Fenton KA, *et al.*, 2001b). The CT prevalence was 2.7% (95% CI 1.2% - 5.8%) in men and 3.0% (95% CI 1.7% – 5.0%) in women aged 18-24 years. These results are slightly lower than that found in the Chlamydia Pilot Study, and prompted the question- what is the prevalence of CT infection in the UK? Natsal 2000 data will be included in the systematic review and analysis (Chapter 3). Additionally, the Natsal 2000 research team kindly provided individual level sexual behaviour and GUM clinic attendance data from the survey respondents that will be used for the dynamic model parameterisation (Chapter 5).

2.4 Screening for genital chlamydial infection

2.4.1 Rationale and ethics of screening

In 1968, Wilson and Jungner published a report containing ten principles of screening (Wilson JMG, *et al.*, 1968). Their document was not specific to screening for infectious diseases, yet highlights issues for evaluating the appropriateness of a screening programme.

There are many different ways to implement CT screening. These are examined as they pertain to the current NCSP strategy (Figure 2.4).

Figure 2.4 – Wilson and Jungner screening criteria

I. The condition sought should be an important health problem.

Surveillance data and reports from screening studies and the NCSP indicate a high prevalence in young adults in England. While infection is often asymptomatic, pathological changes can occur and complications can develop that require clinic visits or hospitalisation.

II. There should be an accepted treatment for patients with recognised disease.

Treatment for acute infection with antibiotics such as Azithromycin or Doxycyline have high microbiological cure rates, are easy to take, have few side effects and cause minimal interference with daily lifestyle (Horner PJ, *et al.*, 2006). Partner notification and treatment are easily undertaken in a variety of settings.

III. Facilities for diagnosis and treatment should be available.

Traditionally CT has been diagnosed and treated in GUM clinics. Resources in GUM clinics are limited and it was thought that a national screening programme might place an additional burden on clinicians with long waiting times (Foley E, *et al.*, 2001; Health Protection Agency, 2006b). However, CT screening studies (Pimenta JM, *et al.*, 2003b; Pimenta JM, *et al.*, 2003a) and the NCSP have shown that screening can be done in a variety of health care settings and non-clinics setting alike (i.e. university pee in a pot days, prisons, etc). In addition to the clinical support needed for diagnosis and treatment, facilities for laboratory diagnosis of a high volume of samples, programme administration, partner referral, counselling and education are available.

IV. There should be a recognisable latent or early symptomatic stage.

Acute asymptomatic or symptomatic CT infection can be diagnosed and treated early by screening, which is thought to prevent complications such as PID, EP or TFI from developing. Early treatment from screening may break the transmission chain, yielding indirect benefits through herd immunity to those screened and unscreened, provided there is effective PN.

V. There should be a suitable test or examination.

The NCSP and the BASHH recommend using NAAT tests on a non-invasive sample (Section 2.2.4). This is based on their high sensitivity and specificity, quick processing time and yield/throughput, reliability, acceptability, feasibility and costs. However, there are issues about their diagnostic accuracy in low-prevalence populations (PPV, Chapter 2.2.4). Individuals with a positive test may have psychological morbidity relating to the stigma of being positive, the stress of telling partners and the potential damage to a relationship (Duncan B, *et al.*, 2001). If screening is able to reduce the prevalence of CT, the PPV will decrease, and screening may need to be re-examined if the PPV is not high enough.

VI. The test should be acceptable to the population.

NAAT screening tests requiring a self-collected urine or vulvo-vaginal swab are highly acceptable.

VII. The natural history of the condition, including development from latent to declared disease, should be adequately understood.

The basic natural history of chlamydia and associations with subsequent disease has been studied. Strong evidence exists for the probability of neonatal transmission and development of conjunctivitis or pneumonia, and the probability of PID developing into EP or TFI. Gaps in the understanding of disease pathology and progression (particularly the proportion of acute CT infections that progress to PID) remain (Chapter 2.2.1 and 2.2.2). This has implications for the effectiveness and cost-effectiveness of CT screening and will be examined in Chapter 6. Overall, the evidence supports the benefits of screening to identify infection, prevent complications and onward transmission.

VIII. There should be an agreed policy on whom to treat as patients.

Any individual who is diagnosed with symptomatic or asymptomatic chlamydia should be treated. Their partners should also be treated to prevent re-infection.

IX. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

Several studies have examined the cost-effectiveness of screening (Chapter 2.5). The main aim of this thesis is to evaluate the economics of CT screening (Chapter 6).

X. Case finding should be a continuing process and not a once and for all project.

Screening will be implemented for an indefinite period of time, or until the prevalence had changed significantly to warrant stopping the programme or changing the target population. For example, this might occur if the prevalence drops below a certain level and the PPV of testing become unacceptable.

Note: Taken from (Wilson JMG, *et al.*, 1968)

To summarise, CT screening appears to satisfy the Wilson & Jungner criteria. Screening appears to be a socially responsible activity as it has the potential to improve the health of many people. However, some of the issues addressed in the Wilson & Jungner criteria should be revisited as screening is implemented on a wide scale. For example, the PPV of testing may decline to unacceptable levels if the prevalence of CT decreases. The implications are that increasing numbers of individuals screened would be told they have infection and potentially suffer a negative psychosocial impact, without the corresponding benefits that true CT positives have. There are also other unanswered questions such as the impact of CT screening on the incidence of PID and other complications that should be further addressed.

2.4.2 The logistics of screening

Method Most screening programmes have selection criteria to optimise efficiency and minimise unnecessary tests. An alternate method such as universal screening, i.e.

offering a CT test to all individuals, would unnecessarily test many individuals who were not at risk of infection.

Population Specific populations that are at greatest risk of infection and who stand to benefit most from screening are targeted. Targeting can be based on identifying characteristics such as sex, age, ethnic group or sexual behaviour. This is the topic of Chapter 3.

Frequency Individuals can be re-infected with CT, unlike many viral infections such as measles which give lasting immunity to re-infection after initial infection or vaccination. Therefore, a single CT screen would only identify a current infection but not a future infection. The current recommendations from the NCSP are to opportunistically offer a screening test annually to the target group. Other more active methods are available such as a recall method which tests individuals at different intervals depending on their risk group or initial CT test result. An analysis of the optimal screening frequency is presented elsewhere (Turner KME, *et al.*, 2006b).

Setting A variety of healthcare settings have been chosen as the primary location for screening in the NCSP (National Chlamydia Screening Steering Group., 2006). However, to complement the NCSP and reach high prevalence groups that do not attend healthcare settings, screening is also being offered in non-clinical settings (i.e. postal screening kits, pharmacies).

2.4.3 Screening in other countries

In the 1980's Sweden established a national laboratory service for diagnosing CT, along with increased testing, partner referral and treatment (Herrman B, *et al.*, 1995; Egger M, *et al.*, 1998). Until 1994, the CT prevalence declined in Sweden (Herrman B, *et al.*, 1995; Kamwendo F, *et al.*, 1996). PID diagnoses also decreased (suggestive of a causative role of CT screening), and the proportion of individuals with PID and simultaneous CT or

gonorrhoea infection decreased (Kamwendo F, *et al.*, 1996). However, since the late 1990's there has been an increasing trend in CT diagnoses, particularly in younger age groups (Swedish Institute for Infectious Disease Control, 2000). The increases may be due to changes in testing methods to more sensitive tests and greater numbers of tests (Gotz H, *et al.*, 2002), or perhaps lapses in PN or low screening rates in men (Low N, *et al.*, 2002). There may also be increases in risky sexual behaviour (increased partner numbers or less condom use), or perhaps the message about the benefits of continued screening is no longer effective.

In the USA, the Centers for Disease Control and Prevention (CDC) implemented screening programmes in select regions in 1988, increasing to cover all regions by 1995 (Centers for Disease Control and Prevention, 2006). Screening conducted in FPCs in Wisconsin reported a decrease in prevalence from 10.7% to 5.2% in non-urban clinics and from 13.7% to 6.9% in urban clinics from 1986-1990 (Addiss DG, *et al.*, 1993). Reported CT positivity in women in FPCs has remained fairly stable overall in recent years. Some regions have reported increases in prevalence and other decreases, after adjusting for the sensitivity and specificity of the test used (Centers for Disease Control and Prevention, 2006).

CT screening has been introduced on a local or regional level in other countries including the Netherlands (Gotz HM, *et al.*, 2006; Gotz HM, *et al.*, 2005; van Bergen JE, *et al.*, 2006) and Denmark (Ostergaard L, *et al.*, 1998; Ostergaard L, *et al.*, 2000; Andersen B, *et al.*, 2002; Andersen B, *et al.*, 2005). However England is the only country to establish a national programme, although full implementation is still occurring and coverage is not yet 100%.

2.4.4 Screening in England

Based on evidence from other countries about the effectiveness of chlamydia screening, the CMO's Expert Advisory Group report (Department of Health, 1998), and results from the Chlamydia Pilot Study (Pimenta JM, *et al.*, 2003b; Pimenta JM, *et al.*, 2003a; Pimenta JM, *et*

al., 2003a), plans for chlamydia screening in England were made in the National Strategy for Sexual Health and HIV (Department of Health, 2001). In 2002, the Department of Health commenced a phased implementation of the NCSP starting with ten sites across the country. Sixteen additional sites were added in 2004 and the programme is expected to be national by the end of March 2007 (www.hpa.org.uk). The programme offers opportunistic screening in a variety of clinical and non-clinical settings, targeting young men and women (aged less than 25 years). Screening involves an offer of a non-invasive NAAT on self-collected urine or vulvo-vaginal swab, and infection management including diagnosis, treatment and PN. There are a set of core requirements for the programme, but local sites are allowed flexibility in the screening model they adopt (National Chlamydia Screening Programme, 2006). Over 80% of screening tests are done through the NCSP in the chlamydia screening office or health care settings, but screening is also available through postal screening kits, pharmacy based testing, "pee in the pot" days at universities, in prisons or other settings (National Chlamydia Screening Steering Group., 2006). These approaches are complementary to traditional screening, and may reach those who would not otherwise be screened in a health care setting.

The first three years of screening in the NCSP are published, including the number of CT tests and positivity (Table 2.3). There have been year on year increases in the number of men and women screened, and the proportion of screens in men has increased. Positivity is highest in 16-19 year old women and 20-24 year old men, with roughly one in ten positive of those tested. These results will be further discussed in Chapter 3.

Table 2.3 – Number tested and positivity from the National Chlamydia Screening Programme, by sex, year, age group and setting*.

	Number tested						Percent positive					
	Women			Men			Women			Men		
	2003-2004	2004-2005	2005-2006	2003-2004	2004-2005	2005-2006	2003-2004	2004-2005	2005-2006	2003-2004	2004-2005	2005-2006
Age												
<16	1,284	4,336	6,996	65	400	830	7.5%	9.3%	7.4%	1.5%	3.3%	3.4%
16-19	6,544	24,912	37,971	657	3,890	9,136	12.1%	12.7%	11.6%	10.0%	10.8%	8.8%
20-24	7,413	23,855	34,527	450	3,305	7,430	8.8%	9.3%	9.1%	19.8%	14.3%	12.4%
Setting												
FPC/Contraception	9,787	27,416	34,030	529	2,270	3,439	10.9%	11.5%	10.5%	20.0%	16.8%	14.1%
GP	1,615	5,391	12,649	82	740	2,238	10.0%	9.5%	8.8%	11.0%	10.1%	10.8%
CT Screening Office	-	893	2,050	-	389	1,033	-	11.5%	12.2%	-	11.6%	17.2%
TOP/BPAS/MS	376	1,392	2,734	-	-	16	10.4%	10.6%	9.6%	-	-	12.5%
GYN/ANT/INF/COL	218	2,437	3,892	-	19	67	7.8%	8.0%	8.5%	-	5.3%	6.0%
Youth	1,830	11,599	14,373	157	1,358	2,579	8.2%	11.8%	12.0%	7.6%	15.6%	12.3%
Military	28	129	548	56	538	2,472	14.3%	14.0%	7.7%	16.1%	8.9%	2.8%
Prison	-	101	197	-	297	916	-	13.9%	13.2%	-	9.8%	11.8%
University/College/School	500	3,045	5,905	301	1,743	3,395	5.0%	7.0%	6.9%	4.7%	5.6%	4.7%
Other*	887	530	2,861	47	220	1,201	8.3%	10.0%	11.1%	12.8%	8.2%	9.7%
Unknown	-	170	255	-	21	40	-	7.1%	4.3%	-	0.0%	0.0%

*Data for this table comes from the NCSP's first three annual reports on the numbers tested and proportion positive tests (Department of Health, 2004b; National Chlamydia Screening Steering Group., 2005; National Chlamydia Screening Steering Group., 2006).

2.5 Health economics of chlamydial infection

This section will give some background information about economic evaluation and a review of what has already been done for CT screening will be presented at the end.

2.5.1 Approach used

Since the NHS has a finite amount of money to spend on health, it needs to be able to assess the relative costs and benefits of different interventions. The main steps in economic evaluation, adapted from the National Institute of Clinical Excellence (NICE) guidelines (2004) and Drummond *et al* (1997) are:

1) what is the question of interest?
2) what is the perspective for both costs and health outcomes?
3) which type of economic evaluation is most appropriate?
4) which outcome should be used?

Economic evaluations can be used to inform policy decisions on whether or not to implement a specific intervention, or as in the case of CT screening, logistical decisions about implementation to maximise resource use and benefits.

2.5.1.1 Question of interest

> "How much does chlamydia screening cost and is it worth introducing? That is, will the savings from future disease averted offset the screening costs (will it be cost saving?), and if it will not, is the extra health 'bought' by screening worth it, in terms of alternative uses of the same resources?" (Adams EJ, *et al.*, 2006)

The main aim of this thesis is to assess the cost-effectiveness of CT screening. What are the likely benefits and costs of different screening strategies? How does this compare to other screening analyses? In which way can targeting certain subgroups for screening improve its cost-effectiveness? How does the current strategy adopted by the NCSP compare to

alternative strategies? These questions will be answered in Chapter 6, while Chapters 3-5 provide supporting information needed for the cost-effectiveness analysis.

2.5.1.2 Perspective

Various perspectives could be adopted for an analysis, i.e., from the health care provider's viewpoint, or from the patient's viewpoint. In this thesis, the recommendations from NICE will be adopted (Figure 2.5). That is, all health effects will be included, and only those costs to the NHS will be included. Other costs might be important in CT infection, such as the indirect costs. These may include a patient's lost time or money from work, and their personal costs (travel costs, child care while visiting a doctor, etc), and also the emotional or psychological costs of testing or getting a positive test (Duncan B, *et al.*, 2001). Some studies have used just the direct costs, while others have taken the wider perspective including both direct and indirect costs. Indirect costs will not be included in the analyses in this thesis as they are difficult to measure quantitatively and not recommended in the NICE guidelines, but will be discussed (Chapter 7).

Figure 2.5 – Recommended perspective for economic analysis.

Perspective

"For the reference case, the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on costs should be that of the NHS and Personal Social Services (PSS). If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analyses should be presented in addition to the reference case analysis."

Note: Taken from the "Guide to the methods of technology appraisal" (National Institute for Clinical Excellence, 2004), page 22.

2.5.1.3 Type of economic evaluation

In Chapter 4, we will explore the costs of screening, using outcomes such as cost per screening offer, per test and per CT positive case. This is simply a cost analysis as screening is not compared to anything. Chapter 6 of this thesis will present a cost-effectiveness analysis. That is, the overall costs and health benefits of the no screening scenario will be compared to different screening strategies. This allows the additional gains or losses in costs and health from screening to be compared.

For both analyses, a framework is needed to estimate the number of outcomes and the costs. A model is used in both cases, which can be static or dynamic. For the analysis in Chapter 4, a static model is chosen. Static models, such as a decision tree, can explore the progression of events after some initial occurrence, such as a screening offer. It combines probabilities or the number of people passing through each branch of a theoretical decision tree with costs at each node. Sensitivity analysis can be performed to test the assumptions of the screening algorithm.

However, static models cannot incorporate the changes in the risk of infection over time that may occur when treating a large number of people, as with CT screening. Those treated will not pass on infection to others, and therefore screening has indirect "knock-on" effects in the population (Edmunds WJ, *et al.*, 1999). Re-infection from a current or new partner also may occur and impact the dynamics of infection (Burstein G, *et al.*, 1998; Kissinger P, *et al.*, 2002; Michelson K, *et al.*, 1999). Therefore, a transmission dynamic model is the most appropriate model to estimate the impact of screening on CT infection (Roberts TE, *et al.*, 2006), and can yield different results than a static model for CT screening (Welte R, *et al.*, 2005).

A dynamic model can be population-based or individual-based. Population based models explore what happens on average in the population. The population can be subdivided into different groups, such as by sexual activity level or age, but individuals are not explicitly

modelled. However, there are two aspects of CT transmission and control that population based models cannot easily incorporate: PN and screening based on previous results. PN is vital to screening and control of CT, and requires individuals and their partners (past and present) to be tracked explicitly. Certain screening strategies such as recall of individuals after a positive test or after a partner change can only be adequately modelled using individual based models. Therefore, an individual-based model was chosen and will be used in Chapters 5 and 6.

2.5.1.4 Outcome

For cost-effectiveness analysis, the outcome chosen may be intermediate or final (Drummond M, *et al.*, 1997). Intermediate outcomes for CT screening include the number of screening tests done, positive cases detected or cured, or cost per screening offer (as will be used in Chapter 4). Intermediate outcomes may be meaningful in the context of CT screening independent of other interventions and if we were to compare results from other studies of CT screening using the same outcome. However, as mentioned in Drummond *et al* (1997), "For economic analysis to inform resource allocation we are interested in what impact such changes will have on final health outcomes such as mortality and morbidity, (p.237)." For an infection like chlamydia in which death is not an endpoint, we need to find an outcome that can account for the morbidity of infection and complications. The number of major outcomes averted (MOA), such as PID, EP or neonatal complications, and the quality adjusted life year (QALY) will be used. QALY estimates from CT screening can be compared to other health care interventions while MOAs have limited comparability and it could be argued that these are intermediate rather than final and comparable outcomes. This will be discussed further in Chapter 6 when exploring the cost-effectiveness of screening.

2.5.2 Costs and data sources

As mentioned above, only the direct costs to the NHS will be considered in this thesis. To estimate the costs involved in CT infection, complications and screening, the approach of individually listing the cost ingredients and compiling them for the final costs has been taken (Drummond *et al*, 1997, p.33). In this way, the variable and fixed costs are identified separately and a value for each can be estimated. Sensitivity analyses can be done to explore the uncertainty in the cost inputs.

There are various sources for costs. As in previous cost-effectiveness studies (see review below), a combination of published cost estimates from the literature (e.g. national health care costs, medicine costs) and primary costs data from empirical screening studies will be used. The Unit Costs of Health Care describes the costs of different health care personnel employed by the NHS such as GPs and nurses (Curtis L, *et al.*, 2006). The costs of medications are published in the British National Formulary (www.bnf.org). Department of Health Reference Costs provide information on hospital costs (www.dh.gov.uk). Costs can also be estimated from empirical studies and the literature and will be described where they are used in this thesis. The costs of screening will be estimated in Chapter 4 and the costs of acute infection and complications estimated in Chapter 6.

2.5.3 Literature review on past studies

Many studies reporting the cost-effectiveness of chlamydia screening have been published since the late 1980's. Considerable heterogeneity of perspective, methods, outcomes, populations targeted and costs have been used, making comparison of the studies difficult. In general, CT screening has been estimated to be cost-effective, and even cost-saving. Two systematic literature reviews have been done summarising the key findings from the published literature (Honey E, *et al.*, 2002; Roberts TE, *et al.*, 2006). Honey *et al* (2002) reviewed studies published until 2000, and included eight studies that met criteria to be

reviewed further (Buhagh H, *et al.*, 1990; Genç M, *et al.*, 1996; Marrazzo J, *et al.*, 1997; Paavonen J, *et al.*, 1998; Howell M, *et al.*, 1998; Howell MR, *et al.*, 1999; Howell MR, *et al.*, 1998; Sellors JW, *et al.*, 1992). They found that most studies used intermediate outcomes of cases of CT or PID prevented, and that the CT complications included in the costs varied across studies as did the probability of progressing to complications. They concluded that CT screening was cost-effective given the population prevalences modelled by the studies.

Roberts *et al* (2006) again reviewed the literature (studies published until 2004) yet were more critical and included several studies that Honey and colleagues had excluded. They similarly found that it was difficult to generalise and interpret the published literature because of the range of methods used to assess cost-effectiveness and the intermediate outcomes not being comparable among studies. Additionally, they reported that most studies used high probabilities for progression to CT complications, which results in screening appearing favourable and even cost-saving, as high numbers of complications are being averted with every positive CT screen. Roberts *et al* also distinguished between static and dynamic models to estimate the cost-effectiveness of screening. There are advantages to static models (ease of creation and parameterisation, quick to generate results, etc) which make them desirable (Welte R, *et al.*, 2005) and which could be the reason for their continual use even when the their disadvantages have been highlighted (Roberts TE, *et al.*, 2006; Adams EJ, *et al.*, 2006). However, in order to capture all of the benefits of infectious disease interventions, for example reductions in disease prevalence, static models are inappropriate.

Since the reviews published by Roberts *et al* (2006) and Honey *et al* (2002), new cost-effectiveness papers have been published on CT screening. A literature search was done for papers published between January 1, 2004 and April 15, 2007, using the terms "chlamydia*" and "economic*" or "cost*". The abstracts were reviewed and those reporting analyses of the cost-effectiveness of CT screening were read in full. The defining features of the studies and the results were extracted. Where more than one screening strategy was modelled, the one for men or women under 25 years screened was chosen for presentation. If direct and

indirect costs were estimated, only those direct costs were included for increased comparability across studies, and the costs were converted to UK£ using the exchange rate for April 1st (www.bankofcanada.ca/en/rates/exchform.html) and inflated to £2004 using the Hospital and Community Health Services Pay and Prices Index (Curtis L, *et al.*, 2006).

A summary of the identified studies is given in (Table 2.4). Four of the eleven studies used dynamic models to estimate the impact on CT, although all but one study (Low N, *et al.*, 2007) used a static model to estimate the costs and complications. The studies explored screening in a variety of clinical settings, prisons and postal or pharmacy settings, and modelled universal or opportunistic selective screening. Most studies used a high probability of progression to PID, although many explored this in sensitivity analyses. However Low *et al* (2007) used a very low estimate of PID progress, of about 3%. The primary outcome was mainly the cost per MOA, although MOAs were defined differently by each author. Both a single screen and continuous screening were modelled, although it was unclear in some papers which approach was used.

The results varied considerably, from screening being cost-saving given assumptions about input parameters (Blake DR, *et al.*, 2004; de Vries R, *et al.*, 2006; van Bergen JE, *et al.*, 2004; Ward B, *et al.*, 2006; Welte R, *et al.*, 2005) to about £30,000/MOA (Low N, *et al.*, 2007), however most other studies estimated roughly £100-£600 per MOA (Table 2.4). Wallesser *et al* (2006) used QALYs as an outcome, and estimated that annual screening in a GP surgery would cost £1,316/QALY gained, which is similar to earlier estimates of £1888/QALY (UK£2004) by Hu *et al* (2004).

Table 2.4 – Studies published between January 1, 2004 and April 15, 2007 that report the cost-effectiveness of chlamydia screening.

Author/year	Type of screening/ setting	Sex	Age	Type of model	Outcome measure	MOA includes	% PID	Result	Converted (£2004)*	Note
Anderson *et al*, 2006	Postal/home sampling	M/F	15-24	D & S	Cost/MOA	PID, CPP, EP, TFI, NP	20%	362/MOA ($US2002)	£282/MOA	10 years of screening
Blake *et al*, 2004	Universal, youth detention	M	14-18	S	Cost/PID	PID, CPP, EP, TFI, epidid	35%	CS	CS	
Chen *et al*, 2007	Universal, TOP	F	All	S	Cost/MOA	PID, CPP, EP, TFI, ureth(m), epidid	30%	890/MOA (RMB2002)	£84/MOA	
de Vries *et al*, 2006	Postal screening	M/F	15-29	D & S	Cost/MOA, cost/PID averted	PID, CPP, EP, TFI, NP	20%, 25%	765/MOA (PID-20%), CS (PID-25%) (2002Euro)	£526/MOA	High % symptomatic CT, one-off screening but effects modelled for 10 years after
Gift *et al*, 2006	Universal, prison	M	<25	S	Cost/ CT&GC treated, cost/ PID averted	CT/GC cases, PID	20% untreated CT, 6% treated CT	546/case treated, 32,893/PID averted ($US2001)	£453/case treated, £27,344/PID averted	
Low *et al*, 2007	Postal screening	M/F	16-24	D	Cost/MOA	PID, EP, TFI, NC, NP	3% (annual prob.)	27,125/MOA (£2003)	£29,448/ MOA	High % symptomatic CT, low screen acceptance, 8 years follow up
Norman *et al*, 2004	Opp., antenatal, TOP & FPC	F	<25	S	Cost/MOA	PID, CPP, EP, TFI, ureth(m), epidid, NC, NP	30%	481/MOA (£2001)	£568/MOA	Unclear time horizon for sequelae.

van Bergen *et al*, 2004	Pharmacy/ postal screening	F	15-24	S	Cost/PID averted	PID, CPP, EP, TFI	10%-40%	CS (PID-40%); 2,325/PID averted (PID-10%), (2001 Euro)	£1706/MOA (PID-10%)	
Walleser *et al*, 2006	Annual GP	F	16-24	S	Cost/QALY	PID, CPP, EP, TFI	25%	2,968/QALY (AU$2004)	£1,265/ QALY	25 year time horizon for sequelae, IOM QALY estimates**
Ward *et al*, 2006	Opp.	F	15-34	S	Cost/PID	PID, CPP, EP, TFI, TOA, ureth(m), epidid, NC, NP	20% treated CT, 30% untreated CT	No costs & 8047 PIDs averted (prev. 5%), CS (prev. 10%), (US$2002)	CS	Single screen
Welte *et al*, 2005	Opp.	F	15-24	D & S	Cost/MOA	PID, CPP, EP, TFI, NP	25%	700/MOA (static), CS (dynamic), ($US1997)	£577/MOA (static), CS (dynamic)	10 years of screening

Note: *Currency converted using the exchange rate for April 1st, on the website: http://www.bankofcanada.ca/en/rates/exchform.html, and costs were inflated using inflated to GB £2004 using the Hospital and Community Health Services Pay and Prices Index (Curtis L, *et al.*, 2006).
**IOM-Institute of Medicine (2002)
Abbreviations: TOP-termination of pregnancy clinic, FPC-family planning clinic, Opp.-opportunistic; MOA-major outcome averted; PID-pelvic inflammatory disease, M-male, F-female; D-dynamic model, S-static model; CPP-chronic pelvic pain, EP-ectopic pregnancy, TFI- tubal factor infertility, NP-neonatal pneumonia, NC-neonatal conjunctivitis, epidid.-epididymitis, ureth(m)-urethritis (male), CT/GC-chlamydia/gonorrhoea, TOA-tubo-ovarian abscess; CS-cost saving;

Several studies have now been published which use dynamic models of CT infection, coupled with an economic model. A model of CT screening in England estimated the effectiveness and cost-effectiveness using a population-based system dynamic model, with the population stratified by age and sexual activity group (Townshend JRP, *et al.*, 2000). The population comprised 12-40 year olds, and they made a simplistic assumption of an overall prevalence of 5% across all age classes, although this is not matched by surveillance data (Figure 2.3). They modelled screening 16-25 year old women once a year or screening after a partner change. Results focused on sensitivity analyses of possible outcomes, as many of the parameter estimates were based on opinion. They estimated that screening would cost £26 million annually and yield net cost savings of £3 million per year after 5 years increasing to £13 million per year after 10 years in England. Findings from this study estimate that roughly 30,000 cases of PID, 7,000 cases of TFI and 700 cases of EP per year would be prevented after five years of screening.

Another more complex dynamic model was developed in the Netherlands comprising sexual behaviour, CT infection and screening (Kretzschmar M, *et al.*, 1996; Kretzschmar M, *et al.*, 2001). The model estimated that screening men and women aged 15 to 24 would reduce chlamydia prevalence in asymptomatic women from 4.2% to 1.4% in 10 years (Kretzschmar M, *et al.*, 2001). It was used to explore the cost-effectiveness of screening in Denmark and the Netherlands, and results vary from CT screening being cost-saving to costing about £300/MOA (Andersen B, *et al.*, 2006; Welte R, *et al.*, 2000; Welte R, *et al.*, 2005). De Vries *et al* (2006) developed a different population-based dynamic model that estimated that screening may be cost saving if the probability of progression to PID is 25% or higher. Low *et al* (2007) created a dynamic model based on that of Kretzschmar *et al* (2001), incorporating disease progression and costs into the dynamic model. They estimated the impact of postal screening of men and women aged 16-24 years in England. They assumed that 30% and 75% of infections in women and men were symptomatic, and assumed a low probability of progression to complications. This resulted in a high cost per MOA, because

screening did not have a big impact on the prevalence or complications since many people would have been treated because of symptomatic infection (Low N, *et al.*, 2007), and also because their response rate to a screening offer was low.

In all the published studies, different perspectives have been taken; some considered only the direct medical costs of infection, complications and screening, and others considered the wider societal costs and estimated the indirect costs. In general, including both direct and indirect costs makes screening more favourable (that is, more cost-effective) than only considering the direct costs (see, de Vries *et al*, 2006, Welte *et al*, 2000). In Table 2.4, only results using the direct costs have been reported for comparability.

These models can be updated in several ways to improve estimates of the cost-effectiveness of CT screening in England. Detailed Natsal 2000 data (Chapter 2.3.5) on sexual behaviour, reported CT treatment history and CT prevalence estimates for Britain (Johnson AM, *et al.*, 2001; Fenton KA, *et al.*, 2001b) can be used to parameterise the model. Additional empirical data are now available from the Chlamydia Pilot Study (Pimenta JM, *et al.*, 2003b; Pimenta JM, *et al.*, 2003a), which can be used to estimate the impact and costs of screening and prevalence of CT. Using an individual-based model should improve its ability to model PN and a recall method of screening.

2.6 Plan for the thesis

As the NCSP is implemented across England, it is important to update and improve our understanding of chlamydial infection and CT screening in England. Work has already been done in England and other countries, but to keep discussions about CT screening relevant we need to revisit aspects of screening. Who do we target for screening? How much does screening cost? How do we model it realistically? What is the cost-effectiveness of screening and is it worth doing? These questions will be addressed in this thesis.

First, an updated systematic review of CT prevalence and analysis of studies gives a more accurate picture of the epidemiology of infection in the UK (Chapter 3), and inform the question "who do we screen?" Together with the results from the Chlamydia Pilot Study, the question "how much does screening cost?" can be answered (Chapter 4), including a detailed analysis of the cost components of a screening programme, highlighting areas where costs could be minimised. We also need to understand the wider context of screening, that is, its value as one of many interventions funded by the NHS. While the decision to screen was taken part way through this thesis, screening should be explored further, and its evaluation should be an ongoing process to inform programme management decisions. Therefore, an individual based sexual network model of CT transmission and screening (Turner KME, *et al.*, 2006a) is used to estimate the cost-effectiveness of screening, addressing the question, "how do we model it realistically?" This model aims to be the most realistic to date, by fitting the sexual behaviour of individuals in the model as closely as possible to what is observed in reality, specifically Natsal 2000 (Chapter 5). The biological parameters that simulate the epidemiology of infection in England are fitted to data on the CT prevalence in different groups (Chapter 3) and prior CT treatment (Natsal 2000). Chapter 6 then uses the parameterised model to answer the question "what is the cost-effectiveness of CT screening, and is it worth it". This thesis finishes with a broad discussion addressing some of the wider issues around the cost-effectiveness of screening (Chapter 7).

CHAPTER 3 - THE PREVALENCE OF CHLAMYDIA IN THE UNITED KINGDOM

"SEX DISEASE RIFE AMONG TEENAGERS"

The Observer, June 08, 2003

3.1 Aims

- To perform a systematic review to identify studies reporting chlamydia prevalence in the UK including unpublished studies;
- To report the findings of the review and a summary of the studies found;
- To extract data from the studies and use them to explore which factors affect prevalence estimates;
- To estimate the prevalence for various populations and explore which populations have the highest rates of infection.

3.2 Introduction

Chlamydia has been the most commonly diagnosed sexually transmitted infection in GUM clinics in the UK in recent years, and diagnoses have been increasing (Health Protection Agency, 2006a) (Chapter 2.3.1). While data from GUM clinics provide information on CT trends, they may not reflect the current prevalence in the general population or population subgroups including sexually active individuals. Results from the Chlamydia Pilot Study (Chapter 2.3.5) suggested that there was a high prevalence of CT in young adults in various health care settings (Pimenta JM, *et al.*, 2003b; Pimenta JM, *et al.*, 2003a). However, for a national chlamydia screening programme to be considered, we needed to know if the prevalence is similarly high in other settings. Estimates from the Natsal 2000 survey suggested that the prevalence in the general population was lower than that found in the Chlamydia Pilot Study (Fenton KA, *et al.*, 2001b; Pimenta JM, *et al.*, 2003a). This conflicting evidence warrants further investigation to understand the epidemiology of CT in the UK. At this point in the thesis work, there had been no comprehensive systematic review of CT prevalence undertaken in the UK, although a study on CT prevalence in asymptomatic women in Europe had been published (Wilson JS, *et al.*, 2002). The most recent comparisons of data and overviews of chlamydia prevalence in the UK had been published in 1998 or earlier (Simms I, *et al.*, 1996; Department of Health, 1998), were not done systematically, had excluded the largest, most recent studies, or had focussed on prevalence in limited settings (Stokes T, 1997b; Oakeshott P, *et al.*, 1995; Stokes T, 1997a).

Of the studies reporting CT prevalence in the UK, there is considerable heterogeneity in methodologies used, making interpretation and comparison difficult. However, statistical methods are available to explore these differences. Data from individual studies can be extracted and combined to understand the factors that influence the overall prevalence. This chapter will present the findings from the studies identified in the systematic review, and then use the data extracted from the studies to explore the factors associated with CT prevalence in the UK. Because this study was completed three years ago, an update of more

recent papers will be included in the Discussion. Results from this chapter will help build a robust understanding of the epidemiology of CT in the UK and inform parameterisation of the dynamic CT model (Chapter 5).

3.3 Method

3.3.1 Study identification

Electronic databases (Medline via PubMed (from 1966), EMBase (from 1980), Web of Science- Science Citation Index and Social Sciences Citation Index (from 1981), SIGLE-System for Information on Grey Literature in Europe (from 1980) and HMIC: DH Data-Health Management Database) were searched using the keyword 'chlamydia' with one of the following: 'England', 'Wales', 'UK', 'Scotland', 'Ireland' or 'Britain' for studies published up to July 2002. References from chlamydia reviews were also searched. To reduce the effects of publication bias, a letter was sent to a selection of experts in the field who had published recently on CT prevalence, requesting additional published or unpublished data, and names of researchers who might have additional information. Thirty letters were sent in total and 22 responses were received (73% response rate).

3.3.2 Exclusion criteria

There were two stages at which studies could be excluded, first after identifying studies in the systematic review, and second, before the statistical analysis. For the first stage, studies were included in the systematic review (and included in the qualitative statistics) if a specific UK population was tested for *C. trachomatis*, and if the number of people tested and positive was reported. A study was excluded from the systematic review if it:

- Reported on prevalence in neonatal or prepubescent populations,

- Selected populations of CT positive individuals (i.e. for follow-up, diagnostic comparability or treatment outcomes),
- Reported only prevalence among partners,
- Recruited only individuals with symptoms (i.e. urethral/vaginal discharge or abdominal pain),
- Estimated CT prevalence in individuals with another infection,
- Used serology for diagnosis (although studies that used serology for diagnosis but didn't report it may be included in the "unknown" group for diagnostic test; see below).

For the statistical analysis, studies were excluded if there was incomplete or uncodeable information from the extracted variables (see below for details).

3.3.3 Data extraction

Nine variables were extracted from each study (Figure 3.1). These were determined because of their likely importance to prevalence in various subgroups (Chapter 2.2.3).

Figure 3.1 – Variables extracted for the chlamydia prevalence analysis

A. Date of testing. Grouped by 5-year bands, as data from many studies were collected over several years
   a. Before 1985
   b. 1985-1990
   c. 1990-1995
   d. 1995-2000
   e. After 2000
   f. Other
   g. Unknown

B. Diagnostic test
   a. Nucleic acid amplification [NAAT] (LCR/PCR/TMA)
   b. Antigen (EIA/ELISA/DFA/MIF)
   c. Culture
   d. Mixture of tests
   e. Unknown

C. Specimen collected
   a. Urine
   b. Endocervical/cervical swab
   c. Urethral swab
   d. Mixture of specimens
   e. Other
   f. Unknown

D. Gender.

a. Female
b. Male
c. Both
d. Unknown

E. Age of population. There was no standard way of reporting age data in the studies extracted. Age classes were defined to provide meaningful results and that would include the greatest number of studies. Classification by the age bands listed was chosen instead of computing the mean or median age, as the age stratification was unknown for most studies.

a. <20 years old
b. 20-24 years old
c. 25-29 years old
d. 30+ years old
e. Other
f. Unknown

F. Setting. The setting of attendance (and not reason for attending) was recorded.

a. General practice or community clinic (GP)
b. Family planning clinic (FPC)
c. Termination of pregnancy clinic (TOP)
d. Genitourinary medicine clinic (GUM)
e. Postal or population-based survey
f. Teenage/youth clinic
g. Antenatal clinic
h. Other (including infertility, colposcopy, gynaecology, laparoscopy, unspecified or other)
i. Unknown

G. Number of tested individuals. This reports only the number of individuals actually tested, and does not include individuals who were offered a test and refused, as in a screening programme.

H. Number of positive individuals. If no numerator was listed but a proportion positive and denominator given, then the number positive was computed.

I. Study ID

If a study reported disaggregate results (i.e., prevalence in men and women, multiple age groups, various settings, etc.), these strata specific results were reported as separate "observations", each one comprising the population tested within each strata and the strata characteristics. These observations were then expanded to provide individual records, each

representing a person within each strata of age group, gender, setting, etc. These individual level data were treated as such in the regression analyses. When a variable did not fit into one of the specified groups, it was coded as 'other'. Data from many studies were collected over several years, and longitudinal studies were coded in the appropriate band when possible. Similarly, there was no way of standardising age data in the studies extracted.

Geographical location was extracted from each study and is included in Appendix 2. However, it did not appear to be associated with CT prevalence and was dropped from the regression analysis. Information on patient selection and the proportion who accepted a test offer was also extracted (Appendix 2), but not used in the model. The proportion of individuals with symptoms might have influenced the prevalence, since symptomatic individuals may be more likely to appear in clinical settings. It was extracted from the studies but was not included in the analysis because of problems comparing this variable across studies. Similarly, sexual behaviour is also thought to be an important determinant of prevalence, but very few studies included this information and so it was not included in the data extraction or analysis.

After applying exclusion criteria to the studies identified in the systematic review, there was still variation in the completeness and quality of the extractable data from the remaining studies. While some studies included details about selection of study participants or population sampled, others did not. Papers were not graded for quality, and it was not used as an exclusion criterion per se if all other criteria were met.

3.3.4 Statistical analysis

The data were analysed using Stata version 8. The prevalence and 95% confidence interval (CI) of each observation was computed using an exact binomial method (Armitage P, *et al.*, 2001). A weighted average of prevalence by setting for all studies was computed.

Two approaches, mixed-effects logistic regression and random effects meta-analysis, were used to estimate the CT prevalence and explore the effect of the explanatory variables on the prevalence. In both methods, observations and their extracted patient level data were included only for "complete" observations, i.e., if there was no coding of 'unknown' or 'other'. That is, observations were excluded from that statistical analysis if there were missing information for one or more variables. Observations for men and women were explored separately, as these were considered to be separate populations. Since there were few data from men, a separate regression analysis could not be performed, but the prevalence (and 95% CI) was extracted from the available studies.

3.3.4.1 Logistic regression

A mixed-effects logistic regression analysis was used to assess the association between each categorical explanatory variable (setting, test, specimen, age group, date, location) and the outcome, positive or negative CT status for women. The model was fitted via Gauss-Hermite quadrature using the `xtlogit` command in Stata, which treated all explanatory variables as fixed, and study ID was fitted as a Gaussian random effect. While it is well recognised that variable selection can introduce biases into the analysis, a backwards elimination of those explanatory variables that were apparently unimportant variables ($p>0.05$ likelihood ratio test) was performed in order to maximise the number of observations in the model. The `quadchk` command was used to check the stability of the likelihood and parameter estimates. Interactions between the explanatory variables were explored.

3.3.4.2. Meta-analysis

A random effects meta-analysis was performed and compared to the results of the mixed-effects logistic regression model. An arcsin square root transformation of the observed prevalence of each strata was performed. This results in both an approximate Gaussian distribution and stabilises the variance, the standard deviation being estimated by:

$1/(2^* (n^{0.5}))$. This was used as an estimate of the within study standard deviation in the `meta` command within Stata. The meta-analysis was performed separately for women by age group and setting, based on the results from the mixed-effects logistic regression model suggesting these were the most important explanatory variables. Estimates of the prevalence and 95% CIs for the different strata were obtained from a back-transformation to provide an estimated prevalence and 95% CI.

3.3.4.3. Sensitivity analysis

A sensitivity analysis was done to assess the impact of the larger studies on the estimated prevalence. Observations with populations of over 1000 individuals were dropped from the data and the mixed effects model re-run. However, age and setting remained the only explanatory variables that were associated with the prevalence.

3.4 Results

3.4.1 Study identification

A total of 357 studies were identified in the literature search for consideration in the analysis. Ninety (27%) met the inclusion criteria for the systematic review and were included in the descriptive statistics, one of which was unpublished (see Appendix 2 for a description of the studies and extracted variables). The studies included in the analysis comprised a total of 149,430 individuals tested for chlamydia, subdivided into 255 strata (different combinations of age, sex, setting etc).

3.4.2 Description of included studies

Selected studies varied in the strata within which they investigated the prevalence, some had estimates for one specific population, while others included changes in prevalence over time,

differences in prevalence by age, prevalence comparisons among different geographical regions, large multi-centre screening studies, and any combination thereof. The reported prevalence from all studies included in the systematic review, by gender, setting and age group are shown in Figure 3.2 and Figure 3.3 (women and men, respectively). Trends in prevalence by age group were consistent across settings, with those aged less than 20 years old having the highest prevalence in each setting. Many of the studies had missing data for one or more of the variables extracted, and nearly half of the studies had no useable information on patient age.

The majority of studies (84, 93%) were conducted in health care settings, the rest were postal surveys (Pierpoint T, *et al.*, 2000; Macleod J, *et al.*, 1999; Stephenson J, *et al.*, 2000; Rogstad KE, *et al.*, 2001), door-to-door interviews (Fenton KA, *et al.*, 2001b) or studies in military recruits (McKay L, *et al.*, 2003). Among the health care settings, most individuals (70%) were tested in GP surgeries, FPC or GUM clinics, and 6% of individuals were tested in TOP clinics (see Table 3.1 for a summary of observations and individuals included in the analysis). Studies were based on tests done between 1973 and 2002, with over half of the observations (63% of individuals) tested from 1995 to the present. Half of the individuals were tested using NAATs and nearly a quarter with antigen tests.

Figure 3.2 – Reported chlamydia prevalence for women by age group and setting (bubbles) for all studies included in the systematic review, and the estimated prevalence (lines) from the mixed-effects logistic regression model.

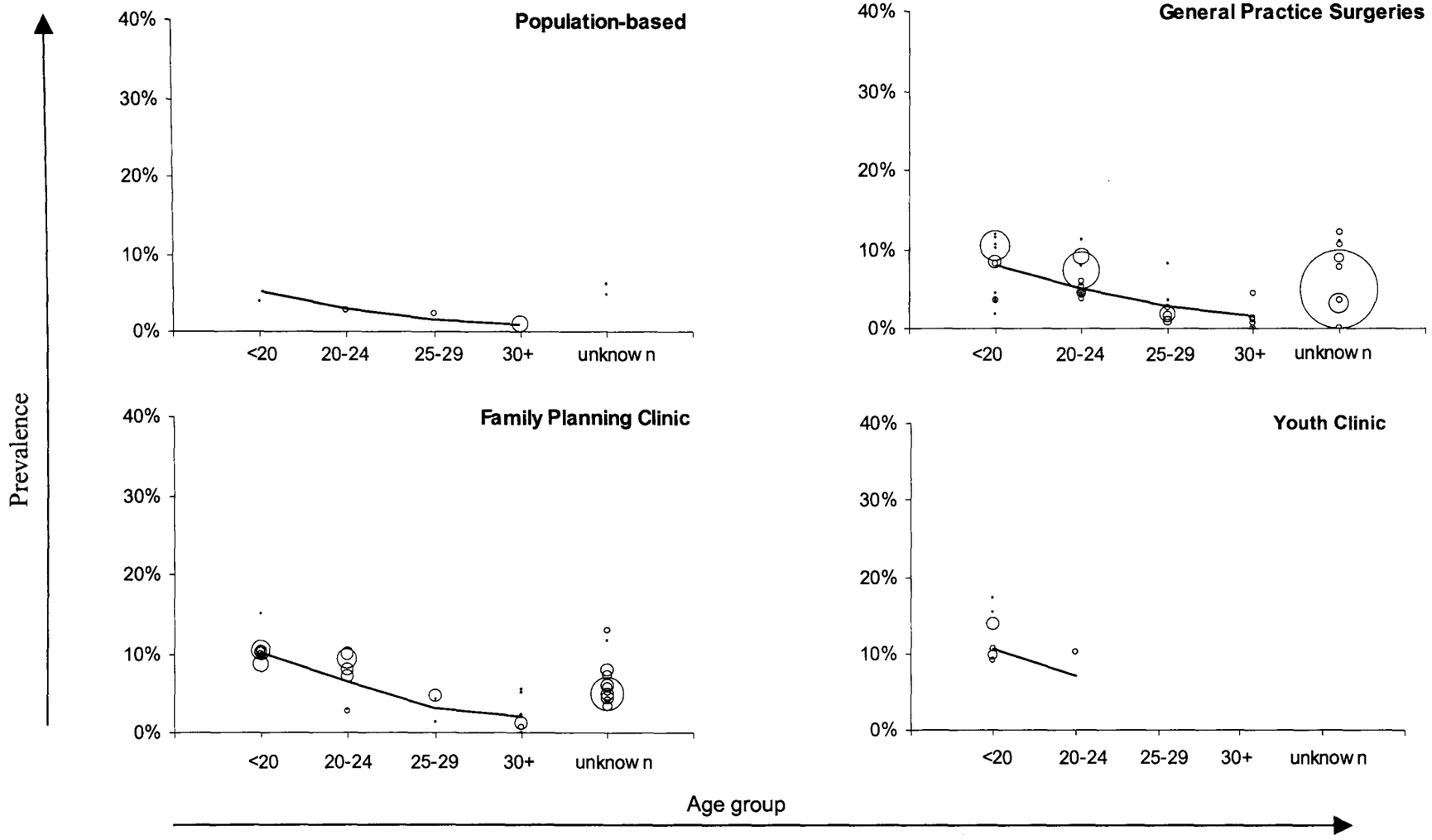
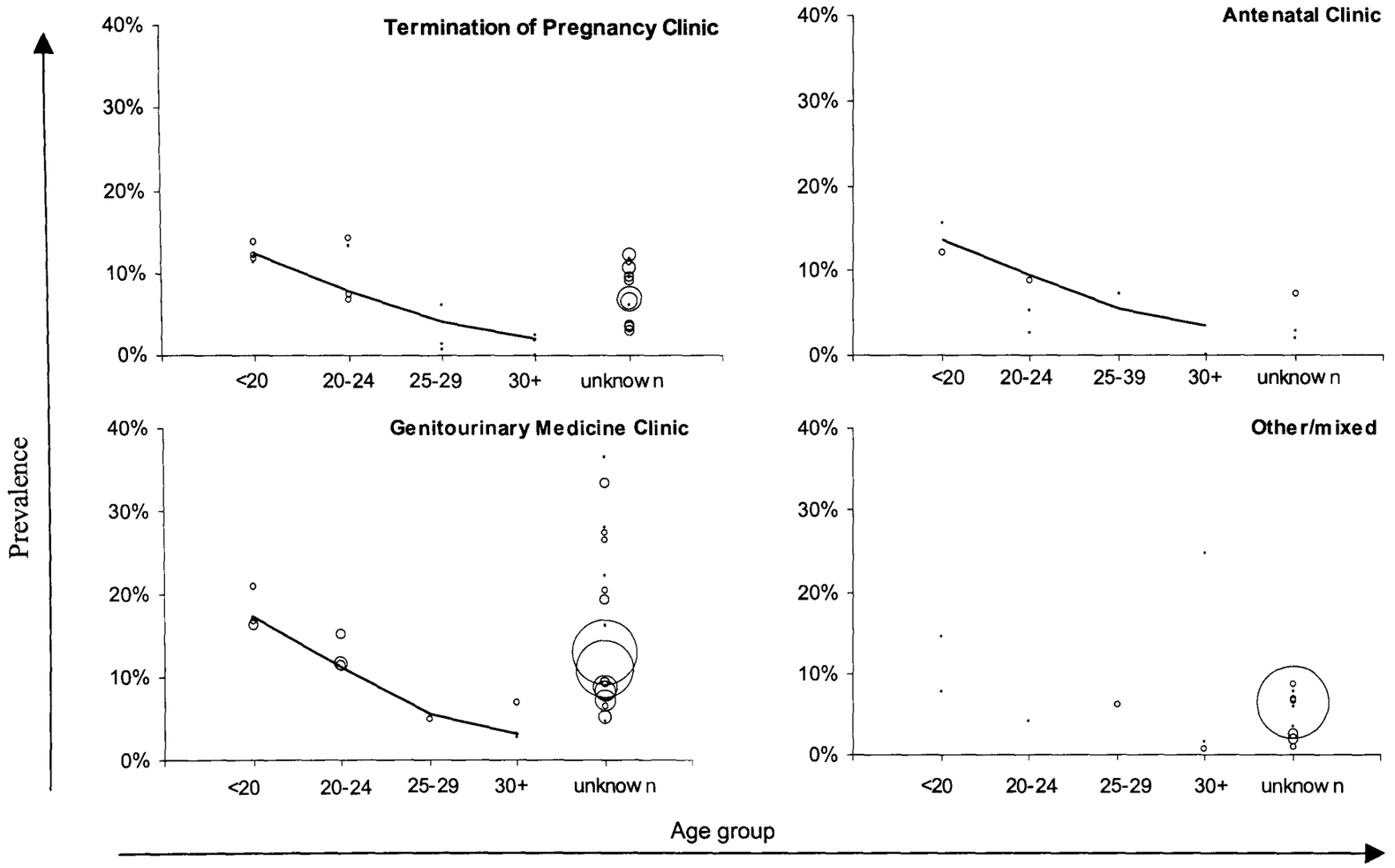
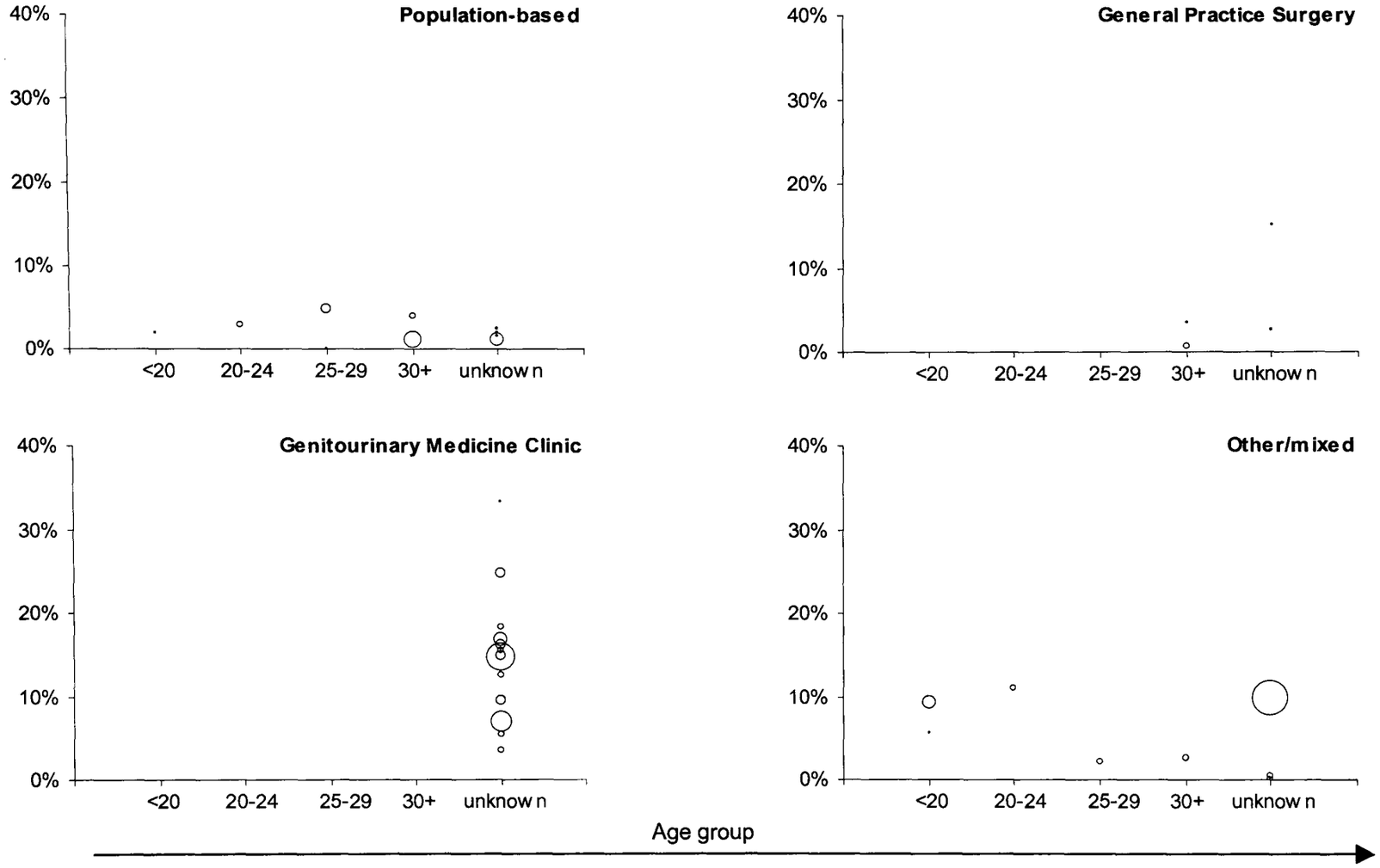


Figure 3.2 (continued)



NOTE: Reported prevalence (clear bubbles) from all studies meeting the systematic review inclusion criteria, by setting and age group (irrespective of diagnostic test, specimen and date). Bubble size represents the size of the population tested (each population has a specific set of characteristics; e.g., test, specimen, etc.). The estimated prevalence from the logistic regression (line) excludes data from studies with missing explanatory variables.

Figure 3.3 – Reported chlamydia prevalence for men by age group and setting.



NOTE: Reported prevalence (clear bubbles) from all studies meeting the systematic review inclusion criteria, by setting and age group (irrespective of diagnostic test, specimen and date). Bubble size represents the size of the population tested (each population has a specific set of characteristics; e.g., test, specimen, etc.).

Table 3.1 – Descriptive statistics of the studies identified in the literature search meeting inclusion criteria. Results are listed as number and percentage of the total, at both the study level and extracted patient level.

		Study level		Individual level	
		Number of observations	Percent of total (%)	Number of Individuals	Percent of total (%)
Gender	Female	205	80.3	121,152	81.1
	Male	38	14.9	16,178	10.8
	Both	6	2.4	8,946	6.0
	Unknown	6	2.4	3,154	2.1
Date of testing	Before 1985	8	3.1	2,377	1.6
	1985-1990	28	11.0	26,419	17.7
	1990-1995	36	14.1	15,264	10.2
	1995-2000	81	31.8	68,494	45.8
	After 2000	51	20.0	25,224	16.9
	Other	5	2.0	1,175	0.8
	Unknown	46	18.0	10,477	7.0
Diagnostic test	NAAT	84	32.9	73,368	49.1
	Antigen	89	34.9	34,936	23.4
	Culture	27	10.5	18,163	12.1
	Mixture	20	7.8	11,433	7.7
	Unknown	35	13.7	11,530	7.7
Specimen	Urine	75	29.4	31,064	20.8
	Cervical/endocervical swab	99	38.8	36,090	24.2
	Urethral swab	8	3.1	3,036	2.0
	Mixture	31	12.2	49,573	33.2
	Other	2	0.8	3,963	2.6
	Unknown	40	15.7	25,704	17.2
Age group	<20 years	54	21.2	13,397	9.0
	20-24 years	35	13.7	14,218	9.5
	25-29 years	20	7.8	4,120	2.7
	30+ years	38	14.9	6,917	4.6
	Other	56	22.0	61,794	41.4
	Unknown	52	20.4	48,984	32.8
Setting	GP	58	22.7	45,262	30.3
	FPC	40	15.7	17,825	11.9
	TOP	34	13.3	9,120	6.1
	GUM	45	17.7	40,001	26.8
	Population-based	16	6.3	4,963	3.3
	Youth clinic	8	3.1	1,996	1.3
	Antenatal	12	4.7	1,256	0.8
	Other/ mixed	42	16.5	29,007	19.5
Total		**255**		**149,430**	

The number of individuals tested in each study varied considerably, ranging between 20 (Barlow RE, *et al.*, 2001) and 42,944 (Scoular A, *et al.*, 2001), with a mean of 593 and

median of 180 people tested. Over 80% of the prevalence estimates were from women and about 11% from men (the others were unknown or mixed populations). The age groups were chosen to ensure that the maximum number of individuals tested in each study could be included in the statistical analysis and that their results were informative. However the majority of individuals tested did not fit into a distinct category or the age group was unknown (74% of individuals). Of the remaining 26% that fell into one of the age groups, 36% were aged less than 20 years, 37% were aged 20-24 years, 11% were aged 25-29 and 16% were over 30 years old.

Forty-two percent of studies reported information on the presence of symptoms among individuals tested (Table 3.2). Studies reported excluding individuals with symptoms, the proportion of CT-positive individuals with symptoms, aggregate information on proportion of all patients with symptoms, and information on symptoms in both CT-positive and CT-negative individuals.

Table 3.2 – Summary of studies reporting symptomatic chlamydial infection.

Symptoms reported	**Study**
Individuals with symptoms excluded from the study	(Smith J, *et al.*, 1991; Thompson C, *et al.*, 1994; Mohanty KC, 1990)
Proportion of chlamydia positive individuals with symptoms estimated	(Pierpoint T, *et al.*, 2000; Rogstad KE, *et al.*, 2000; Opaneye A, *et al.*, 1994; Harry T, *et al.*, 1994; Berry J, *et al.*, 1995; Southgate L, *et al.*, 1989; Fish A, *et al.*, 1987; Sin J, *et al.*, 1996; Uthayakumar S, *et al.*, 2000; Blackwell AL, *et al.*, 1999; Harvey J, *et al.*, 2000; Butt A, *et al.*, 2001; Tobin C, *et al.*, 2001; Arya OP, *et al.*, 1981; Dixon L, *et al.*, 2002; McKay L, *et al.*, 2003)
Aggregate information on proportion of all patients with symptoms	(Willmott F, *et al.*, 2000; Horner P, *et al.*, 1995; Ross JD, *et al.*, 1991)
Information provided on symptoms in both chlamydia positive and chlamydia negative individuals	(Grun L, *et al.*, 1997; James NJ, *et al.*, 1999; Rogstad KE, *et al.*, 2000; Southgate L, *et al.*, 1983; Zelin JM, *et al.*, 1995; Crowley T, *et al.*, 1992; Fish A, *et al.*, 1989; Longhurst H, *et al.*, 1987; Oriel J, *et al.*, 1978; Paul I, *et al.*, 1990; Macaulay M, *et al.*, 1990; Hopwood J, *et al.*, 1995; Simms I, *et al.*, 2000a; Hunter JM, *et al.*, 1981; Oakeshott P, *et al.*, 1992)

There were 25 studies that reported the prevalence from males (Table 3.3 and Figure 3.2). A total of 16,178 males were tested across all settings (population-based, GP surgery, FPC, GUM and other settings). The ages of individuals tested were mainly unknown in GUM clinics, but varied in the other settings. Prevalence estimates ranged from 0% to 33%, and the crude mean prevalence estimates by age and setting were similar for those in females.

Table 3.3 – Extracted male prevalence and estimated 95% confidence interval, by setting and age group.

Setting	Study	Age group	Prevalence (%, 95% CI)
Population-based	Fenton *et al* (2001b)	18-19	2.0 (0.2 - 6.9)
		20-24	2.8 (1.2 - 5.4)
		25-29	4.8 (2.7 - 7.6)
		30-44	1.1 (0.6 - 1.9)
	Macleod *et al* (1999)	18-45	1.9 (0.0 - 10.3)
	Pierpoint *et al* (2000)	18-24	1.5 (0.2 - 5.4)
		25-29	0.0 (0.0 - 3.4)
		30-35	3.9 (1.6 - 7.9)
	Rogstad *et al* (2001)	19-21	1.2 (0.5 - 2.2)
	Stephenson *et al* (2000)	18-35	2.5 (0.3 - 8.7)
GP/ Community clinic	Ainsworth *et al* (1996)	<40	14.8 (4.2 - 33.7)
	Berry *et al* (1995)	18-34	2.6 (0.3 - 9.1)
	Kudesia *et al* (1993)	<30	15.2 (8.7 - 23.8)
		30-40	3.4 (0.4 - 11.7)
		>40	0.7 (0.0 - 4.1)
FPC	Harvey *et al* (2000)	<20	5.7 (1.2 - 15.7)
GUM	Butt *et al* (2001)	Unknown	15.5 (10.1 - 22.4)
	Caul *et al* (1997)	Unknown	33.3 (25.1 - 42.4)
	Crowley *et al* (1992)	Unknown	24.6 (20.5 - 29.1)
	Dixon *et al* (2002)	Unknown	14.6 (13.2 - 16.0)
	Evans *et al* (1999)	>13	18.3 (13.0 - 24.8)
	Harry *et al* (1994)	17-46	6.8 (5.5 - 8.3)
	Higgins *et al* (1998)	Unknown	14.9 (11.5 - 18.8)
	Hunter *et al* (1981)	Unknown	16.0 (12.9 - 19.6)
	Matthews *et al* (1989)	Unknown	16.1 (12.7 - 20.0)
	Mohanty (1990)	Unknown	3.5 (1.5 - 6.8)
		Unknown	5.3 (2.9 - 8.8)
	Paul *et al* (1990)	Unknown	16.7 (13.9 - 19.9)
	Young *et al* (1998)	Unknown	12.6 (8.4 - 17.7)
	Zelin *et al* (1995)	17-77	9.6 (6.7 - 13.1)
Other	Madge *et al* (1996)	Unknown	0.5 (0.0 - 2.5)
	McKay *et al* (2003)	16-19	9.3 (6.9 - 12.1)
		20-24	11.0 (7.4 - 15.6)
		>25	8.7 (1.1 - 28.0)
	Pierpoint *et al* (2000)	18-24	0.0 (0.0 - 2.1)
		25-29	2.2 (0.6 - 5.6)
		30-35	2.6 (1.0 - 5.6)
	Scouler *et al* (2001)	15-44	9.7 (8.7 - 10.7)

3.4.3 Model results and prevalence estimates

In the final mixed effects logistic regression and random effects meta-analysis models with age and setting (female data only), 19 studies (21%) representing 32,188 individuals (22%) were included out of those studies identified and included in the systematic review. These comprised studies in which all variables were known and coded; those studies that had unknown or missing variables were excluded from the statistical analysis. All of the population-based data were from the Natsal 2000 study (Fenton KA, *et al.*, 2001b), and 56% of the other settings were comprised of individual data from the Chlamydia Pilot Study (Pimenta JM, *et al.*, 2003a).

In the single variable analysis, all variables were associated with prevalence ($p<0.05$), (Table 3.4). In the mixed effects model, where confounding effects of the other explanatory variables were accounted for, only age group and setting exhibited a strong association with prevalence ($p<0.0001$ and $p=0.002$, respectively). The diagnostic test, specimen type and date of testing did not exhibit an association with p-values of ($p=0.5$, $p=0.09$, $p=0.9$ respectively). For the specimen result, the sign changed from 0.86 in the single variable analysis to 1.37 in the multi-variable model. This is due to confounding and is known as Simpson's paradox (see Julious & Mullee, 1994, for more detail). This occurs because the specimen types are not equally represented across age and setting in the multi-variable model. Overall, the prevalence was lower in urine tests compared to cervical/endocervical swabs, but when this was examined by age and setting, a higher proportion of older women had cervical/endocervical swabs and a lower prevalence, causing the sign to change in the multi-level model. The same effect was seen for the date (in those tested after 2000). Table 3.4 gives the adjusted odds ratios and 95% CIs for all variables considered.

Prevalence estimates from the logistic regression and meta-analysis models are given in Table 3.5. In each setting, the youngest women (aged <20 years) had the highest prevalence, with the prevalence decreasing in each subsequent age group (Table 3.5 and Figure 3.2). For

example, in GP surgeries, the prevalence estimates were 8.1% (95% CI 6.5-9.9) for <20 year olds, 5.2% (95% CI 4.3-6.3) for 20-24 year olds, 2.6% (95% CI 2.0-3.3) for 25-30 year olds and 1.4% (95% CI 1.0-1.9) for >30 year olds. By setting the prevalence estimates also varied. For instance, among <20 year olds, estimates were 17.3% (95% CI 13.6-21.8) for GUM clinics, 12.6% (95% CI 6.4-23.2) for antenatal clinics, 12.3% (95% CI 9.8-15.3) for TOP clinics, 10.7% (95% CI 8.3-13.8) for youth clinics, and 10.0% (95% CI 8.7-11.5) for FPC. Studies performed in GP surgeries also had an overall high CT prevalence of 8.1% (95% CI 6.5-9.9) compared with 5.0% in population-based studies (95% CI 3.2-7.6). Sensitivity analysis from the quadrature check of the final mixed model showed that the maximum relative difference in the parameters was $1.0*10^{-10}$ and all of the other parameters were less than that. This means that the number of quadrature points chosen does not affect the reliability of the estimate, and the estimate appears stable. A global test of the interaction between age and setting gave no strong evidence for an interaction (p=0.44).

The results from the meta-analysis were similar to the logistic regression model results (Table 3.5). Figure 3.4 presents a comparison of the results by age group and setting, and also includes the 2005-2006 NCSP results (proportion of positive screening tests) for women by age group and setting.

The prevalence estimates from the final model appear to be a reasonable fit to the extracted data in Figure 3.2 (including those that were not used to predict the model), for all settings except for population-based studies. This setting did not appear to have such strong decreasing prevalence trends with age (Table 3.5), although there was no strong evidence in the available data to suggest an age-setting interaction. Therefore, the model results (and 95% CIs) of 4.9% (3.2-7.6), 3.2% (2.1-4.9), 1.5% (1.0-2.5) and 0.8% (0.5-1.3) for females aged <20 years, 20-24 years, 25-29 years and 30+ years respectively, are slight overestimates for those aged under 25 years, and slight underestimates for those aged over 25 years compared to the Natsal 2000 data (3.8% (1.0-9.5), 2.7% (1.1-5.5), 2.2% (0.9-4.5) and 0.9% (0.4-1.6) in the respective age groups). However, the 95% confidence estimates from the

Natsal 2000 raw data are very wide and overlapping with the 95% CI from the model. The crude prevalence estimates by setting for just those studies included in the mixed effects model (Table 3.5) were similar to the estimates from this literature review of all female studies in certain settings: population-based, youth clinics, TOP and antenatal clinics, but slightly higher for GP surgeries, FPC and GUM clinics (Appendix 2). Therefore, excluding studies with incomplete data appeared to slightly affect only certain estimates, but not all.

Table 3.4 – Crude and adjusted odds ratios [OR] and 95% CI for the single and multi variable logistic regression models, for women only.

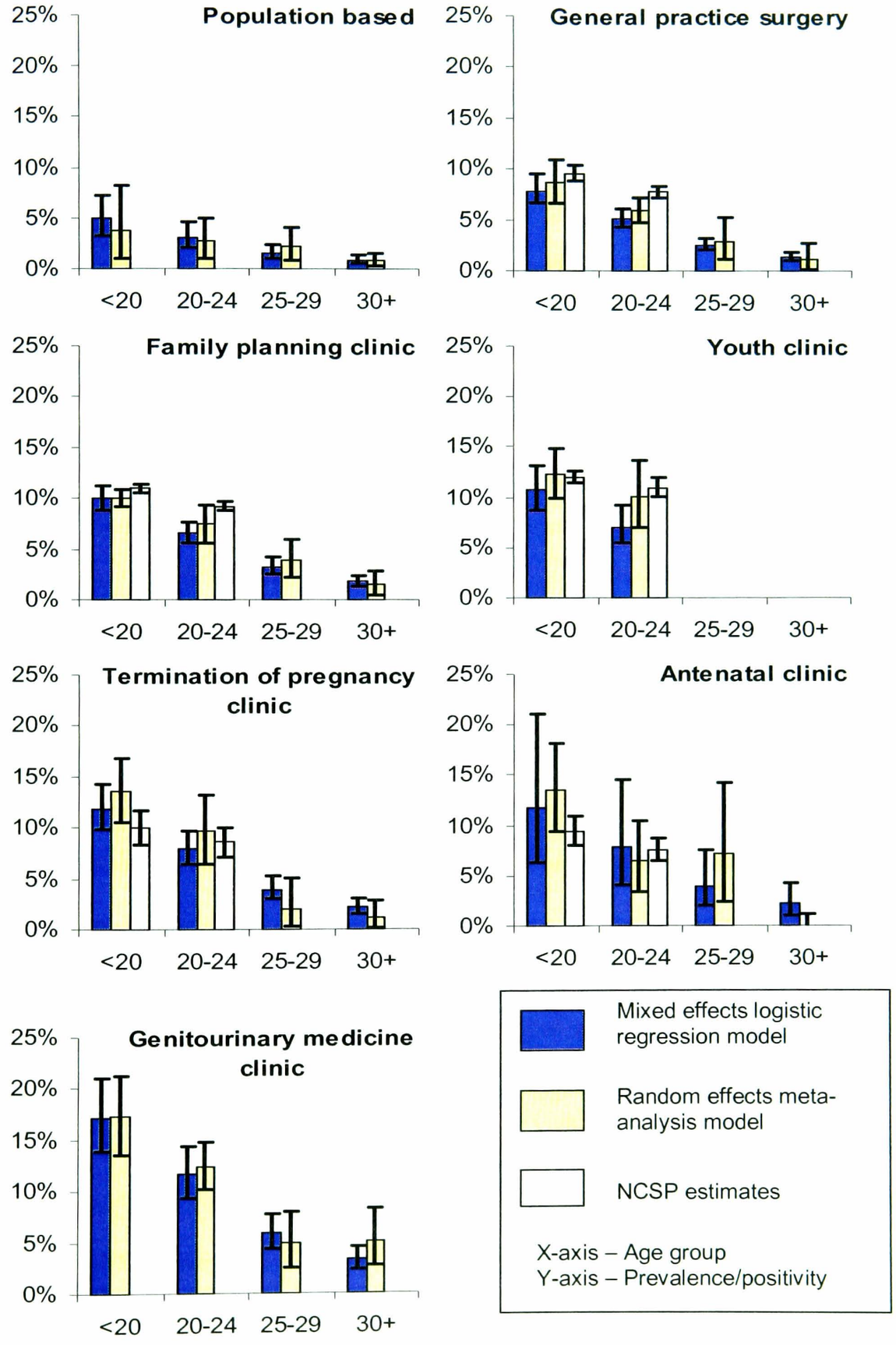
		Crude (Single variable)			Adjusted (Multi variable)		
	Risk Factor	Estimated OR	95% CI	p value	Estimated OR	95% CI	p value
Age group	<20	Reference		<0.0001	Reference		<0.0001
	20-24	0.57	0.47 – 0.67		0.62	0.52 – 0.75	
	25-29	0.28	0.22 – 0.35		0.30	0.23 – 0.39	
	30+	0.14	0.11 – 0.19		0.16	0.12 – 0.22	
Setting	GP/community clinic	Reference		<0.0001	Reference		0.002
	FPC	1.24	0.92 – 1.67		1.27	1.00 – 1.62	
	TOP clinic	1.61	1.23 – 2.10		1.60	0.20 – 2.14	
	GUM clinic	3.08	2.37 – 4.00		2.39	0.72 – 3.33	
	Population based	0.56	0.26 – 1.19		0.60	0.37 – 0.95	
	Youth clinic	2.72	1.92 – 3.84		1.37	0.95 – 1.98	
	Antenatal clinic	1.06	0.58 – 1.94		1.64	0.79 – 3.43	
Date	Before 1985	Reference		<0.0001	NE		0.09
	1985-1989	0.42	0.33 – 0.54		Reference		
	1990-1994	0.30	0.24 – 0.36		0.88	0.40 – 1.96	
	1995-1999	0.25	0.20 – 0.30		0.78	0.43 – 1.40	
	After 2000	0.32	0.27 – 0.37		1.27	0.62 – 2.59	
Diagnostic test	Nucleic acid amplification	Reference		0.04	Reference		0.5
	Antigen	1.06	0.83 – 1.34		1.09	0.82 – 1.45	
	Culture	1.57	1.08 – 2.29		NE		
Specimen tested	Urine	Reference		0.0005	Reference		0.09
	Cervical/endocervical swab	0.86	0.78 – 0.93		1.37	0.96 – 1.95	

Note: The multivariate logistic regression model contained age and setting as the two predictors of prevalence; NE: Not estimable as either all age or setting missing in category.

Table 3.5 – Prevalence estimate (%, 95% CI) from the mixed effects logistic regression and random effects meta-analysis models, for women only, by age group and setting, and the crude overall mean and references from data included in each setting.

Setting	Mixed effects logistic regression model Age group				Random effects meta-analysis model Age group				Crude overall mean	No. ind. in model	Reference
	<20 years	20-24 years	25-29 years	30+ years	<20 years	20-24 years	25-29 years	30+ years			
Population-based	4.8 3.2 - 7.6	3.2 2.1 - 4.9	1.5 1.0 - 2.5	0.8 0.5 - 1.3	3.8 1.0 - 8.3	2.7 1.1 - 5.0	2.2 0.9 - 4.1	0.9 0.4 - 1.5	1.6 1.0 - 2.3	1,725	(Fenton KA, *et al.*, 2001b)
GP surgery	8.1 6.5 - 9.9	5.2 4.3 - 6.3	2.6 2.0 - 3.3	1.4 1.0 - 1.9	8.6 6.6 - 10.9	5.9 4.7 - 7.2	2.9 1.2 - 5.2	1.1 0.2 - 2.7	7.1 6.7 -7.6	13,207	(Grun L, *et al.*, 1997; Pierpoint T, *et al.*, 2000; Clay J, *et al.*, 1996; Hopwood J, *et al.*, 1995; Oakeshott P, *et al.*, 1998; Santer M, *et al.*, 2000; Pimenta JM, *et al.*, 2003a)
FPC	10.0 8.7 - 11.5	6.5 5.5 - 7.8	3.2 2.5 - 4.2	1.8 1.3 - 2.4	10.0 9.1 - 10.9	7.4 5.7 - 9.4	3.8 2.2 - 6.0	1.5 0.5 - 2.8	8.1 7.6 - 8.7	9,512	(Sprague D, *et al.*, 1990; Simms I, *et al.*, 2000a; Murty J, 1996; Macmillan S, *et al.*, 2000; Harvey J, *et al.*, 2000; Kilcoin A, 2001; Pimenta JM, *et al.*, 2003a)
Youth clinic	10.7 8.3 - 13.8	7.0 5.1 - 9.6	-	-	12.3 10.0 - 14.9	10.1 7.0 - 13.6	-	-	12.2 10.8 - 13.7	1,996	(James NJ, *et al.*, 1999; Pimenta JM, *et al.*, 2003a)
Antenatal clinic	12.6 6.4 - 23.2	8.3 4.2 - 15.7	4.1 2.0 - 8.2	2.2 1.1 - 4.6	13.5 9.5 - 19.1	6.5 3.5 - 10.4	7.2 2.4 - 14.2	0.0 0.0 - 1.2	8.5 6.6 - 10.6	803	(Macmillan S, *et al.*, 2000; Pimenta JM, *et al.*, 2003a)
TOP clinic	12.3 9.8 - 15.3	8.1 6.4 - 10.1	4.0 3.0 - 5.4	2.2 1.6 - 3.1	13.6 10.6 - 16.8	9.7 6.5 - 13.3	2.0 0.3 - 5.1	1.2 0.2 - 2.9	8.5 7.4 - 9.8	2,114	(Hopwood J, *et al.*, 1998; Uthayakumar S, *et al.*, 2000; Macmillan S, *et al.*, 2000; Hopwood J, *et al.*, 2001; Pimenta JM, *et al.*, 2003a)
GUM clinic	17.3 13.6 - 21.8	11.6 8.9 - 14.9	5.9 4.3 - 8.1	3.2 2.2 - 4.7	17.3 13.6 - 21.3	12.4 10.3 - 14.7	4.9 2.6 - 8.0	5.1 2.7 - 8.3	12.7 11.5 – 14.0	2,831	(Pimenta JM, *et al.*, 2003a; Crowley T, *et al.*, 1997; Radja N, *et al.*, 2001)

Figure 3.4 – Comparison of the estimated prevalence of chlamydia (95% CI bars) using the logistic regression mixed effects model and the meta-analysis random effects analysis, by setting and age group for women only. The positivity (95% CI bars) as estimated from the NCSP screening data (2005/2006) is also shown by age group and setting, for women only.



Note: Data from the NCSP by age group and setting for women having screening tests was kindly provided by Alireza Talebi (National Chlamydia Screening Programme)

3.5 Discussion

3.5.1 Review of findings

This was the first systematic review of CT prevalence in the UK. It revealed a large degree of heterogeneity in the sampling and testing methods used in CT prevalence studies. The logistic regression method gave insight into the most important variables predicting CT prevalence in these studies, and provided estimates of CT prevalence for women among different groups. The results highlighted the high prevalence in younger age groups and certain clinical settings, regardless of other factors, and also the few data available on the prevalence of CT in men.

Most factors investigated appeared to have little impact on overall prevalence estimates. Neither diagnostic test nor specimen was associated with the estimated prevalence in women. While high test sensitivity and specificity are important to minimise false positive and false negative test outcomes (Chapter 2.2.4), testing methodology did not appear to have a large impact on overall chlamydia prevalence estimated here. However, the test and specimen were intrinsically linked (NAAT on urine) within all studies, except for one, included in the regression analyses. Since this analysis was completed, a study published by Burckhardt *et al* (2006) explored the changes in prevalence estimates when a laboratory switched to NAAT testing from other methods. They found that the reported proportion of positive tests increased 50-60% when NAATs were introduced, which was not explained by other variables (age, sex, year of test, and test type) in a logistic regression analysis. The results in this chapter did not find the type of test to be associated with prevalence estimates, but as mentioned, this may be because of insufficient data to detect this. With the recommendation now to use only NAAT for CT screening tests (National Chlamydia Screening Programme, 2006), this may become a redundant argument in further analyses of data, as the heterogeneity among studies will be further reduced therefore making the data more comparable.

The majority of studies included in the analysis were conducted in health care settings. This is often the most practical and feasible way to obtain prevalence estimates because test acceptability is generally high among individuals presenting for other health related reasons, especially when offered a non-invasive urine test (Pimenta JM, *et al.*, 2003b), and testing is facilitated within the existing clinic infrastructure. Of the 30% of studies that reported the proportion of individuals that accepted CT testing, a higher proportion of individuals accepted testing in GP surgeries compared to population-based studies (crude mean of 82% [range 45% - 99%] and 46% [range 29% - 71%] respectively). This suggests that there may have been less participation bias in reported estimates from GP surgeries than in the general population surveys. However, it is unknown if the individuals who accepted testing were representative of individuals from those populations, and therefore the extent of any selection bias is unknown. Results from the ClaSS published since this study was completed indicated a low acceptance rate of about 30% for population-based postal screening (Macleod J, *et al.*, 2005b). Of those who did submit urine for testing, the prevalence for men and women aged under 25 years was 5.1%; (95% CI 4.0% - 6.3%) and 6.2%; (95% CI 5.2% - 7.8%), respectively (Macleod J, *et al.*, 2005b). Their results also indicated that those individuals who were harder to reach also had higher CT prevalence than those who accepted a screening test without further prompting. While the ClaSS study claimed to be population-based, individuals were recruited from GP registration lists which made it different from a study such as Natsal 2000, in which recruitment was not linked to a health care setting. Therefore it is difficult to draw conclusions on it being purely a population based study. Another recent study published by Senok *et al* (2005) explored the differences between opportunistic screening in a GP clinic and postal screening using GP registration lists to identify women aged 16-30 years, similar to the ClaSS methodology. They found that overall, postal screening had a higher uptake rate than opportunistic screening (21% vs. 48%), and that the proportion of positive tests identified from opportunistic screening was higher than that from postal screening (14% vs. 5%). This suggested that there might be a difference in the individuals who would accept screening through either method.

Additionally, they found that among a subset of women aged under 20 years, opportunistic screening had a higher uptake than postal screening (60% vs. 22%), although the sample size was small, so results should be interpreted cautiously. But it does suggest that groups recruited in health care settings may be different from those in the general population.

Notwithstanding, results from this analysis suggested that prevalence in health care settings may be, in general, higher than in population-based studies. This difference may be due to individuals at a higher risk of infection attending health care settings. For example, in the Chlamydia Pilot Study nearly 40% of females who accepted opportunistic screening listed contraception as the main reason for attendance at various health care settings (Pimenta JM, *et al.*, 2003b). This might represent a more sexually active population than those tested in non-health care settings. Sexual behaviour data was not available from most studies and was not included in the analyses, but might be a good marker of infection (Fenton KA, *et al.*, 2001b). One or more new sexual partners in the last year was associated with increased risk of CT infection (Fenton KA, *et al.*, 2001b). A recent study of CT incidence and re-infection in England found a high incidence of CT in GP clinics, FPCs and GUM clinics (5 – 10 per 100 person years) (LaMontagne DS, *et al.*, 2006). Young age, a new sexual partner and a previous CT infection were all associated with incidence, and acquiring a new partner and not treating current partners were associated with re-infection. Similarly, an analysis of data from the first year of screening found that setting, young age and two or more partners in the last year were associated with high CT prevalence in women (LaMontagne DS, *et al.*, 2004).

The presence of genital symptoms may be another reason for higher chlamydia prevalence among health care setting attendees. In the Chlamydia Pilot Study 8% of individuals tested listed genital tract symptoms as the primary reason for attending the clinic (Pimenta JM, *et al.*, 2003b). This information was not consistently reported among the studies identified in the literature search, and in those included in the regression model only four studies included the proportion of positive and negative individuals with symptoms (James NJ, *et al.*, 1999; Grun L, *et al.*, 1997; Hopwood J, *et al.*, 1995; Simms I, *et al.*, 2000a). However, this

information might be a potentially useful means of comparing the groups and may partly explain the differences in prevalence, especially in non-health care settings. Results from the NCSP in 2005/2006 suggest that roughly 5% of all tests were performed as diagnostic testing (Alireza Talebi, personal communication), most likely because the patient has symptoms which prompted treatment.

3.5.2 Implications of these results

Results from these models can help inform policy on CT screening. As screening is rolled out nationally to more health care sites across England (National Chlamydia Screening Programme, 2006; National Chlamydia Screening Steering Group., 2006), the results from this analysis strongly support the continued need for high coverage in younger age groups, across all health care settings. The prevalence among attenders screened in GP surgeries may be high, which is supported by NCSP results (National Chlamydia Screening Steering Group., 2006) (Table 2.3 and Figure 3.4). The GP surgery is the first point of contact with the health system for many individuals, with 60-70% of men and 75-90% of women aged under 35 years attending a GP surgery each year (Airey C, *et al.*, 1999; Salisbury C, *et al.*, 2006). Therefore, offering screening in GP surgeries may be an effective way of identifying and treating large numbers of CT positive individuals.

This review highlights the paucity of prevalence data in men (Table 3.3). When this analysis was done, there were very few published studies, generally with a small sample size, and not stratified by age. However, the available data suggest that the prevalence in men may be as high as that in women, although the peak in prevalence may occur at a later age (Figure 3.3) (Health Protection Agency, 2006a). Current NCSP data also indicate a high positivity among men aged under 25 years (National Chlamydia Screening Steering Group., 2006) (Table 2.3). The positivity is higher in those aged 20-24 than aged 16-19, in contrast to data from women, but similar to data from GUM clinics (Health Protection Agency, 2006a). In the past, infected men were mainly identified through PN of positive women, or by attending a

GUM clinic. However, it is possible to screen men in a variety of settings, and men comprised nearly 20% of all screens in 2005/2006 (National Chlamydia Screening Steering Group., 2006). Further studies on prevalence in men may help elucidate the burden of infection in this group.

3.5.3 Methodological issues and further research

The approach used allows the associations between predictors and prevalence to be explored. The estimations from this analysis were based purely on reported studies, and there may be some bias from the initial literature review from oversampling in certain populations. In particular, as with prevalence in men, there were few studies on CT prevalence from the general population.

The results from the meta-analysis were very similar to those of the logistic regression model, as would be expected. Unlike the meta-analysis techniques used for randomised controlled trials in which stringent inclusion criteria can be defined based on study methodology, it is difficult to do this with observational studies such as the ones presented here. Since the estimates obtained are from such studies, they may be prone to biases such as sampling or recruitment biases. While all studies reported on the test setting, other variables were often missing, and therefore contribute to uncertainty in the interpretation of results.

One of the implicit inclusion criteria for the final model was that a study must have extractable data for age group and setting. While much information was lacking, 19 studies (21% of the total identified in the systematic review) still had sufficient data to include them in the logistic regression model and meta-analysis. Including additional data in the model, i.e. from the NCSP including data from men or the general population, might make results more robust. Ideally, these would be from well-designed studies with specific information about the individuals tested (and those not tested), and information about age, screening methodology, presence of symptoms and sexual behaviour.

3.5.4 Update

Since this work was done in 2003, new data have been published on CT prevalence in the UK, and are broadly consistent with what is reported in this chapter (Table 3.6).

Table 3.6 – Studies published since July 2002, reporting chlamydia prevalence (and number tested) by gender, setting and age group.

Reference	**Gender**	**Setting**	**Age group**	**Total tested (Prevalence)**
Arnot *et al* (2006)	M	GUM	N/A	3155 (15%)
Baird *et al* (2002)	F & M	Youth/FPC	13-20	616 (12%)
Dixon *et al* (2002)	M	GUM	N/A	2952 (13%)
Harris (2005)	F	GP	16-24	81 (6%)
Kettle *et al* (2002)	F	Emergency contraception (in FPC)	<20 20-24 25-29 30+	79 (8%) 197 (8%) 187 (5%) 139 (1%)
Logan *et al* (2005)	F	Antenatal (miscarriage)	N/A	207 (4%)
Low *et al* (2003)	F & M	College students	16-20 21+	88 (10%) 21 (5%)
Macleod *et al* (2005b)	M F	Postal screening invitation (from GP registration lists)	16-24 (m) 16-24 (w)	1477 (5%) 2132 (6%)
McKay *et al* (2003)	M	Military intake	16-25	785 (10%)
McMillan *et al* (2006)	F	Antenatal, infertility & FPC	<25 25+	264 (9%) 681 (2%)
Menon-Johansson *et al* (2005)	M	Prison	18 (mean) 3.3 (SD)	108 (13%)
Norman *et al* (2004)	F	Antenatal TOP	<20 20-24 25-29 30+ <20 20-24 25-29 30+	256 (12%) 404 (4%) 435 (1%) 434 (1%) 182 (13%) 211 (11%) 171 (3%) 206 (3%)
Powell *et al* (2004)	M	Orthopaedic outpatient & university sports facilities	17-20 21-24 25-29 30-35	93 (6%) 154 (5%) 100 (8%) 46 (4%)
Senok *et al* (2005)	F	Postal invitation GP	16-30 16-30	59 (5%) 28 (14%)
Watson *et al* (2004)	F	GUM	14-46	131 (14%)

Note: M-males, F-females; other studies published include: Underhill *et al* (2003), these are a re-analysis of the Chlamydia Pilot Study and are already included in the analysis; Basarab *et al* (2002)- different laboratory tests for mainly symptomatic individuals; Lee *et al* (2004) – follow up of patients from the Chlamydia Pilot Study, not a prevalence study.

Results from the first three years of the NCSP roll-out (Department of Health, 2004b; LaMontagne DS, *et al.*, 2004; National Chlamydia Screening Steering Group., 2005; National Chlamydia Screening Steering Group., 2006) are also consistent with results in this chapter (Table 2.3). There is a high positivity in young women, and NCSP positivity estimates for women in 2005/2006 by setting and age group are comparable to that found in the analyses from this chapter (Figure 3.4). Analysing the NCSP core dataset for both men and women further may help explain about risk factors for infection and re-infection, and how screening and treatment changes the prevalence of CT.

3.6 Summary

There is a high prevalence of chlamydia in the UK, particularly in young adults and those attending health care settings. There were few data from specific populations such as men and the general population when this analysis was done, although new data from the NCSP suggest that the prevalence of infection is also high. Extracted data from the studies identified in the literature review were used in a statistical model to provide prevalence estimates that may then be used to inform CT screening strategies. The results can also be used in used to parameterise a model of sexual behaviour and CT infection (Chapter 5) and used to estimate the cost-effectiveness of screening (Chapter 6).

CHAPTER 4 - ESTIMATING THE COSTS OF A CHLAMYDIA SCREENING PROGRAMME IN ENGLAND

"SEX BUG TEST PLEA"

The Mirror, August 04, 2003

4.1 Aims

- To estimate the costs of a chlamydia screening programme including the cost per screening offer, cost per testing episode, and cost per positive episode;
- To explore which factors are most important to the costs.

4.2 Introduction

Evidence in Chapter 3 indicated a high CT prevalence in the UK and particularly among young women attending health care settings. Combined with results from the Chlamydia

Pilot Study that screening is acceptable and logistically feasible in a variety of settings (Pimenta JM, *et al.*, 2003b), screening appears to be quite favourable. To be considered for national implementation, it is necessary to estimate the likely costs of screening. This analysis was done after the Chlamydia Pilot Study but before screening was implemented nationally. The reasons for doing the analysis were to provide data for the cost-effectiveness analysis (Chapter 6) and to inform those involved in planning the NCSP. This chapter uses costs data directly from the Chlamydia Pilot Study, answers from a questionnaire from members of the Chlamydia Pilot Study team about their screening activities, and is supplemented with data from standard sources and the published literature.

4.3 Methods

4.3.1 Screening methodology

This analysis is based on the Chlamydia Pilot Study (full details in Pimenta *et al,* 2003a, 2003b, summarised in Chapter 2.3.5). This study will be referred to simply as "the pilot" in this chapter. Young women (16-24 years) were offered opportunistic screening in GUM clinics, FPCs, antenatal clinics, TOP clinics, youth clinics and GP surgeries. The study period was 1 September 1999 to 31 August 2000. Some men were also offered screening opportunistically at GUM and youth clinics, but these data are not included in this analysis.

If a woman accepted screening, a urine sample was requested and tested using two types of NAAT tests (Chapter 2.2.4). Ligase chain reaction (LCR) was used, which was confirmed by a second LCR test for positive and equivocal results and polymerase chain reaction (PCR) for any discrepant results. Negative and insufficient results were not retested, but given a final diagnosis. For a final diagnosis of positive, insufficient or equivocal, patients were notified and asked to return to speak to a health advisor about their results and follow-up. At this appointment, treatment was given (Azithromycin or Doxycycline; alternative regimen

used for pregnant women), and the patients were asked to notify any sexual partners from the past 3 months. PN was attempted for all reported partners, by contacting them (either by the patient or the health advisor), asking the partner(s) to attend, giving partners presumptive treatment and requesting a urine sample for LCR testing. A few partners were tested using other methods (n=20) and were excluded. For the female patients, a test of cure was offered 4 weeks after treatment completion (excluded in the model, as there were problems with data interpretation and a test of cure is not recommended in the current management guidelines).

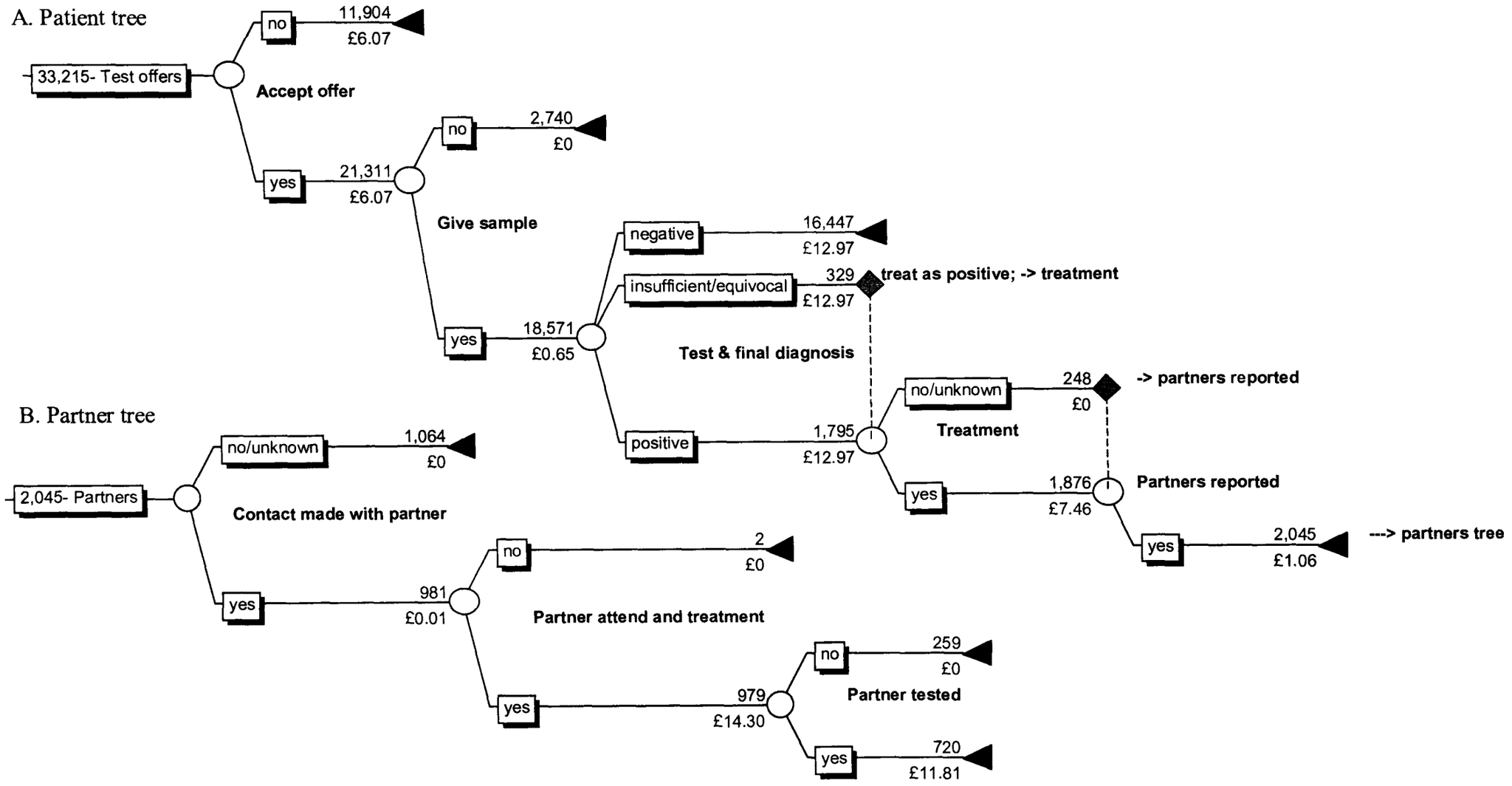
4.3.2 Analytical model

Decision trees (Precision Tree, @Risk, Palisade software) were selected to model the flow of individuals and their partners from initial test offer to PN (Figure 4.1). This framework was chosen because it was simple, flexible and effective and allowed the actual screening pathway to be visualised and analysed. The number of people who flowed through each node of the decision tree are shown above each branch, and the average cost of that branch (per person) is shown below. Many of the nodes had the same outcomes or next steps; these were linked in the model by a dotted line. For example, all women who had a final diagnosis of positive, equivocal or insufficient went to the treatment node. Triangles indicate a branch termination, and dotted lines flow to another node. Each node of the model returns the expected value of the model at that point.

4.3.3 Patient data extraction

The screening protocol in the pilot involved various health care settings. For example, the place where a woman was initially offered a test may not have been the same as where treatment was offered or PN done. The number of individuals flowing through each step of the tree was combined across health care settings. Data were also combined from both screening sites (Portsmouth and Wirral), giving an average estimate of the value of such a screening strategy.

Figure 4.1 – Schematic diagram of the screening tree used in the analysis; A. patient tree, B. partner tree.



4.3.4 Costs

This study aimed to estimate the direct costs paid for by the screening programme (and funded by their budget) and also the wider NHS health care costs. Incorporating both was thought to estimate the true costs of a CT screening programme, by accounting for the wider health care costs (but excluding the social costs and costs to the patient). Direct costs were taken from preliminary invoiced expense forms for the pilot study (supplied by the Department of Health, Economics and Operational Research Division). Additional costs to the health care system included the costs of personnel directly involved in selecting, recruiting and screening individuals and in treating CT positives (receptionists, GPs, practice nurses, GUM consultants), and health advisors and administrators who ran the screening programme and managed positive patients.

The planning and set-up costs of the screening programme were included, based on the pilot invoiced expenses. Costs associated with the research side of the pilot screening programme were excluded from the analysis. For example, personnel costs for analysis relating to the study evaluation were not included since the pilot was a research study to evaluate the feasibility and effectiveness of CT screening, and many of these costs would not be necessary if screening were normalised as part of a national screening programme. Recruitment of staff and laboratory upgrade costs (from EIA to NAAT testing) were also excluded.

In the pilot, a fee was paid to the clinicians for each CT test initiated. However, this cost was excluded from the analysis, as it was unlikely to occur in a national screening programme. Instead, the cost of their time was estimated by the cost of a consultation with a health care clinician to offer screening to a potential patient (see below).

All costs were adjusted to reflect 2001 prices (£ sterling), using the Hospital & Community Health Services inflation indices for either prices or pay (Table 4.1) (Netten A, *et al.*, 2002).

Table 4.1 – Inflation rate for pay or prices

	Pay	Prices
Inflation rate (1999-2000)	7.1%	-0.3%
Inflation rate (2000-2001)	4.0%	0.1%

Reference: Netten *et al* (2002)

Salaries were adjusted using the pay inflation rate, and all other goods took the prices rate. The adjusted costs included all overhead costs and some of the unit costs (noted in Table 4.2 and Table 4.3).

4.3.4.1. Overheads

There was an overhead fixed cost for the screening infrastructure, personnel and running the programme. These costs were taken from the pilot invoiced expense reports and included one-off and recurring costs.

While the patient flow data was taken over a 12-month period, the screening study and associated costs were incurred roughly over two years. Therefore, the total costs were annualised to allow for comparison to the study period data. One-off costs, including refrigerators, computers and office furnishings, were assigned an estimated lifespan of five years, and an annual cost per item was estimated (Drummond M, *et al.*, 1997) using a discount rate of 3.5% (National Institute for Clinical Excellence, 2004). Only one of the sites supplied these one-off costs, so these total annualised costs were doubled to account for both sites. The personnel (i.e., administrators, screening coordinator, etc.) and running (i.e., telephones, travel/transport, etc.) overhead costs from both the Portsmouth and Wirral sites (including set-up and pilot costs) were halved to estimate an annual cost per item. An overhead cost per patient screening episode was estimated from the total overhead costs.

Table 4.2 – Total annual costs based on invoiced expenses from the pilot study.

Item	Cost (£)*
Total personnel overheads	***36,974***
Programme administrator	11,138
Consultant coordinator	14,362
Administration & clerical	11,474
Total capital overheads	***17,164***
Refrigerators	4,421
Computer & Printers	4,851
Office furnishings	2,621
Accommodation: Rent/Alterations	5,271
Total running overheads	***22,329***
Travel & transportation	1,244
Telephone & fax	323
Stationery & postage	12,178
Advertising	671
Other costs	7,913

Source: Preliminary cost data provided by the Department of Health, Economics and Operational Research Division, and data from the questionnaire on time and patient flow.
*Costs converted to 2001 £UK.

4.3.4.2. Costs at each branch of the decision tree

Variable costs were added at each branch of the decision tree (Table 4.3). To estimate these, costs of materials and personnel were summed (derived from the mean Portsmouth and Wirral costs when data were available).

Table 4.3 – Total variable costs at each node of the decision tree and their constituent inputs.

Item	Baseline	Min.	Max.	Distrib.*	Unit	Source†	Comment
Overall: personnel							
Receptionist	0.13			Fixed	£/Minute	Assumption	
General practitioner	1.01			Fixed	£/Minute‡	(Netten A, *et al.*, 2002)	
Practice nurse/Health advisor§	0.42			Fixed	£/Minute‡	(Netten A, *et al.*, 2002; Centre for Innovation in Primary Care, 1999)	
Medical genitourinary medicine Consultant	1.40			Fixed	£/Minute‡	(Netten A, *et al.*, 2002; Centre for Innovation in Primary Care, 1999)	
1. Accepting the test	**3.77**	**1.50**	**5.42**		**£/Episode**		
Information leaflet	0.31			Fixed	£/Item	A	Cost converted to 2001 £UK
Receptionist time	1.8	0.5	3	Uniform	Minute	A	Screening selection & invitation
General practitioner/nurse time to discuss screening	4.5	2	7	Triangular	Minute	A	Depends on setting/clinician
% general practitioner time compared to nurse time	50	0	100	Uniform	%	Assumption	
2. Giving a sample	**0.65**				**£/Episode**		
Sample container	0.50			Fixed	£/Item	B	Cost converted to 2001 £UK
Request form	0.15			Fixed	£/Item	B	Cost converted to 2001 £UK
3. Testing & final diagnosis	**12.97**	**10.71**	**15.25**		**£/Episode**		**Cost converted to 2001 £UK**
LCR test- materials and personnel	11.81	10.49	13.14	Uniform	£/Item	B	Average of both sites, cost converted to 2001 £UK
Health advisor time to notify patient	2.8	0.5	5	Uniform	Minute	A	

Item	Baseline	Min.	Max.	Distrib.§	Unit	Source†	Comment
4. Treatment	**7.46**				**£/Episode**		
Azithromycin	7.33			Fixed	£/Treatment	C	Recommended dosage
Doxycycline	4.98			Fixed	£/Treatment	C	Recommended dosage
Health advisor time for treatment	5			Fixed	Minute	A	PN not included
% receiving Azithromycin compared to Doxycycline	15.6	0	100	Triangular	%	D	
5. Partners reported	**1.06**	**0.85**	**1.27**		**£/Episode**		
Health advisor time for eliciting partner information	2.5	2	3	Uniform	Minute	A	
6. Partners contacted	**0.01**	**0.00**	**0.13**		**£/Partner episode**		
Health advisor time to contact partner	1	0	10	Triangular	Minute	A	
% partners contacted by health advisor compared to patient contacted	3			Fixed	%	D	
7. Partner attendance and treatment	**14.30**	**7.16**	**10.74**		**£/Partner episode**		
Time for partner clinic visit	12.5	10	15	Uniform	Minute	A	
% partners seen by health advisor compared to genitourinary medicine consultant	70	40	100	Uniform	%	Assumption	
8. Partner tested	**11.81**	**10.49**	**13.14**	**Uniform**	**£/Partner episode**	**B**	**See #3 above.**

Note: * Distributions used in the sensitivity analysis. Uniform distributions were used to represent a large degree of uncertainty (a randomly chosen value over the range); triangular distributions were used when the most likely value was known (the value drawn for each simulation was more likely to be closer to the mean value). † Legend: A - data from interview with primary research nurses in Portsmouth and Wirral; B- preliminary pilot expenses provided by the Department of Health, Economics and Operational Research Division; C- British Medical Association and the Royal Pharmaceutical Society of Great Britain (2003), D-pilot database. ‡ Patient related minute § Mid-scale grade F nurse.

Personnel costs (Table 4.4) were derived from the estimated salary of a typical health care worker who would see a patient or partner (receptionists, GPs, practice nurses/health advisors and GUM consultants). The total cost included any qualification costs, ongoing training and other additional costs, summed to get an overhead cost, to estimate the actual opportunity costs (Netten A, *et al.*, 2002; Centre for Innovation in Primary Care, 1999). However, the costs of home visits or travel were excluded in the adjusted calculations for general practitioners and practice nurses, and the cost of other activities was excluded from GUM consultants.

In the pilot, women were screened at various clinical settings and would have spoken to various health care personnel. It was assumed that the salary of a practice nurse or health advisor (both assumed to be a Grade F nurse in the NHS pay scale (Netten A, *et al.*, 2002)) would give a lower cost estimate, and that of a GP clinician an upper estimate. The relative involvement of a nurse/GP clinician was assumed to be 50%, but was allowed to vary in the sensitivity analysis. These annual costs were used to derive the cost per patient related minute (cost per minute for receptionist), using data on the average number of weeks worked per year, and the average number of hours per week (Table 4.4, Netten *et al* 2002).

These data were then combined with estimates of the time spent on different screening and related activities. To obtain this, a questionnaire was sent to the two primary research nurses involved in the pilot study in both sites, asking about the time spent on specific activities during the screening process (Figure 4.2). These estimates were not directly measured while the pilot was conducted, and therefore are based on retrospective accounts. The baseline estimates represented an average when data from both sites were available.

The total cost of a patient (or partner) flowing through various parts of the tree (with different outcomes) was simply the sum of the branch costs through which she or he flowed. These included the cost per screening offer, cost per testing episode and cost per positive screen. Costs were estimated both with and without the associated partner costs.

Table 4.4 – Salary adjustments for personnel costs.

Activity	General Practitioner[2]		GP surgery Practice Nurse[2]		Genitourinary Medicine Medical Consultant[2]		Ancillary Staff (GP Receptionist)[2]	
	% time spent in activity	Adjusted annual cost/ activity (£)	% time spent in activity	Adjusted annual cost/ activity (£)	% time spent in activity	Adjusted annual cost/ activity (£)	% time spent in activity	Adjusted annual cost/ activity (£)
Surgery consultation[1,2]	44%	42,495	54%	15,577	69%	79,011	-	-
Home visit/travel[1,2]	10%	9,658	5%	1,442	n/a	-	-	-
Consultation linked activity[1,2]	21%	20,282	25%	7,212	n/a	-	64%	8,124
Other patient linked activity[1,2]	8%	7,726	-	-	n/a	-	8%	1,016
Other activity[1,2]	17%	16,419	16%	4,616	31%	35,497	28%	3,554
Overhead[2]	-	16,875	-	8,655	-	-	-	-
Total cost		**113,455**		**37,502**		**114,508**		**12,694**
	Crude	**Adjusted***	**Crude**	**Adjusted***	**Crude**	**Adjusted***		
Number of worked weeks/year[2]	46.5	41.9	42.0	39.9	41.0	28.3	-	42.0
Number of worked hours/week[2]	44.7	40.2	37.0	35.2	48.2	33.3	-	37.5
Cost/patient related hour	£54.58	£60.65	£24.13	£25.40	£57.94	£83.98	-	£8.06
Cost/patient related minute	£0.91	£1.01	£0.40	£0.42	£0.97	£1.40	-	£0.13

Note: 1- Centre for Innovation in Primary Care (1999); 2- Netten *et al* (2002); *Adjusted to exclude the cost of home visit and travel for general practitioners and GP practice nurses, and also the other activity costs for GUM consultation.

Figure 4.2 – Questionnaire for the two primary research nurses in the screening pilot.

The time and cost of chlamydia screening

The purpose of these questions is to understand the different elements involved in chlamydia screening, and the people involved at various steps. We need this information to understand and estimate the costs associated with a screening programme. There may have been different ways of screening and people involved in different sites: we are looking for a range, and also the average (if possible). If a question (or part of a question) is not applicable, please write X in the space provided, as this information is also important to us.

Personnel costs

1) Does a receptionist invite a patient to be screened and give information? How much time is spent on that?

2) Does a health care worker discuss chlamydia screening with the patient?
   a) Which clinician is responsible for answering these questions (i.e., consultant, nurse, health advisor)?
   b) How much time is spent on it?

3) How are patients notified of their chlamydia test results (phone call, letter, etc)?
   a) How long is spent doing this?
   b) How is treatment given (clinic visit or is a prescription phoned in)?
   c) Who gives treatment?
   d) How long is spent on this?

4) How is partner notification done, and when (at time of clinic visit for test results, separate visit, etc)?
   a) Who does partner notification? (health advisor, GP, consultant)
   b) How long is spent on this?

5) Once the partner is contacted, is the partner asked to go for chlamydia screening?
   a) Where is the partner asked to go (GUM clinic, chlamydia office, etc)?
   b) Is it just for a chlamydia test, or a full STI screen?
   c) Who sees the partner for their test (consultant, health advisor, etc)?

6) How is the test of cure done (specific appointment for test of cure, drop off urine)?
   a) How long does this visit take?
   b) Who sees the patient for this visit?

Additional questions about the pilot cost

7) What was the cost of the promotional material for the pilot? (i.e., pamphlet, cards, posters, etc).

8) Are there personnel training costs for the chlamydia screening?
   a) How much are they?
   b) Is it a one-off cost, or does it happen more than once (and how often)?

9) Are there any additional activities (and their costs) related to chlamydia screening? What are they?

4.3.5 Sensitivity analyses

Sensitivity analyses were done to assess which costs and patient flow values were most important to the outcomes, and to explore the range of possible outcomes (given some parameter uncertainty) for this screening programme. The costs were variable and depended on the personnel involved in counselling and testing (i.e., whether a GP, health advisor or GUM consultant discussed screening with a patient), the cost of the LCR test (which often varied between laboratories), and the numbers of patients and their partners who flowed through the screening and partner decision trees.

Parameter values were drawn from specified distributions. The patient flow through the model was based on data from the pilot and was binomially distributed (proportion at each branch and the total number). The cost and the time components were mainly drawn from uniform distributions to represent a large degree of uncertainty (with any value randomly drawn from the range). Triangular distributions were assigned when there was considerable evidence that the mean closely approximated the baseline value. Then, the value used for each simulation was more likely to be closer to the mean. The baseline and maximum and minimum values used are given in Table 4.3 along with the assigned distribution.

The screening programme modelled here was just one of many possible options. Therefore, univariate sensitivity analyses were performed, varying model assumptions one at a time, and then results were compared to the baseline model outcomes. The input parameters were varied between the minimum and maximum values given in Table 4.3. Additionally, several other "what-if" scenarios were tested. This included a) changing the relative time a receptionist versus GP spent with a patient during screening recruitment (i.e. if a receptionist spends 3 minutes recruiting each patient then a GP spends only 3 minutes per patient; or no receptionist involvement then 10 minutes of GP time per patient), b) excluding the cost of a consultation with a clinician for non-test acceptors, c) varying the test acceptance rate from 34% to 94% (roughly a 50% change from the baseline of 64%), d) including a lower LCR

test cost estimate of £9, thought to be more realistic of the test costs for a larger scale screening programme, and e) changing the CT prevalence of tested patients. The prevalence ranged from 3% from estimates of 18-24 year old women in a population-based survey (Fenton KA, *et al.*, 2001b) (Chapter 2.3.5), to 18% from women aged 16-24 years attending GUM clinics (Pimenta JM, *et al.*, 2003a) (Chapter 3). The estimate for prevalence was driven by data from the decision analysis model, and assumed that positivity approximated prevalence (Webster DL, *et al.*, 1998). Prevalence was calculated: (positive + equivocal + insufficient tests)/total tests. The baseline prevalence was estimated to be 11.4%, which differed slightly from the estimated prevalence in the pilot study (Pimenta JM, *et al.*, 2003a).

A probabilistic multivariate sensitivity analysis was also performed using @risk (version 4.0.5, Palisade Corporation) running within Excel (version 2000, Microsoft). The analysis was run 1000 times, and at each simulation, parameter values were randomly drawn using Latin Hypercube Sampling (LHS). Parameter values were chosen by sampling from specified distributions. All parameters were sampled independently in each realisation, to explore a large parameter space efficiently. Each parameter was defined by either a minimum and maximum value (uniform distribution), or other distributions (i.e. normal distribution with a given mean and SD). This was repeated, once with the costs of partner notification included and once with these costs excluded. The parameters that varied were the input costs and times with ranges given in Table 4.3 and the distribution of individuals flowing through the tree (drawn from binomial distributions described above). Distributions for the outcome variables (cost/offer, cost/tested, cost/positive) were generated along with non-parametric 90% credibility intervals (CIs). That is, 90% of the model simulations fell within the upper and lower CI.

4.4 Results

4.4.1 Overall costs

The estimated overall annual cost of the opportunistic screening programme based on offering screening to 33,215 women aged 16-24 was £493,412. Of these costs, 80% (£394,429) were the variable patient costs, 5% (£22,515) were associated with partner management costs, and 15% (£76,468) were overhead costs for running the programme. Thirty-nine percent of the costs were personnel costs (including overheads and variable costs). About a third (37%) of the total costs was associated with the test kit cost (excluding testing personnel). These estimates were specific to the number of screening episodes examined in the analysis.

4.4.2 Cost per screening offer, testing episode and positive episode

The estimated average cost per test offer given the flow of individual testing episodes in the pilot was £14.88 (90% CI £10.34 - £18.56), which included all of the downstream costs of testing, notifying patients of results, and treatment and PN for positives. The average cost per testing episode was £21.83 (90% CI £18.16 - £24.20) including all downstream costs and PN. The estimated average cost per positive episode was £38.36 (90% CI £33.97 - £42.25), which included a proportion of positive episodes having treatment and PN. Comparisons of results with PN costs included and excluded are given in Table 4.5. If the partner tree was examined alone, the expected average cost per partner contact was £11.01 (90% CI £9.12 - £13.23), a weighted average of the costs of contact made with a proportion of partners, treatment and testing.

Table 4.5 – Average cost per offer, test and positive individual (90% CI).

	Cost/offer (£)	Cost/tested (£)	Cost/positive (£)
With PN	14.88 (10.34-18.56)	21.83 (18.16-24.20)	38.36 (33.97-42.25)
Without PN	14.18 (10.01-17.80)	20.57 (17.18-22.63)	27.35 (24.29-29.98)

Note: PN = partner notification and treatment

4.4.3 Sensitivity analyses

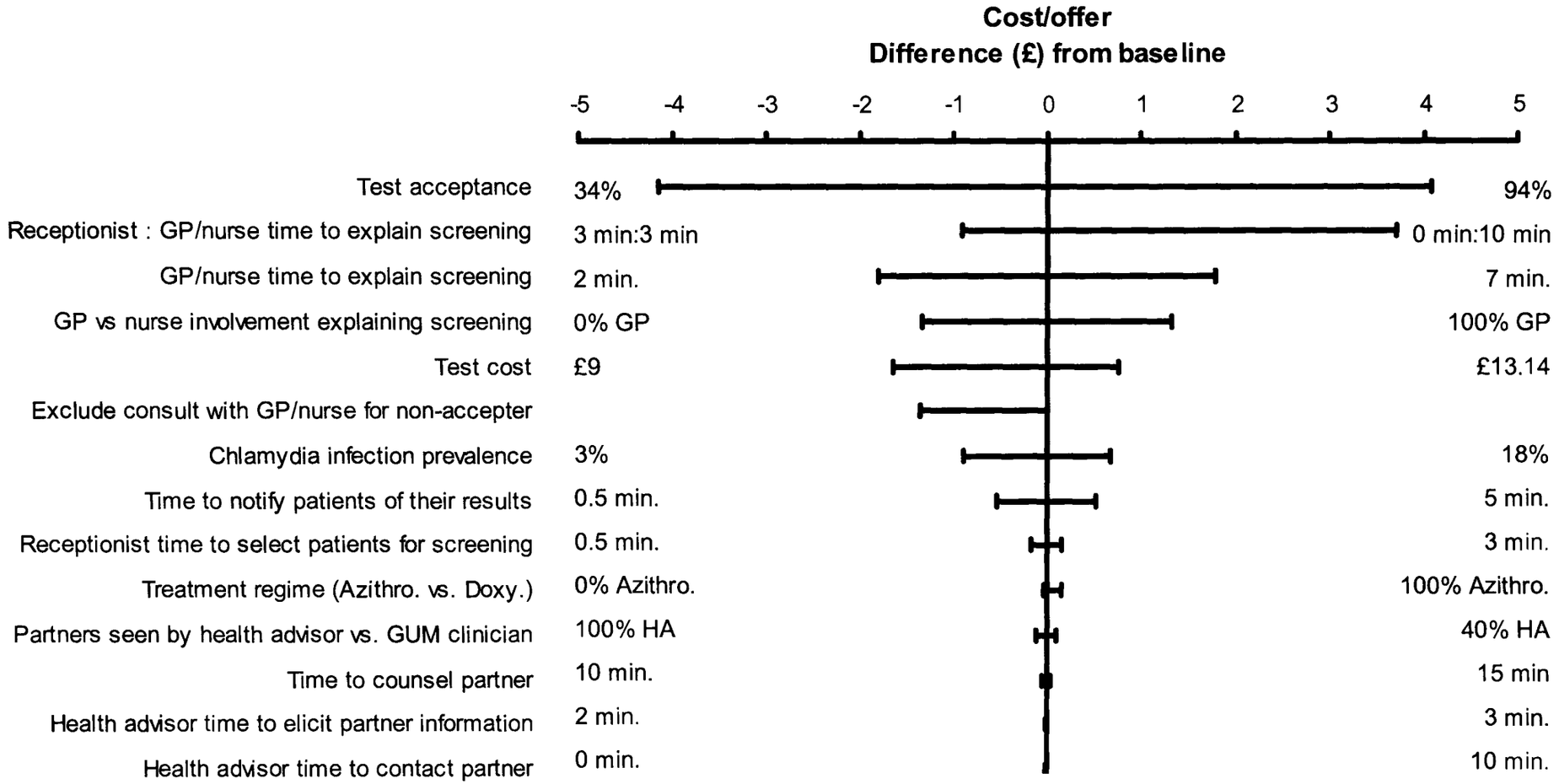
Results from the univariate analysis are given in Table 4.6 for the three outcomes. In the univariate sensitivity analysis, varying the proportion accepting the test offer had the greatest expected impact on the cost per screening offer compared to the baseline result (Figure 4.3). As the test acceptance increased, so did the cost per offer, and vice versa as the acceptance decreased (£18.98 for 94% acceptance; £10.74 for 34% acceptance). The relative role of the receptionist in explaining screening (compared to GP involvement) also had a large impact (25% difference from baseline) on the cost per offer. As the receptionist spent more time explaining screening and the clinicians spent less time (3 minutes each, compared to no receptionist involvement and 10 minutes of clinician time), the average cost per offer declined from £18.59 to £13.98. Similarly, as the time associated with primary care clinicians (doctors or nurses) explaining screening to patients decreased, so did the average cost per offer. Some results from the sensitivity analysis, such as the receptionist to clinician time for screening or the test cost, are not symmetrical. This is because the input parameters for the minimum and maximum values are not symmetrical around the baseline value.

Several of the parameters had a moderate impact on the outcomes (12% or less change from the baseline results). These included the relative involvement of GP versus practice nurse explaining screening to patients, excluding the health care worker consultation for non-test accepters, the test cost and the prevalence of CT infection. A 2-way analysis indicated that the prevalence had little impact on the cost per test offer compared to the proportion accepting a test (Figure 4.4).

Table 4.6 – Results from the univariate analysis for the cost per offer, cost per tested and cost per positive.

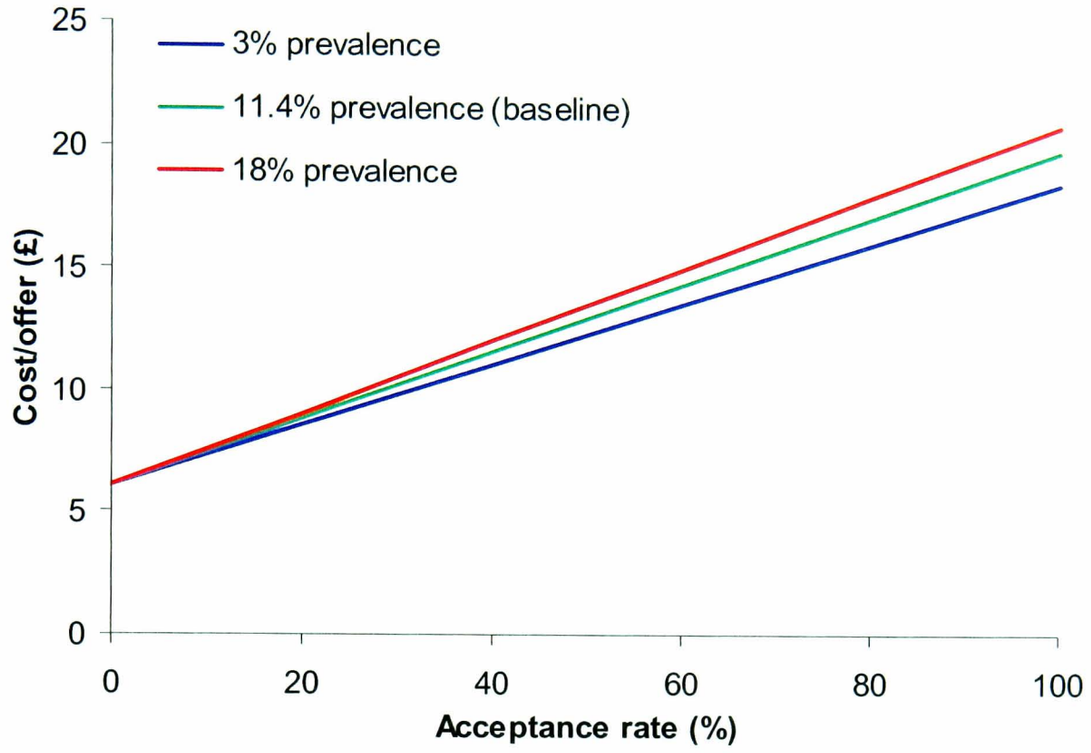
Parameter	Minimum				Maximum			
	Value	Cost/Offer (£)	Cost/tested (£)	Cost/positive (£)	Value	Cost/Offer (£)	Cost/tested (£)	Cost/positive (£)
Receptionist time to select patients for screening (minutes)	0.5	14.72	21.66	38.19	3	15.05	22.00	38.52
GP/nurse time to explain screening (minutes)	2	13.09	20.04	36.56	7	16.68	23.62	40.15
GP vs. nurse involvement explaining screening	0% GP	13.56	20.51	37.03	100% GP	16.21	23.15	39.68
Test cost	£9	13.25	18.91	34.56	£13.14	15.65	23.21	40.15
Time to notify patients of their results (minutes)	0.5	14.35	20.88	37.40	5	15.42	22.78	39.31
Treatment regime (Azithromycin vs. Doxycycline)	0% Azithro.	14.85	21.77	37.86	100% Azithro.	15.06	22.14	41.05
Health advisor time to elicit partner information (minutes)	2	14.87	21.81	38.14	3	14.90	21.86	38.57
Health advisor time to contact partner (minutes)	0	14.88	21.83	38.35	10	14.89	21.84	38.41
Partners seen by health advisor (HA) vs. GUM clinician	100% HA	14.77	21.63	36.60	40% HA	15.00	22.03	40.11
Time to counsel partner (minutes)	10	14.83	21.73	37.50	15	14.94	21.93	39.21
Receptionist : GP/nurse time to explain screening (minutes)	3:3	13.98	20.92	37.45	0:10	18.59	25.54	42.07
Exclude consult with GP/nurse for non-accepter		13.53	21.83	38.36				
Test acceptance	34%	10.74	21.83	38.36	94%	18.98	21.83	38.36
Chlamydia infection prevalence	3%	14.00	20.26	38.36	18%	15.57	23.06	38.36

Figure 4.3 – Results from the univariate sensitivity analysis of the cost per chlamydia screening offer.



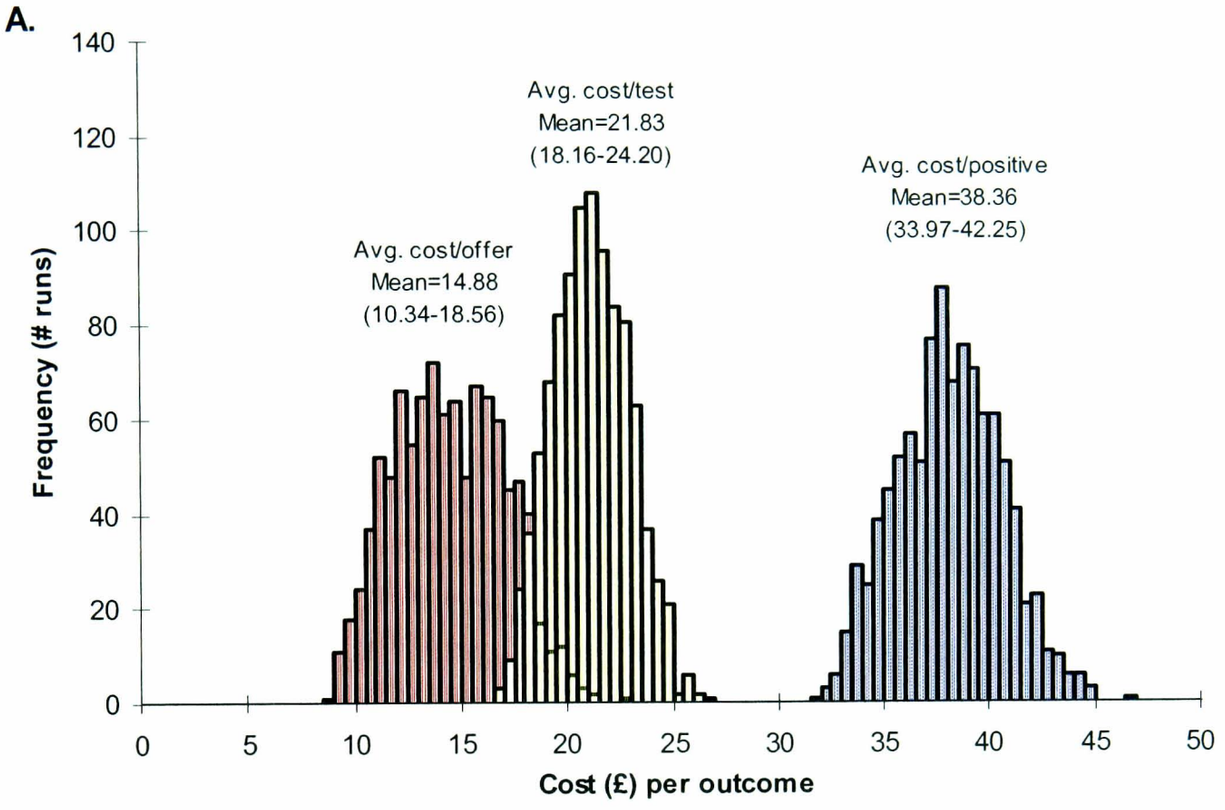
Note: The difference from the baseline cost/offer for various parameters tested individually from their minimum to maximum values. Negative differences denote a cost-savings from the baseline.

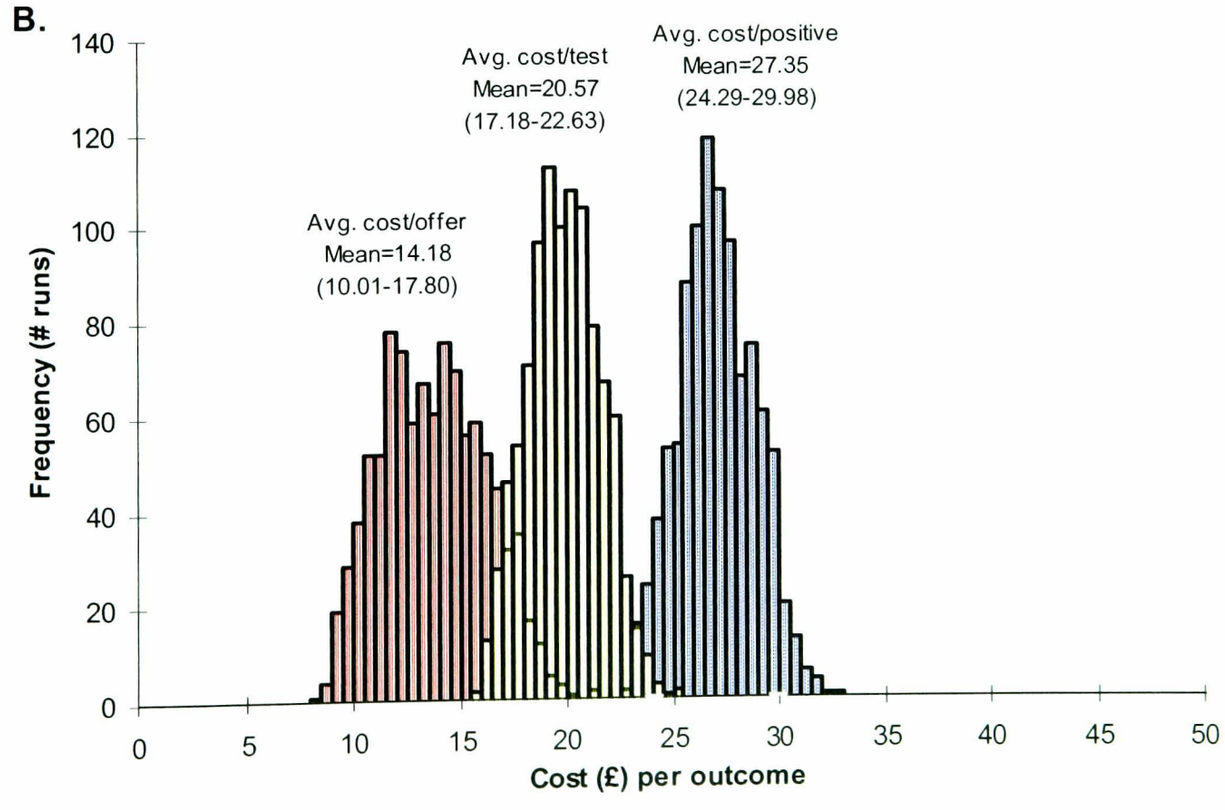
Figure 4.4 – Results from the 2-way sensitivity analysis of prevalence and acceptance rate; change in the cost (£) per offer.



The distribution of the results from the multivariate sensitivity analysis is shown in Figure 4.5. The parameters that had the most impact on the outcomes were (in order of importance): the proportion accepting a screening offer, the relative importance of GP versus nurse involvement in discussing screening and patient recruitment, the GP/nurse time to discuss screening before test acceptance, the total laboratory test cost, the time to notify patients of their results and the receptionist time spent selecting and recruiting patients.

Figure 4.5 – Frequency distribution of outcomes from the multivariate sensitivity analysis (90% CI); A: including partner management costs, B: excluding partner management costs.





4.5 Discussion

This analysis provided estimates of the average cost of screening from the health care perspective. The average cost per screening offer was about £15 including partner management. The cost per person tested was £7 more (£21 total), and an addition £16 per person positive (total about £38).

Varying the proportion that accepted a test had the largest effect on the cost per offer, since the participants largely drove the overall costs of the screening programme. While a high test acceptance rate accounts for higher costs, more infections may be identified if the correct population is tested, such as groups with high prevalence (Chapter 3). Increasing case finding will reduce transmission and may prevent sequelae and therefore may save money in the longer term. This will be addressed in the cost-effectiveness study (Chapter 6).

Since the laboratory test cost was important in the sensitivity analysis (more than one third of the total screening cost came from LCR testing), an accurate value for this variable will improve the estimated overall costs of screening. Variations in laboratory cost may be explained by differences in the LCR test kit cost and lab personnel, and some local variation was expected. There were also various laboratory options for the testing process including leasing or buying equipment and reagents that could be examined to minimise test costs and overall laboratory costs.

Partner notification contributed only 5% of the overall costs, yet it is an important part of a screening programme. While screening females will detect their infection, PN will identify male partners at risk who may not otherwise be tested, and treating partners may prevent both re-infection and onward transmission of chlamydia. The importance of including PN on the transmission dynamics of CT infection will be further examined in the next chapter and its impact on the cost-effectiveness of screening will be explored in Chapter 6. The costs of PN did not appear to make a difference to the cost per screening offer or cost per testing

episode if it was included or not (the CIs overlap, Table 4.5) although it does impact the cost per positive episode.

The infrastructure in place for screening may remain (i.e., the overheads), irrespective of the numbers being tested and treated, at least in the short–run. Roughly 25% of the overhead costs were one-off costs such as capital items (refrigerators, office furnishings, computer equipment) that would probably not be incurred again if more tests were done. These costs, however, may be necessary in new screening sites. Screening start-up costs may be used for these capital costs, unless they could be accommodated and streamlined within the current health care infrastructure. This could be explored in future analyses as data from the NCSP becomes available.

The multivariate and univariate sensitivity analyses highlighted areas of uncertainty in the data that influenced the costs of screening. For example, the time spent by clinicians explaining screening had a large impact on the costs because of its high variability and impact on all screening offers. Refining this and other estimates may give more precise estimates of the costs involved. However, some of the costs incurred in the pilot study, such as clinician time explaining screening, may not be incurred in future screening paradigms if patients are expected to self-select for screening, therefore, there would be minimal involvement of staff for recruitment. Time and motion studies could help better understand the flow of people through screening and the costs involved in each step. This information could be used to streamline the process and reduce costs within the existing infrastructure.

The decision tree could also be used to estimate the costs of similar screening programmes and may serve as a basis for comparison to other programmes in England and elsewhere. Sites in the NCSP could examine their costs using this structure since costs and resources will be dictated at a local level to a certain extent and therefore variation in the outcomes would be expected. The basic model may stay the same while the variable personnel and recurring costs may differ, as would the flow of people through the tree. The sensitivity

results highlighted which information should be collected to estimate the costs, such as the relative involvement of different clinicians, the time at each step of the programme, etc.

The costs in this analysis from the pilot study can be compared to that from ClaSS (Low N, *et al.*, 2004). Although a different screening paradigm was used by their study (Chapter 2.3.5), the resulting costs were similar. They reported what the cost per offer would be if they used the acceptance rate from this analysis (64%) instead of their test uptake of 34% (Robinson SM, *et al.*, 2007). Inflating our estimate to £2005 (Curtis L, *et al.*, 2006) give similar results: £17 for our analysis compared to £19 in theirs. The estimated cost of managing a positive individual and PN (regardless of whether or not treatment including PN was done by trained nurses in GP clinics or in GUM clinics), were £35 for the ClaSS study (Low N, *et al.*, 2006) and £45 in our study (inflated to £2005 for both studies).

The health provider perspective was assumed for this analysis. It included study costs and also those of other health care personnel involved in the screening process. However, other costs were not included, such as patient costs and the wider societal costs. For example, patients may incur costs in terms of time lost from work to travel to a clinic to receive treatment, and similar costs for a partner. The ClaSS study asked patients who were screened to complete a questionnaire about their costs incurred (Robinson SM, *et al.*, 2007). They included the costs of transportation to the clinic, treatment and PN for positives, opportunity costs of time lost from screening, treatment and leisure time. They estimated the total patient costs to be £6.82 (95% CI £5.48 to 10.22) per patient (£2005) (Robinson SM, *et al.*, 2007). These costs might be included in further cost analyses, particularly relating to the NCSP.

4.6 Summary

This analysis adds greatly to the current knowledge about the cost of CT screening. First, the model input data on the patient and partner flow are taken directly from the pilot study. Second, much of the cost data also come directly from the pilot invoiced expenses, so is thought to accurately represent the current costs of a screening programme. Third, the individual patient data allow direct estimates of the mean and variance in proportions at each node. Fourth, the uncertainty analyses provides information about the relative importance of different components of the screening model that may inform what information should be collected in future studies, and has already been used by the NCSP in their Core Requirements (National Chlamydia Screening Programme, 2006). The use of appropriate data, combined with the flexible model structure and ability to simulate alternative scenarios, provides a powerful tool to explore the average costs of screening, the uncertainty in these estimates, and the cost under different scenarios. Chapter 6 will use the cost results estimated here, combined with results from the dynamic model (Chapter 4) and a progression model for complications and costs, to assess the cost-effectiveness of different CT screening strategies.

CHAPTER 5 - PARAMETERISING A DYNAMIC MATHEMATICAL MODEL OF CHLAMYDIA TRANSMISSION

"UNSAFE SEX FUELLING INFECTION CRISIS"

news.bbc.co.uk, August 3, 2003

5.1 Aims

To use a dynamic individual-based chlamydia transmission model to estimate the parameters needed to accurately describe:

- The sexual behaviour of the UK population;
- The natural history of acute chlamydial infection;
- Intervention parameters.

5.2 Introduction

The NCSP is being rolled out nationally, in part because past evidence suggested that it was an effective and cost effective intervention (Chapters 2.4 and 2.5). Prevalence of CT is high (Chapter 3) and screening may be warranted to treat infection and prevent onward transmission. However the decision to implement the NCSP is based on work which needs updating. In order to assess the current value of screening from a wider perspective, theoretical modelling work is needed.

A model of CT screening must be able to track individuals 1) being screened and treated, 2) having their partners treated, and 3) being re-infected and re-screened over time (i.e. it must be individual-based). Secondly, the model needs to be able to evaluate the potential reduction in CT prevalence over time and the potential add-on benefit of fewer complications and associated costs of screening (i.e. accounted for by using a dynamic model). Lastly, it must simulate as closely as possible the sexual behaviour currently observed in the population and the observed epidemiology of infection, so that meaningful predictions about the likely impact of screening can be made (i.e. it must be well parameterised and fitted to appropriate data).

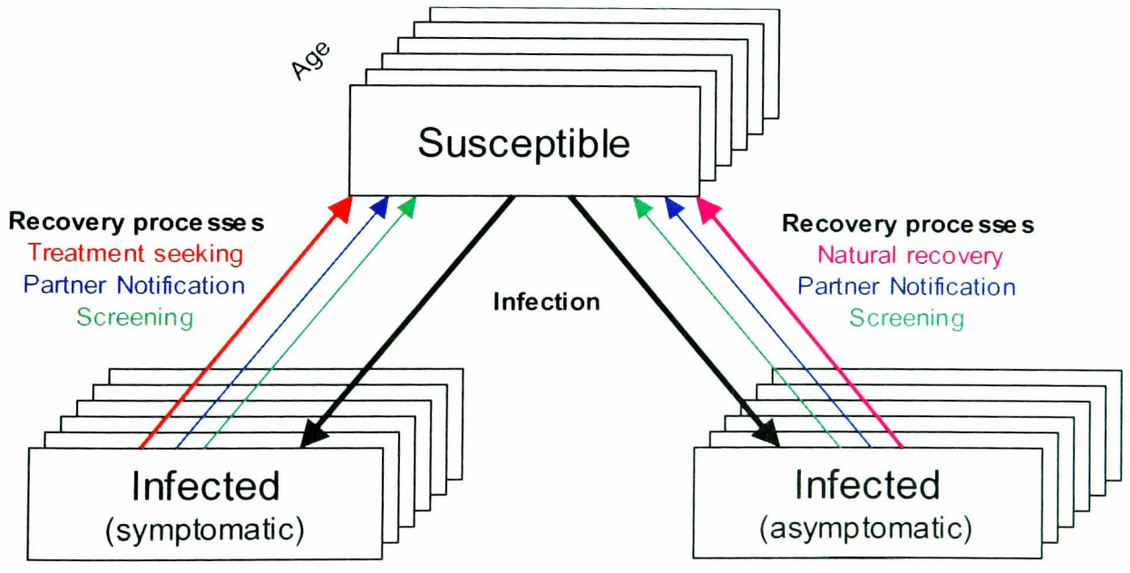
Several other studies have used complex dynamic models of sexual behaviour and CT transmission to estimate the impact of screening and its cost-effectiveness (Chapter 2.5.3). However, none of these studies used formal fitting techniques to estimate the input parameter values that simulated a population with realistic characteristics, rather they were calibrated to data. Methods exist to estimate how well the model results fit to the data, and formal fitting processes have been used for other infectious diseases models (Vickerman P, *et al.*, 2006; Melegaro A, *et al.*, 2004). This chapter will present a brief overview of the model, followed by separate sections on the behavioural and biological parameters and the methods of the fitting process and results for each.

5.3 Model overview

A model was developed by Turner *et al* (2006a), based on previous work by Ghani *et al* (1997). The model structure and details can be found in Appendix 1 and in Turner *et al* (2006a). A brief explanation will follow so that the fitting process can be understood.

The model simulated a population of heterosexual individuals defined by gender (20,000 men and 20,000 women), age (16 to 45 years old, to correlate with the Natsal 2000 data), and sexual activity preferences. Several probabilistic events occurred including demographic (population changes), sexual behaviour (forming and dissolving partnerships), chlamydial infection (infection and recovery) and interventions (screening and partner notification and treatment) (Figure 5.1). This chapter will concentrate on the parameterisation of the last three.

Figure 5.1 – Chlamydia infection and recovery processes.



The behavioural parameters in the model were fitted to data from Natsal 2000 (Chapter 2.3.5). An individual level extract of this dataset, including key survey questions was kindly

provided by Cath Mercer and others from the Natsal 2000 team. Data were analysed in Stata using the survey weights assigned based on individual characteristics (see Johnson *et al* (2001) for weighting methods). Data from individuals were excluded if they did not report at least one lifetime heterosexual partner.

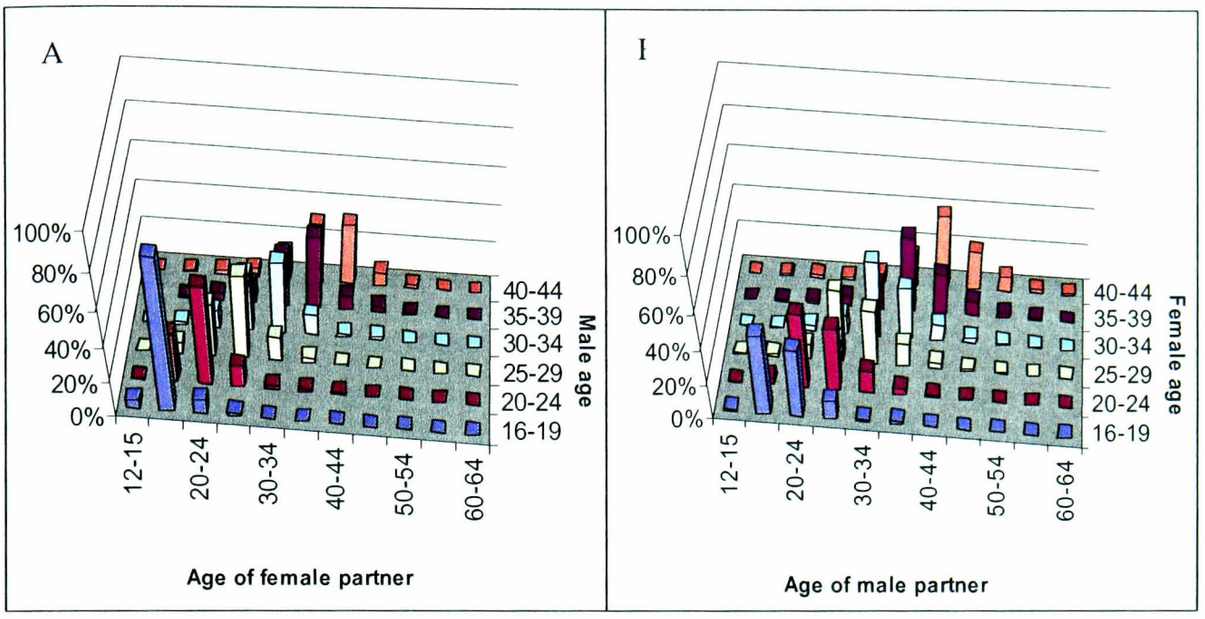
The biological parameters were fitted to the CT prevalence results by age group from Chapter 3 and Natsal 2000 data on the proportion of men and women reporting prior treatment for CT infection.

5.4 Sexual behaviour

5.4.1 Model structure: partnership formation and dissolution

The observed distribution of partnerships is an outcome of underlying processes that occur during partnership formation and dissolution. Sexual partnerships can form among individuals who do not currently have their desired number of partners. Two individuals are randomly selected from the population, and if they both desire a new partner, the probability of them forming a partnership is controlled by an age-mixing matrix based on their ages, which was derived from the Natsal 2000 data. Mixing is assortative with respect to age, i.e. individuals tend to choose partners in the same age group, although men tended to choose partners somewhat younger than themselves (Figure 5.2).

Figure 5.2 – Natsal 2000: Proportion of men (A) and women (B) of a given age group whose current or most recent partner is of a given age group.



If a partnership forms, one individual's preference for the partnership duration is chosen. A partnership cannot form if the two individuals are already in a partnership together or recently had been for a given time period, or if they had recently dissolved any partnership in a given period (age and sex dependent).

The probability of a partnership breaking at each time step is calculated by:

$$p(\text{breaking}) = 1 / (\text{partnership duration})$$

5.4.2 Individual sexual behaviour characteristics

Individuals in the model are assigned characteristics that influence their sexual behaviour and generate the overall observed sexual behaviour in the population. These are their desired number of partners and desired partnership duration, which are allowed to change with age. All individuals are assumed to be sexually active, desiring at least one current partner. Five

percent of individuals aged less than 35 years old were assumed to desire two concurrent partners.

Population level parameters estimated for the model determine each individual's sexual behaviour characteristics. There are many parameters, which make the model fitting process complicated. These parameters were the initial proportion of 16 year olds desiring short partnerships in the population (men/women), the initial average length of long partnerships (men/women), the proportion of individuals desiring short partnerships that change to desire long partnerships annually (men/women), the annual increase in desired partnership duration for long partnerships (men/women), and the mean and dispersion governing the negative binomially distributed gap period between partnerships (men/women and aged <20 years/20+ years).

Natsal 2000 collected data on the length of individuals' partnerships. However, this information is for current or most recent partners (i.e. it includes *ongoing* partnerships), and therefore the true duration of the partnership may be longer than that observed in the data. The desired partnership duration needed for the model is a *prospective* quality that individuals have, while the observed duration from the data is *retrospective*. Therefore the Natsal 2000 data on partnership length cannot be used directly as an input parameter. However, two general patterns can be observed from the data, which suggest the patterns needed in the model. First, a proportion of individuals reported short partnerships and this proportion decreased with age from 16 years (Figure 5.3). Since only the month in which partnerships began and ended was recorded in the data, short partnerships were assumed to last two weeks on average. Second, for individuals who desired long partnerships, the duration of partnership increased annually with age (Figure 5.4). Hence, the probability of a partnership breaking decreased with age.

Figure 5.3 – Natsal 2000: Proportion of men and women by age who reported their current or most recent partnership to be short (less than 1 month).

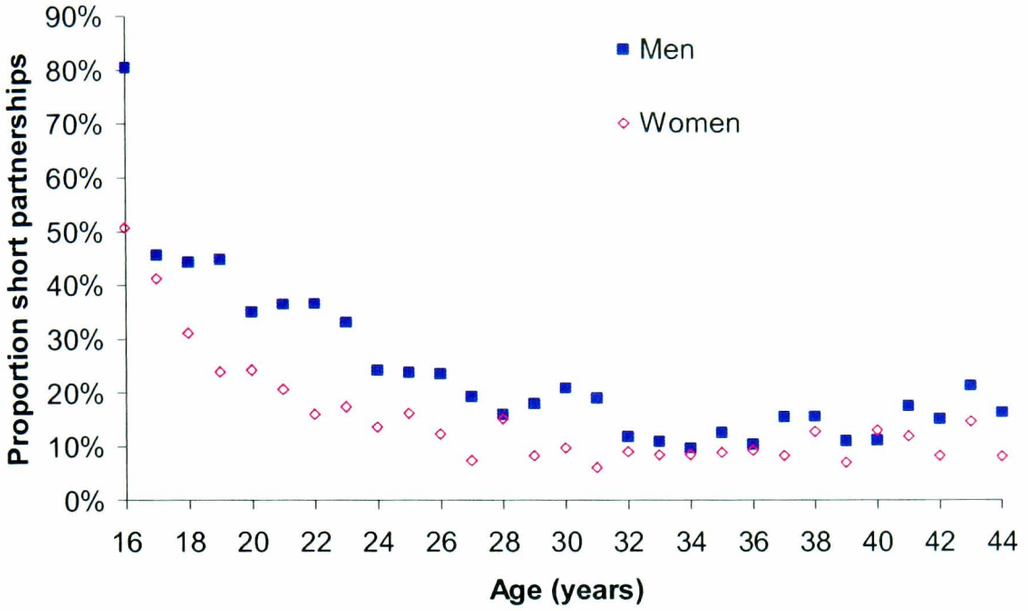
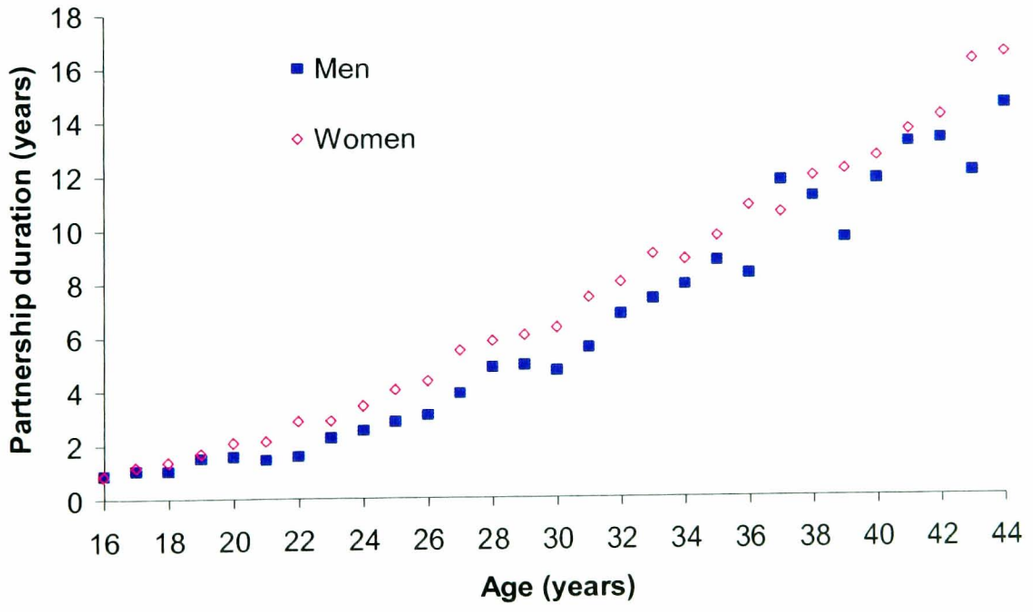


Figure 5.4 – Natsal 2000: Average duration of current or most recent partnerships that were long (lasting over one month), reported by men and women, by age.

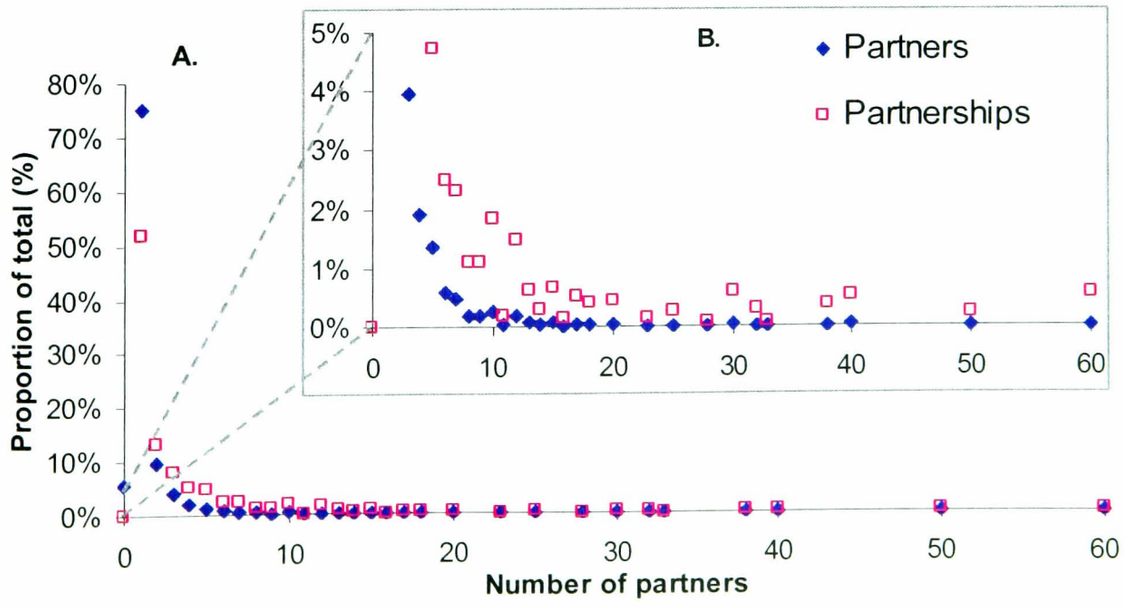


5.4.3 Sexual behavioural parameter estimation

The aim of this section is to find the input parameters that generate sexual behaviour in the model most similar to the observed Natsal 2000 data. The attribute thought to be most indicative of sexual behaviour relevant to the spread of CT was the total number of partners and partnerships in the last year and the number of new partners and partnerships in the last year, stratified by age and sex. These can be estimated from Natsal 2000 and extracted from the model, and are directly comparable.

The average values for the numbers of partners in the last year, by age group, sex, and type (total or new), were estimated for each parameter set and for Natsal 2000. The number of partnerships contributed by each group was also estimated (number of individuals with x number of partners * number of reported partnerships). In Natsal 2000 only a few individuals report high numbers of partners. However these partnerships contribute disproportionately to the total number of partnerships in the population (Figure 5.5), and these individuals play an important role in maintaining chlamydia prevalence in the population. Therefore, the number of partnerships in the last year gives more weight to the higher activity group than using the number of partners.

Figure 5.5 – Natsal 2000: Proportion of the total partners and partnerships in the last year, men and women combined, all ages; A. all data, B. magnified y-axis.



The number of partners and partnerships were grouped into sexual activity classes s (0-1, 2-3, 4-7 and 8+ partners). The proportion of all partners/partnerships in each sexual activity class, by gender g (men, women), age class a (aged 16-19, 20-24, 25-29, 30-34, 35-39, 40-44 years), and type t (total or new) were generated from the Natsal 2000 data (D) and the model (M). There were differences in the reported behaviour between men and women in Natsal 2000 with men reporting on average 1.5 times as many partners as women (Johnson AM, *et al.*, 2001). However it was unclear from the data if this was due to under-reporting in women or over-reporting in men. Therefore, men and women were examined separately for the exploratory stage of fitting.

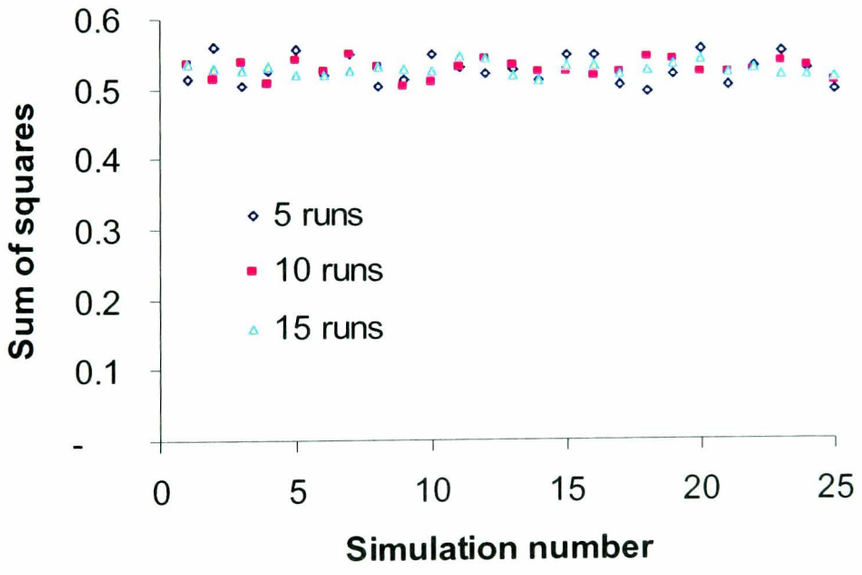
Preliminary work was done to assess the population size, number of stochastic runs, and the length of the runs needed for the fitting process, and to decide on the initial range of values for the fitting routines. For the behavioural fitting, a population of 6000 (3000 men and 3000 women) was chosen as it appeared to give results consistent with larger populations, with only slightly more variation and given the logistical constraints (computing power, time), allowed a larger parameter space to be explored. Sexual behaviour was estimated after the model had run for 10 years, as preliminary model runs indicated that behaviour had stabilised by that point.

There were two stages to the fitting process, due to the large number of unknown parameters that needed to be estimated and the complexity of such a task. The first fitting stage was exploratory to evaluate the impact of parameter values on the sexual behaviour in the model and narrow the range of parameters to be estimated. In the second fitting stage the final parameter set was chosen.

5.4.3.1 Stage 1: initial search of parameter space

Natural stochastic variation is expected from the model. Therefore, the average of several runs is needed to assess the model fit. The sum of squares (SS) was estimated (model compared to Natsal 2000 data for grouped male numbers of partners), for either groups of 5, 10 or 15 runs (over 400 individual model runs). For the average of all runs, the average SS was 0.53, and the SD was 0.02, 0.01 and 0.01 for 5, 10 and 15 runs, respectively (Figure 5.6). Therefore the average of five runs appeared to give similar results as greater numbers of runs while maximising the fitting efficiency.

Figure 5.6 – Stochastic variation in the model output, result of the average sum of squares for preliminary runs (sexual behaviour data for the model compared to Natsal 2000), averaged over 5, 10 or 15 runs.



In the exploratory runs of stage 1, Latin hypercube sampling (LHS, see methods in Chapter 4.3.5) was used to generate over 800 different parameter sets for the unknown parameters. The results from initial LHS sampling prompted additional exploratory runs using LHS for some parameters as a different range of values was likely (Table 5.1). Parameter ranges were chosen based on the likely values from the Natsal 2000 data (i.e., the likely duration of long

partnerships or proportion of short partnerships) or were modified based on the preliminary runs.

Table 5.1 – Range of parameter values for stage 1 behavioural fitting.

Parameter	**Range**
Duration of long partnerships (men/women)	100 – 1100 days
Duration increase of long partnerships (men/women)	100 – 3000 days
Proportion of short partnerships in 16 year olds (men/women)	20% - 70%
Proportion of individuals who change from desiring short to long partnerships (men/women)	1% - 15%
Duration of the gap period between partnerships (men/women aged <20 years, men/women aged 20+ years)	14 – 365 days

A least squares (LS) method was chosen to evaluate the fit of the model to the data. This is a computationally simple method to describe how similar the model results were to data. The sum of squares (SS_{gt}) was estimated separately for each gender g and type t (total or new partners), given by the formula:

$$SS_{gt} = \sum_{a} \sum_{s} \left(D_{asgt} - M_{asgt}\right)^2$$

Where D are the observed data from Natsal 2000 and M are the model results of the proportion of partners/partnerships in each sexual activity class s by age group a, gender and type. The fit estimates were ordered and the 20 with the lowest values (best fit) were selected. The corresponding input parameter values for these runs were examined. For most of the parameters, this allowed for a smaller range of likely values to be selected to determine a minimum and maximum for more precise fitting routines in stage 2.

5.4.3.2 Stage 2, refining parameter estimates

In stage 2 the parameters were allowed to vary over a more limited range, based on the results of the exploratory stage. Combinations of the most likely parameters (chosen from stage 1) were systematically combined to determine the best fit (Table 5.2). A total of 10 stochastic runs were done for each parameter combination to further minimise the effect of the model's stochasticisity on the results.

Based on the results of the exploratory stage, three parameters were fixed (Table 5.2). These were the average duration of long partnerships (900 days), the annual increase in long partnership duration (200 days) and the duration of the gap between partnerships for young and old individuals (14 days). Men and women were assumed to have the same values for these three. The partnership duration and increase in duration were fixed because their likely values appeared close to the chosen value and their exact value did not appear to have a large impact on the fit of the model. A long gap between partners (i.e. 365 days) was the *minimum* period individuals had between partners, which artificially limited the total number of partners they could have in a year, and prevented the range of partners needed to fit to the data, therefore this was chosen to be two weeks. Varying the remaining parameters (proportion of short partnerships at 16 years old, and the proportion that change from desiring short to long partnerships, for men and women) was shown to generate sufficient differences in sexual behaviour to capture the range of observed behaviour.

Table 5.2 – Range of values for the behavioural fitting routines, stage 2.

Parameter	**Fixed values**	**Values for fitting**
Duration of the gap between partnerships	14 days	
Duration of long partnerships (men/women)	900 days	
Duration increase in long partnerships (men/women)	200 days	
Proportion of 16 year olds desiring short partnerships (men/women)		40%, 50%, 60%, 70%
Proportion of individuals who change from desiring short to long partnerships Men Women		 4%, 6% 8%, 12%

Results from the exploratory stage suggested that fitting the total male partnerships in the last year gave the most variation in sexual behaviour, including a few individuals with many partners, as is observed in the Natsal 2000 data. Therefore, this measure was used for subsequent fitting in stage 2.

For the second stage, maximum likelihood (ML) estimation was chosen to find the parameter values that generated model results most similar to the observed Natsal 2000 data. The LS method is an approximation of ML, and therefore ML was thought to give a better estimate of the goodness of fit. A multinomial model was assumed, and the log likelihood L_{beh} and saturated log likelihood L_{beh}* (that is, the log likelihood if the model fits the data perfectly) from model data were calculated for total male partnerships in the last year:

$$L_{\text{beh}} = \sum_{a}\sum_{s} Q_{as} * \log(y_{as})$$

$$L_{\text{beh}}* = \sum_{a}\sum_{s} Q_{as} * \log(z_{as})$$

Where Q_{as} is the number of men in age group a (16-19, 20-24, 25-29, 30-34, 35-39, 40-44) and sexual activity group s (1, 2-3, 4-7, 8+ partners) observed from Natsal 2000, and y_{as} *and*

z_{as} are the proportion of males, age group a in s sexual activity class, observed in the model and in Natsal 2000 data, respectively.

The deviance was then calculated by:

$$Dev_{beh} = \left(-2 * \left(L_{beh} - L_{beh}*\right)\right)$$

which was minimised to find the best fitting set of behavioural parameters.

Univariate sensitivity analysis was done for the final four fitted parameters to assess the impact on changing the inputs to the model fit. All parameters were held constant and then each of the four was varied individually over the values in Table 5.2, and the deviance estimated.

5.4.4 Results of the behavioural parameter estimation

The behavioural parameters that produced the best fit to the Natsal 2000 data are shown in Table 5.3.

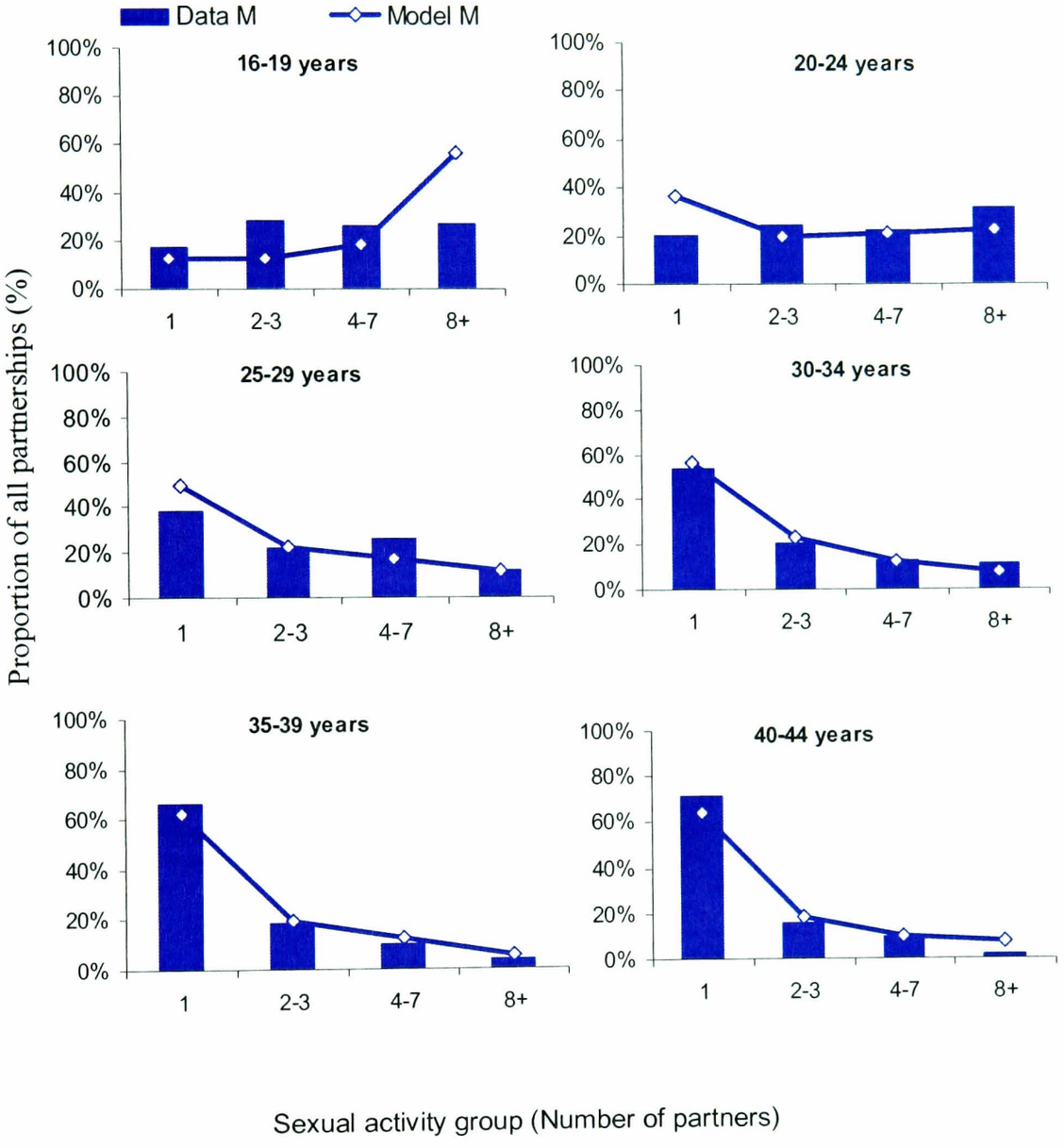
Table 5.3 – Final behavioural parameters estimated in the fitting routines.

Parameter	**Value**
Proportion of 16 year olds desiring short partnerships	
Men	60%
Women	50%
Proportion of individuals desiring short partnerships who change to desire long partnerships per year	
Men	4%
Women	8%

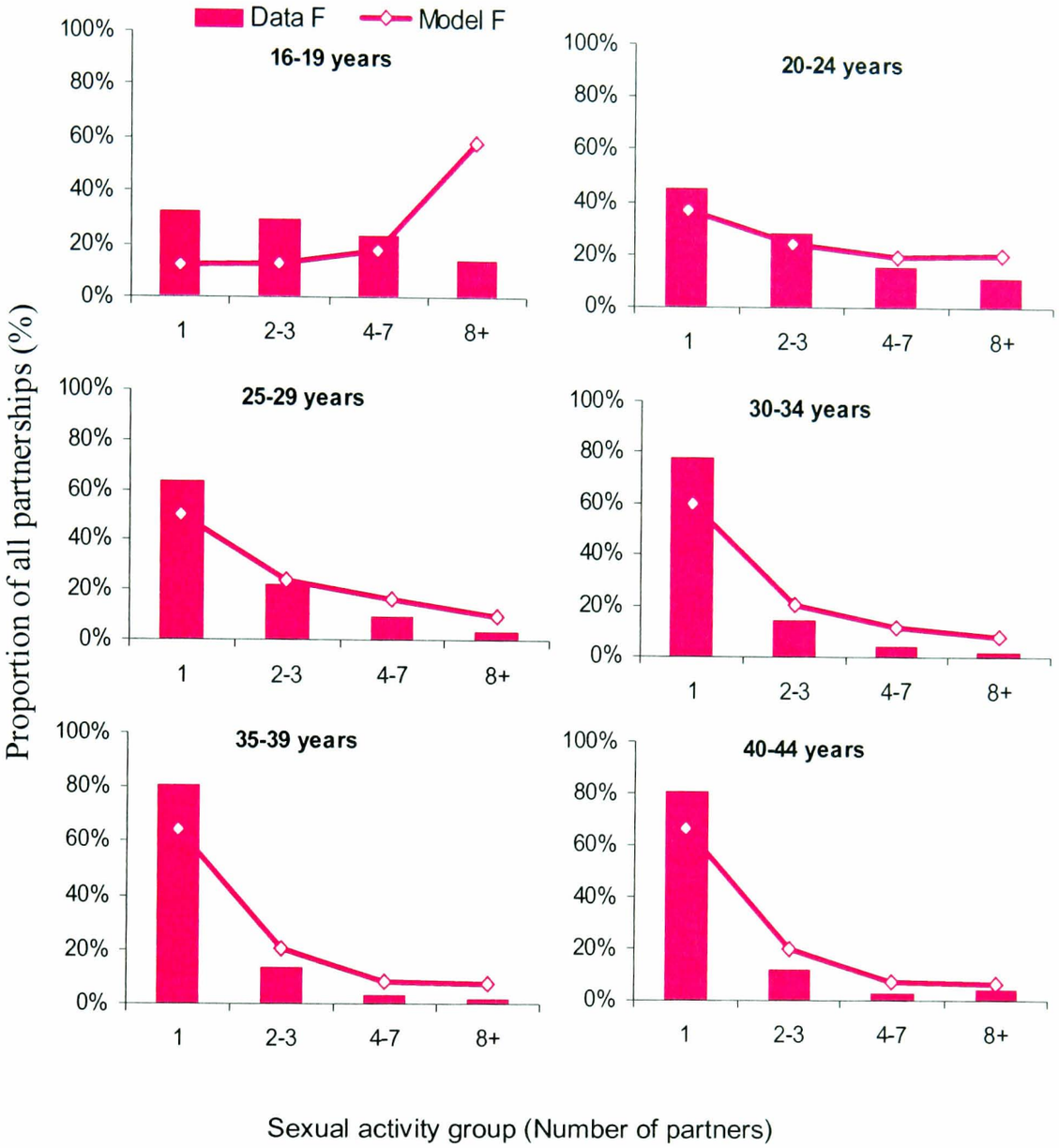
A comparison of the model results to data for the number of male and female partnerships in the last year is presented in Figure 5.7. The results show the changing behaviour by age, with younger individuals having more partners than older ones. The model fit to the male behaviour was expectedly better than that to the females, because of the decision to fit to male partnerships. However, this meant that the model overestimated the partner change rate for women. The model also overestimated the partner change rate in both the youngest age groups (men and women) and slightly underestimated the number of partners in the older age groups. This is seen in half of the total estimated deviance (difference between the model and data) in the 16-19 year old group, and over a quarter in the 20-24 year olds. That is, the 25-44 year old groups fit much better than the younger ages, with only a quarter of the estimated deviance. However, this may have been because sexual behaviour is more constant in the older age groups, and also perhaps due to the structural assumptions and not a result of fitting per se.

Figure 5.7 – Proportion of partnerships contributed by different sexual activity groups for the best fitting model, model output compared with Natsal 2000 data by age group; A. men, B. women.

A. Men

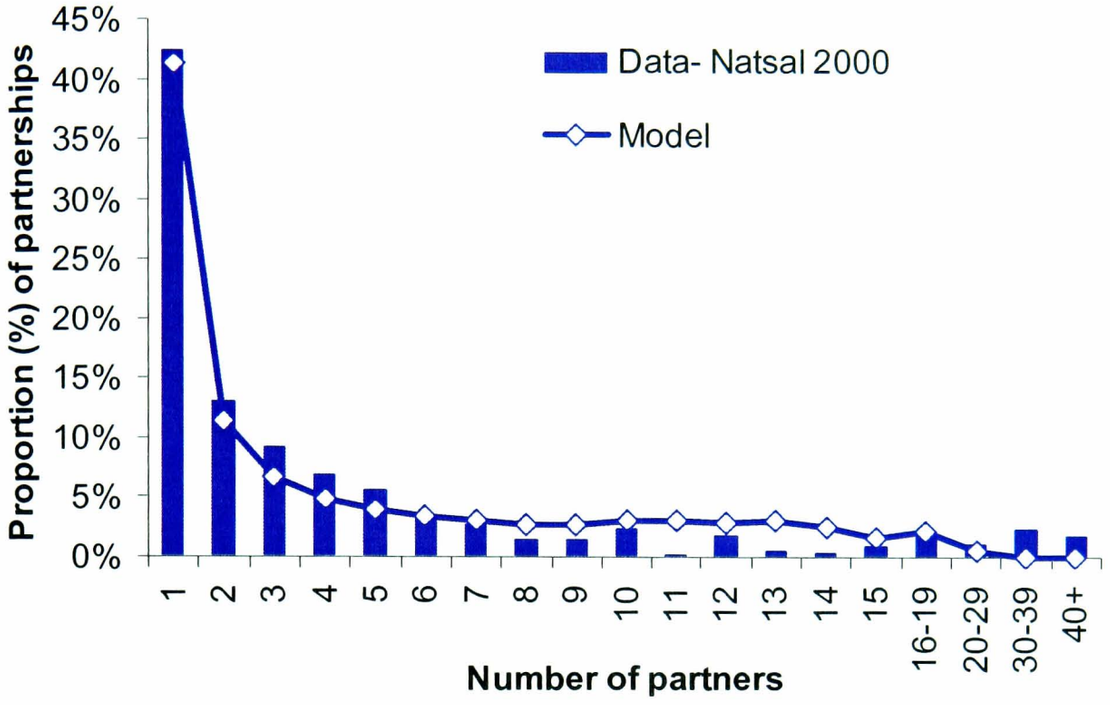


B. Women



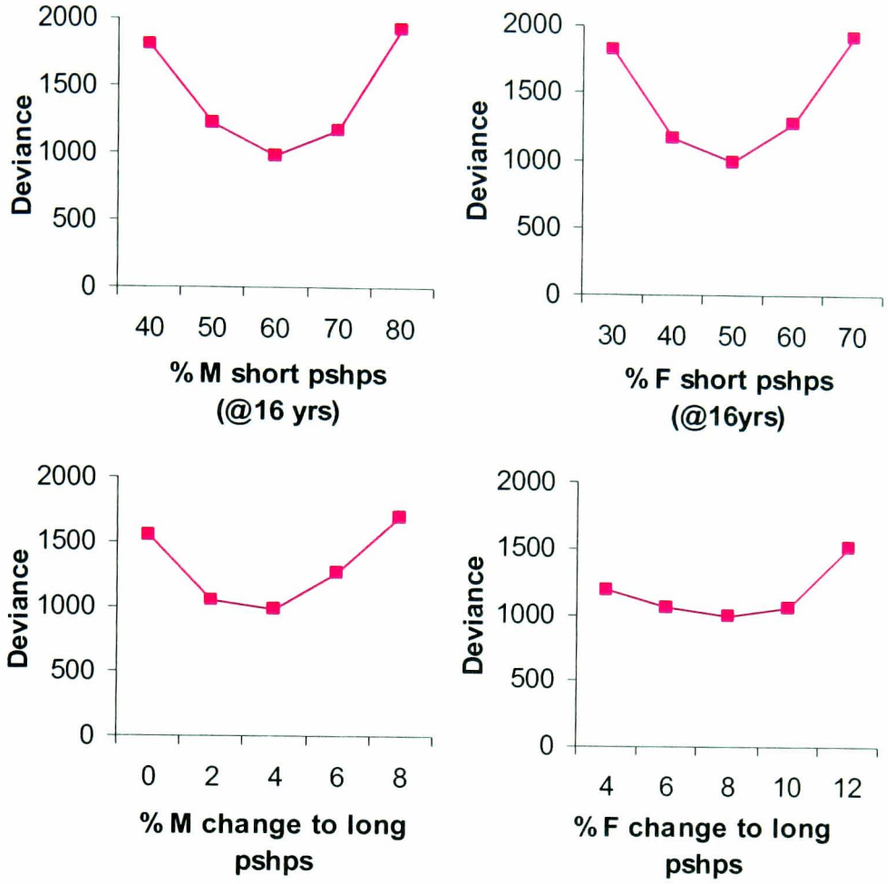
In order to simplify the fitting process yet yield meaningful results, the number of partnerships was grouped. If these are shown ungrouped (except for the highest numbers of partnerships), then the model fits reasonably well to male data (Figure 5.8). There is a slight underestimation for the lower activity individuals, and slight overestimation for the higher activity group, except for the highest activity group (30+ partnerships) which the model was unlikely to generate. The model does not have any non-sexually active individuals (those with 0 partners in the last year) although the Natsal 2000 data did.

Figure 5.8 – Proportion of male partnerships by number of partners; model results compared to Natsal 2000 data (all ages).



The univariate sensitivity analysis results showing the impact of changing the parameters on the fit of the model is shown in Figure 5.9. A low deviance indicates a good fit of the model to the data.

Figure 5.9 – Univariate sensitivity analysis of behavioural parameter fit, deviance of the model compared to Natsal 2000 data.



5.5 Chlamydial infection & partner notification

5.5.1 Model structure: dynamics of infection

Chlamydial infection was modelled as an SIS infection (**S**usceptible-**I**nfected-**S**usceptible). That is, susceptibles could become infected from an infected partner and then return to a susceptible state probabilistically. Although immunity to infection may develop (see Chapter 2.2.1), no immunity was assumed in the model, making re-infection from either a current or new partner possible. It was assumed that that there was one sex act per day in short partnerships and 0.25 sex acts per day in long partnerships (Kretzschmar M, *et al.*, 2001).

Chlamydia prevalence is determined by the transmission probability, the proportion of those actively seeking treatment due to symptoms, duration of infection, and the levels of partner notification and treatment. Asymptomatic individuals were assumed not to seek treatment and therefore their average duration of infection was longer than individuals with symptomatic infection. After an individual recovered following treatment (from symptomatic infection or PN), it was assumed that on average there were seven days during which re-infection was prevented. This represented the continued protection from antibiotic use, and prevention messages about abstaining from sex until the partner was treated and increased condom use being heeded, and was based on recommendations (Horner PJ, *et al.*, 2006).

Partner notification could occur in all partners of infected individuals (identified either because they sought treatment or were screened). For PN, a proportion of current and past partners from within the last 3 months, in line with assumptions in Chapter 4 from the Chlamydia Pilot Study and current recommendations (Horner PJ, *et al.*, 2006), were treated with a given efficacy. A gap of seven days was assumed between treatment of the index individual and the partners. PN only occurred for one round, i.e. individuals who were partner notified did not notify their partners.

5.5.2 Biological parameter estimation

Not all of the biological characteristics of CT are fully understood or quantified (Chapter 2.2.1). The input parameters needed for the model were the duration of infection (men/women, treatment seeking and non-treatment seeking individuals), proportion of individuals who sought treatment for their infection (men/women), proportion of all partners effectively partner notified and treated (men/women), and the transmission probability (men/women). It was assumed in the base case scenario (without screening) that a certain level of active treatment seeking (due to symptoms or because of individuals attending health care settings for sexual health screening) and PN was already occurring. Since the overall

prevalence is mediated by both, the proportion of symptomatic cases that seek treatment and the transmission probability were fitted simultaneously with PN. The transmission probability and duration of infection are closely linked parameters and therefore any combination of these might generate the same prevalence. Hence, the duration of infection was fixed since there is some evidence from the current literature on the likely value (Chapter 2.2.1.2). The average duration of infection in individuals seeking treatment due to symptoms was assumed to be one month and in asymptomatic untreated infection six months in men and women. For simplicity and based on what is assumed in the model by Kretzschmar *et al* (2001), the probability of CT transmission per sex act was assumed to be the same from men to women and vice versa.

As with the behavioural parameters, exploratory runs were conducted to find the likely range of the biological parameters, and were made purposefully wide to explore the parameter space (Table 5.4).

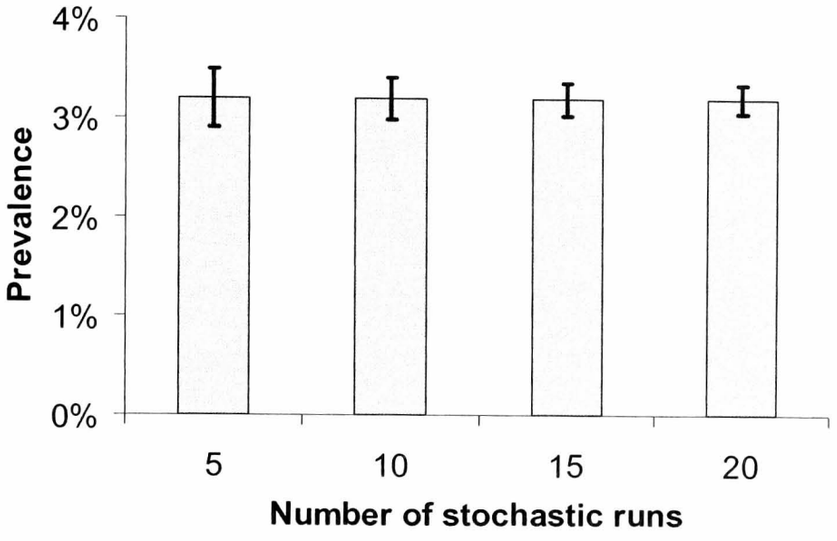
Table 5.4 – Range of biological parameter values

Parameter	**Range**
Effective partner notification	0-100%
Proportion seeking treatment	0-50%
Transmission probability per sex act per partner	0-5%

Exploratory runs suggested that the prevalence took 15 years to stabilise in all ages, at which point the fitting routine was performed. The average of 15 stochastic runs was estimated for each parameter set. More runs were needed than were done for the behavioural parameterisation, because of the sensitivity of the prevalence to small changes in the input

parameters. Fifteen runs gave only slightly more variation than 20 or more runs, seen by estimating the mean and 95% CI for each number of runs (Figure 5.10).

Figure 5.10 – Impact of the average number of stochastic runs on the model prevalence estimates (all ages, men and women); bars are 95% CI limits.



The model was simultaneously fitted to CT prevalence in women (Chapter 3) and the proportion of men and women that reported ever being treated for CT infection (Natsal 2000). The estimates from Chapter 3 for prevalence in women in GP clinics by age groups (16-19, 20-24, 25-29 and 30+) were chosen, as the majority of women attend a GP surgery annually (Chlamydia Recall Study Advisory Group, 2004; Salisbury C, *et al.*, 2006). Data on prevalence in men was not used in the fitting process, as at the time of this study, limited information was available for a comparable population to that of the women. For the fitting routines (see below), the numerator and denominator values were needed for the prevalence estimates. Since the prevalence estimates were based on the results of a regression analysis and not on primary source data (Chapter 3), values for the numerator and denominator were generated that produced the same prevalence and 95% CIs as estimated in Chapter 3 (Table 5.5).

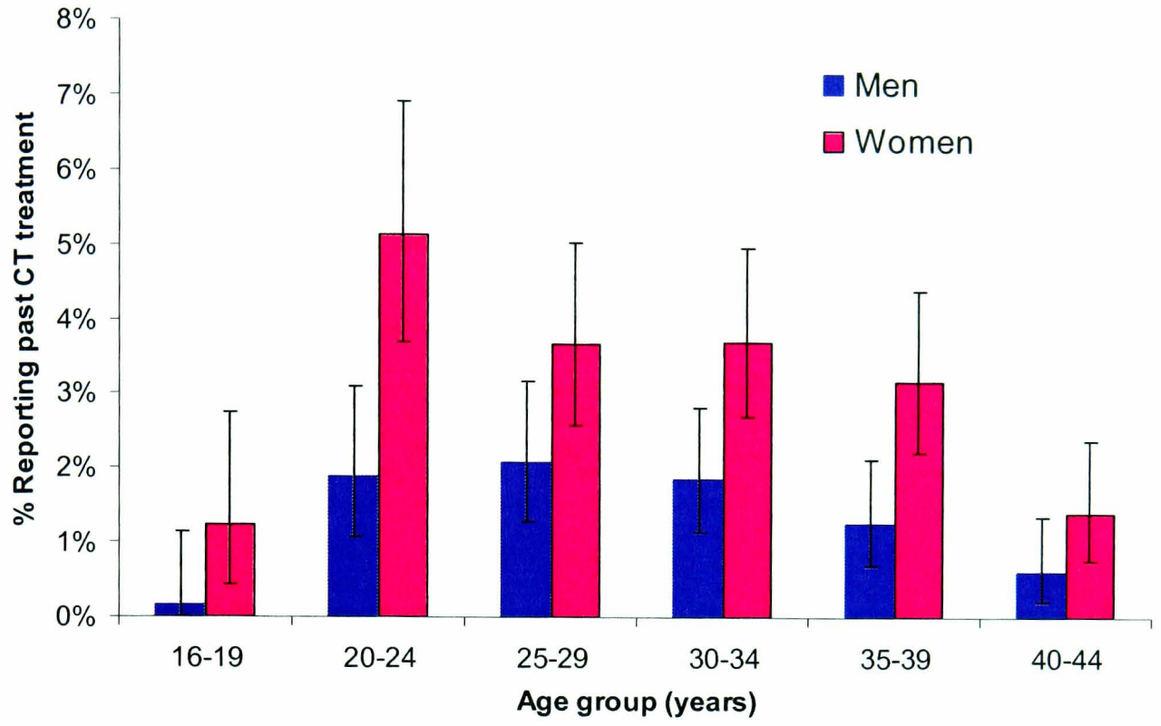
Table 5.5 – Estimated number of individuals positive and negative for CT infection needed to generate the same 95% CIs as in the regression analysis in Chapter 3.

Age group	Estimated total tested	Estimated total negative	Estimated total positive	Proportion positive	Lower 95% CI	Upper 95% CI
16-19	1,074	987.1	87.0	8.1%	6.5%	9.9%
20-24	1,894	1795.7	98.5	5.2%	4.2%	6.3%
25-29	2,519	2453.7	65.5	2.6%	2.0%	3.3%
30-44	2,893	2852.4	40.5	1.4%	1.0%	1.9%

Note: Estimates taken from Table 3.5.

The proportion of men and women who reported past treatment for CT infection was estimated from the Natsal 2000 data (Figure 5.11). Natsal 2000 was completed before CT screening was implemented in England, and before there was widespread awareness about infection, so this was thought to serve as a reasonable baseline estimate. This was not directly used as an input parameter for the model, but was used in the fitting routine as it is directly comparable to the model output. Individuals who reported prior treatment for CT were assumed to have had symptomatic CT infection or who were asymptomatic but who might have otherwise attended a health care setting for STI screening or PN and have their infection diagnosed. In the data, we would expect the cumulative proportion of those reporting past treatment to increase with age and this is not seen. This may have been due to possible increased awareness and testing for young adults in the youngest ages in the late 1990's. The data may also underestimate the true proportion treated for CT, because of recall bias, under-reporting, presumptive treatment of partners, or because individuals with high numbers of partners and who may have been treated were not captured in Natsal 2000. Because of the discrepancies in the data and doubt about the reliability and comparability of data from the older age groups (25 years and older), only the two youngest age groups (16-19 and 20-24 years) were used in the fitting routines.

Figure 5.11 – Natsal 2000: Proportion of men and women who reported prior treatment for chlamydia (bars indicate estimated 95% CI).



Maximum likelihood was used to estimate the best fit to the data for the 8 data points (prevalence in women for four age groups, and proportion of men and women treated for two age groups). As the data are binomial, the model log likelihood (L_{bio}), saturated log likelihood (L_{bio}*) and deviance for each subgroup (L_{bio_prev} for CT prevalence estimates and L_{bio_treat} for the proportion ever treated) are calculated by:

$$L_{bio} = L_{bio\_prev} + L_{bio\_treat}$$

$$L_{bio}^* = L_{bio\_prev}^* + L_{bio\_treat}^*$$

The calculations for L_{bio_prev} are given by:

$$L_{bio\_prev} = \sum_a \left(I_a * \log x_a\right) + \left(S_a * \log\left(1 - x_a\right)\right)$$

$$L_{bio\_prev}^{*} = \sum_{a}\left(I_a * \log\left(\frac{I_a}{S_a + I_a}\right)\right) + \left(S_a * \log\left(\frac{S_a}{S_a + I_a}\right)\right)$$

where I_a is the observed number of infected, S_a the observed number of susceptibles, and x_a is the model estimate of the proportion of infected, by age group a (16-19, 20-24, 25-29, 30-44).

The calculations for L_{bio_treat} are given by:

$$L_{bio\_treat} = \sum_{g}\sum_{a}\left(I_{ga} * \log x_{ga}\right) + \left(S_{ga} * \log\left(1 - x_{ga}\right)\right)$$

$$L_{bio\_treat}^{*} = \sum_{g}\sum_{a}\left(I_{ga} * \log\left(\frac{I_{ga}}{S_{ga} + I_{ga}}\right)\right) + \left(S_{ga} * \log\left(\frac{S_{ga}}{S_{ga} + I_{ga}}\right)\right)$$

where I_{ga} is the observed number of individuals with prior CT treatment, S_{ga} the observed number with no prior CT treatment, and x_{ga} is the model estimate of the proportion of individuals with prior CT treatment, by gender g (men and women) and age group a (16-19, 20-24).

The deviance was minimised in the fitting routine, and calculated by:

$$Dev_{bio} = -2 * \left(L_{bio} - L_{bio}^{*}\right).$$

This range of values was further refined after exploratory runs by systematically combining parameters (proportion seeking treatment in men and women, transmission probability, and PN). Combinations of parameters from a given range (Table 5.6) were selected at given increments to test the regional fit. Once a local best fit was found (lowest deviance), the other parameters were varied to search for a better fit. Thirty model runs were performed for each parameter set for the final fitting routines to reduce stochastic effects, as the results were sensitive the input parameter values. Univariate sensitivity analysis was performed for

each of the five parameters, and the 95% CI was estimated by finding those parameter values that gave a deviance that lay within 3.84 of the best fit.

Table 5.6 – Range of values for the final biological fitting routine.

Parameter	**Range**	**Increment**
Transmission probability per sex act per partner*	0.035 -0.05	0.0025
Proportion seeking treatment: Men Women	 0.0 - 0.05 0.0 - 0.055	 0.005
Partner treatment*	0.0 - 0.5	0.05

Note: * the value is the same for men and women; the duration of infection for treatment seeking and non-treatment seeking individuals was fixed at 30 and 180 days, respectively.

5.5.3 Results of the biological parameter estimation

The set of biological parameter values (and 95% CI) that produced the best fit to the data are shown in Table 5.7. The best fitting model suggested that PN was 20%, the per sex act transmission probability was 0.0375 and that a small fraction of cases are treated as a result of active treatment seeking (less than 5% of female and 0.05% of male cases). That is, most women are treated because of treatment seeking, while men are treated through PN. The overall prevalence was 3.2% (3.6% in men and 2.9% in women). The model results for the prevalence in women and the proportion ever treated of men and women are compared with data in Figure 5.12 and Figure 5.13, respectively. The deviance for the best fit parameter set was 11, fitted to 8 data points. Figure 5.14 shows the results of the univariate sensitivity to find the best overall parameter estimates.

Table 5.7 – Final fitted biological parameters.

Parameter	Best fit	Limits of 95% CI
Transmission probability per sex act per partner*	0.0375	0.035 - 0.04
Proportion of treatment seeking		
Men	0.0	0.04 - 0.05
Women	0.045	0 - 0.005
Proportion of effective partner notification and treatment*	0.2	0.1 - 0.25

* The value is the same for men and women.

Figure 5.12 – Model chlamydia prevalence (95% CI limits are shown by the bars) in women by age group compared with estimated prevalence in general practice attendees (Chapter 3).

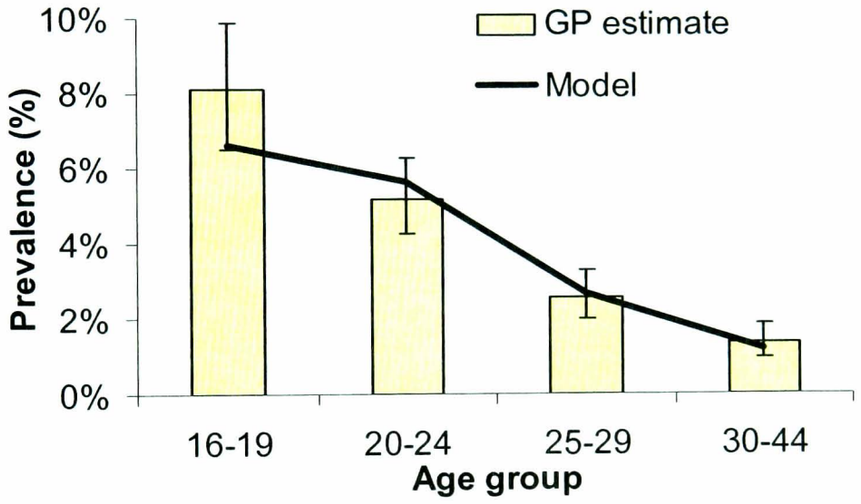


Figure 5.13 – Proportion of men and women ever treated for chlamydia, by age group, Natsal 2000 data compared to model estimates (95% CI limits are shown by the bars).

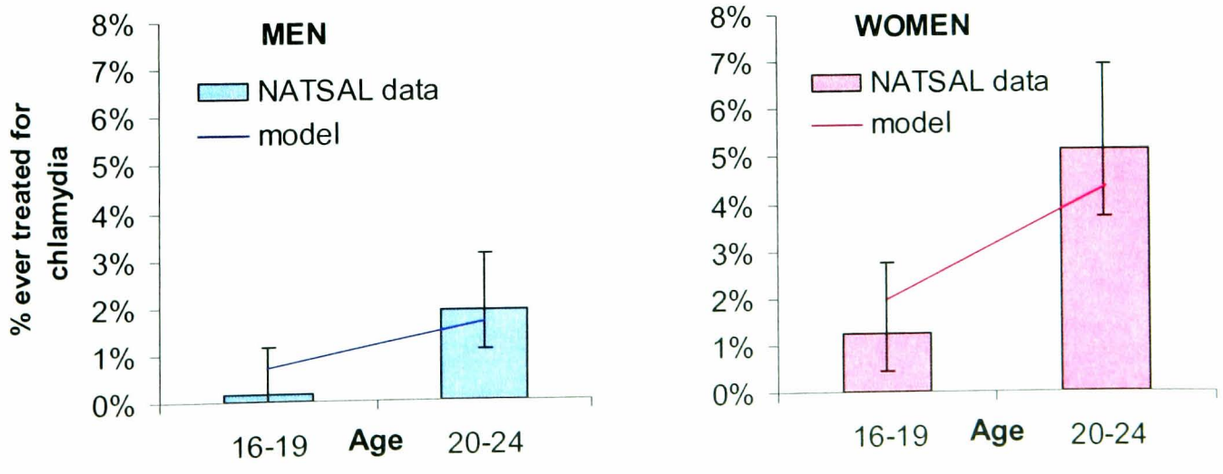
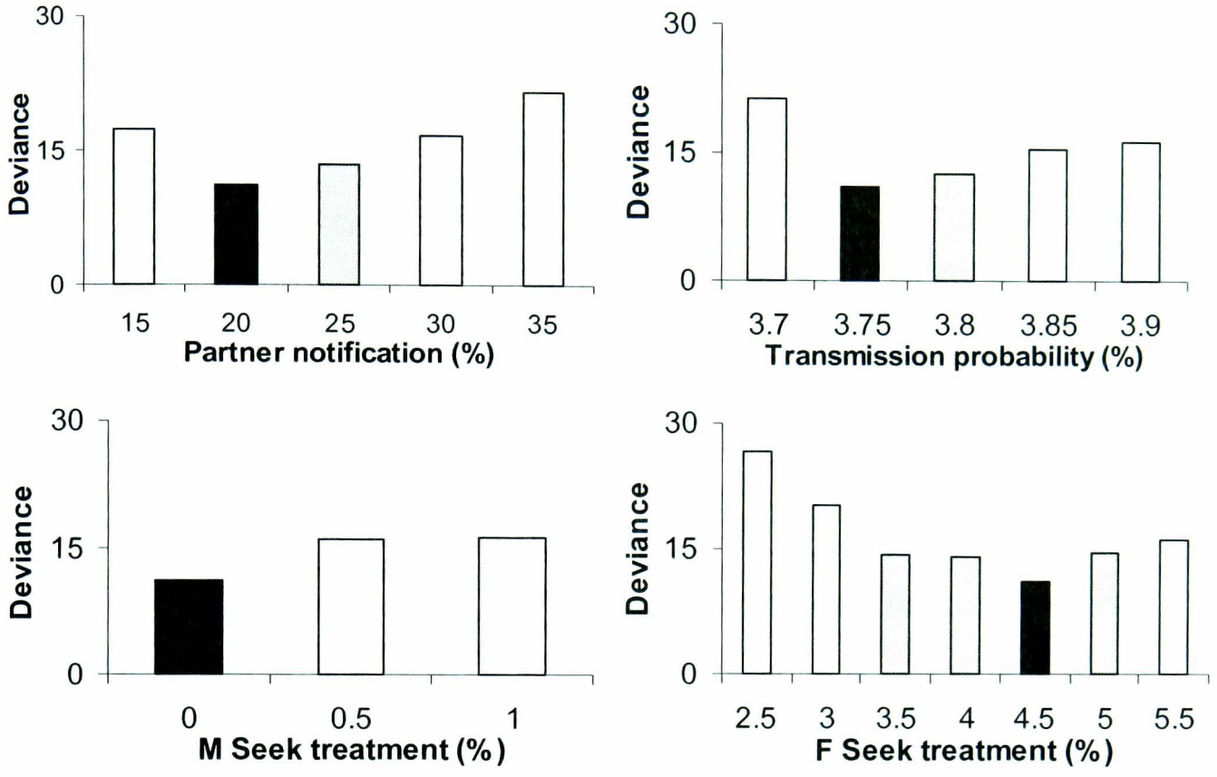


Figure 5.14 – Univariate sensitivity analysis of biological parameters fit, estimated deviance of the model compared to data.



Note: Black bars are the best estimate, grey bars fall within the 95% confidence interval, and white bars are outside of the 95% confidence interval.

5.6 Discussion

The aims of this chapter were to generate a model of CT transmission which reproduced observed patterns of sexual behaviour and chlamydia epidemiology. Estimation methods (LS, ML) were used to perform this complex process of model fitting. The parameterisation work represents an improvement over that used in previous dynamic CT models (Chapter 2.5.3). The population described after the fitting process is the best achievable representation of the population with the current model structure.

5.6.1 Behavioural parameter estimation

Determining the behavioural parameter values was a laborious and intensive process. There were several interesting issues and challenges that arose during the fitting process. The behaviour modelled was chosen because it was thought to simplify the complex patterns of sexual behaviour observed in the Natsal 2000 data. The model needed to be able to track individuals and their partners to take account of PN. This made it a complex and time intensive programme to run, and imposed logistical restrictions on the number of runs that could be done within a given time period.

The model was complex with many parameters. Within the set of parameters, the initial starting ranges were largely unknowable (i.e. the preferred duration of long partnerships) and therefore very wide. These two features together (many parameters * unknown ranges) meant that many different combinations of unknown parameters had to be sampled and the fits compared to investigate correlations. A number of combinations of the parameters may have given the same answer in terms of the fit. Therefore, it was decided to fix certain parameters after the exploratory runs, either because they did not seem to make a difference to the fit, or because all of the best fitting parameter combinations had a parameter in a small range (i.e. the proportion of individuals who switch to prefer long partnerships), and the

focus could be on estimating the remainder. Latin hypercube sampling was used in the initial runs to explore the parameter space, and was already a feature of the basic model (Ghani A, *et al.*, 1997). The model did not have a fitting routine, and fitting in this chapter was performed in Excel. This added another level of complexity to the model. If further work is done on the model, it would be useful to add a fitting routine within the model, which could automatically search the parameter space and identify the best fit.

The sexual behaviour reported in Natsal 2000 differed for men and women. Men reported more partners and greater heterogeneity in reported partners compared to women, with some men reporting very high numbers of partners in Natsal 2000 (Johnson AM, *et al.*, 2001). This has been observed in other surveys on sexual behaviour (Wadsworth J, *et al.*, 1996; Smith TW, 1992). This may be due to recall bias since it is a retrospective survey. One study found that men reported their partners more consistently than women under survey conditions, and that women under-reported when they thought that the survey was not anonymous and reported more partners when they think their underreporting may be more easily detected (Alexander MG, *et al.*, 2003). There is also some suggestion that surveys such as Natsal 2000 may miss out the small fraction of sex workers or women with high numbers of partners, thereby reducing the mean number of partners and not capturing those individuals who fall in the tail of the distribution (Morris M, 1993; Brewer DD, *et al.*, 2000). Therefore, it was decided to use the male data in the parameterisation routines. This decision meant that the women in the model were more sexually active than observed in the data, and was particularly pronounced in the youngest age groups. Because of the discrepancy in the data, if the model had been fitted to some combination of male and female data, the model would not have fit either data set well and the effect of changing the parameters may have been diluted in the results. Arguably, since the biological parameters were fit to female prevalence and screening strategies in women will be assessed (Chapter 6), then perhaps the female sexual behaviour from Natsal 2000 should have been used instead of the male behaviour. However, as mentioned above, there would have been fewer partnerships in the model than

appear in the male data (which were thought to be more accurate), and also a reduced range of numbers of partners. Future analyses could be done in which the model is fitted twice, first to female data and second to male data, the biological parameters refit for each, and the impact on screening strategies assessed. However, this was not feasible given the timeframe of the thesis. Additionally, in the future the model fitting could be adjusted to account for under-reporting in women, over-reporting in men or some combination of the two, or accounting better for greater variance in female data.

The model appeared to fit adequately to the sexual behaviour data in Natsal 2000. However there are improvements that could be made to the underlying model structure that might improve the fit and solve the problem of the youngest ages being more sexually active in the model than in Natsal 2000. For example, in the current model structure, all individuals enter the population and become sexually active at 16 years old, with the highest proportion of short partnerships assumed to be in youngest ages and decreasing each year with age. However, this is a simplification of sexual behaviour, and there are other patterns of behaviour not captured in the model. There is a distribution around the age of sexual debut which can be younger than 16 years, and individuals may cycle between desiring short or long partnerships. Making improvements to the model structure and possibly the consequent fit are being done currently at the HPA. This model is being used to explore human papilloma virus (HPV) transmission and interventions, and work in this chapter highlights where additional changes to the model could be made to improve the behavioural fit.

5.6.2 Chlamydia transmission

Once the sexual behaviour was parameterised, the biological parameters were estimated to fit to the prevalence of CT in women and the proportion reporting prior treatment for CT. Overall, the set of parameters estimated generated prevalence similar to the available data, and fell within the 95% confidence intervals of the data. These estimates provide insight into the biological features of infection.

The estimated values for PN and proportion seeking treatment are lower that previously cited and used in other studies (Kretzschmar M, *et al.*, 2001; Cates W Jr, *et al.*, 1991; Stamm W, 1999). In this chapter it was estimated that 20% of partners were effectively notified and treated and less than 5% of infected men and women seek treatment for infection (perhaps due to symptoms). Estimates for PN are similar to recent published data. In the third year of the NCSP, 33% of the total *reported* partners of positive index cases were treated (National Chlamydia Screening Steering Group., 2006). If not all partners were reported, then the *actual* number of partners treated will be lower, and perhaps similar to the 20% estimated in this chapter.

In this model, symptomatic and asymptomatic infections were not explicitly modelled. Instead, it was estimated that less than 5% of infected individuals would actively seek treatment, mainly because of their symptoms but also because of sexual health screening (i.e. in a GUM clinic), and those who were asymptomatically infected would not seek treatment. The result is that people who do not seek treatment will have infection for longer. The estimates for proportion seeking treatment in this chapter differ significantly from those in CT modelling work by Kretzschmar *et al* (2001) who used 30% and 50% symptomatic for women and men, similar to assumptions made by Townshend and Turner (2000) and Low *et al* (2007). However, there is evidence to suggest previous estimates are far too high, and recent studies have reported that the proportion of symptomatic infections in screened populations may be less than 10% (Chapter 2.2.1.1). Symptoms may also be intermittent and as such may not prompt treatment seeking (Korenromp EL, *et al.*, 2002). The NCSP in 2005/2006 reported that five percent of all tests done were diagnostic tests prompted in part by symptomatic infection (Chapter 3.5.1). While the best fitting model was that with very low treatment seeking behaviour especially in men, there probably are men who seek treatment that have not been captured in the model. The available data from Natsal 2000 on the proportion of men reporting prior treatment did not support a high level of treatment seeking (Figure 5.11). Natsal 2000 data are similar to that from a re-infection study which

found that 8% of women aged 20-24 reported having ever been treated for CT (Chlamydia Recall Study Advisory Group, 2004). In these data, individuals that had reported being treated for CT may have done so because they sought treatment for symptoms, were partner notified, or attended a GUM clinic and were given a full STI screen. The results in this chapter suggest a lower estimate than previously thought, but further work is warranted, and newer data from the NCSP and treatment history could be used to refine this estimate. The implications of the lower estimate are important for screening. If there is a large pool of untreated infection, then screening has the potential to have a large impact on reducing the prevalence. In previous models which assume that half of individuals with CT infection get treatment, then screening will not have such a large potential impact. This will be explored in more detail in Chapter 6.

The transmission probability was assumed to be the same for male to female and female to male transmission. This was a simplification, which Kretzschmar *et al* (2001) also used in their study. Male and female specific values for this parameter could have been estimated in the fitting routine, but this would have resulted in different estimates for the other parameter values. In reality, there may be a difference in the true values, but whether this impacts the model results is unknown. The transmission probability estimated (0.0375) was slightly lower than that by Kretzschmar *et al* (2001). They estimated a transmission probability per sexual contact of 0.11 (same for men and women), by using the per partnership transmission probability derived by Quinn *et al* (1996) and the estimated number of sexual acts for a casual partnership (10 acts). Their estimate is higher possibly because they used the number of sex acts for casual partnerships, and in this analysis most partnerships were long partnerships, which would lower the estimate. Additionally, the transmission probability is mediated by the duration of infection, and the proportion seeking treatment (proportion with symptomatic infection in Kretzschmar's study), which are both higher in Kretzschmar's study. The study by Low *et al* (2007) used the values from Kretzschmar's study.

Additional information on the prevalence of infection could be included in future modelling work. In particular, male positivity from the NCSP could provide another data source for fitting. This may impact on results, as there is evidence that the peak prevalence in men may be in 20-24 year olds as opposed to the younger (<20 year old) group as is seen in women (National Chlamydia Screening Steering Group., 2006; Health Protection Agency, 2006a). An implicit assumption made in this analysis was that the prevalence estimated in Chapter 3 was in women who were sexually active, as only sexually active men and women are included in the model population. However, not all studies from the systematic review in Chapter 3 reported the sexual activity of the women tested. The NCSP screens only sexually active women, and comparing the results in Figure 3.4 indicates that the prevalence among those in the NCSP is marginally higher than the estimates from Chapter 3. Both the male and female data from the NCSP of those sexually active individuals could be used to refit the model in future analyses.

Adding immunity to CT infection to the model may also impact on the dynamics of infection. If men and women have a reduced risk of transmission following initial infection (holding all other parameters constant), this would reduce the prevalence of infection in older ages. However, if immunity is added to the model, then the biological parameters would need to be refit to the prevalence and proportion ever treated for CT from Natsal 2000. Not enough quantitative data is currently available to add immunity to the model, but this is an area of further work.

5.7 Summary

This chapter presented the results of an extensive fitting process to create a model that was realistic in terms of the available data on sexual behaviour and CT epidemiology. It was based on the best evidence available from the analysis of CT prevalence in Chapter 3, and data from Natsal 2000. Limitations in the data, such as discrepancies in the reported sexual behaviour between men and women, meant that the decision to fit to male partnerships generated higher sexual activity in women than is observed in the data. However the overall fit to the data was acceptable. The biological parameters estimated in this chapter were different from those previously estimated. However they allowed a good fit to the data and are supported by new data. The realistic model of sexual behaviour and CT epidemiology parameterised here can now be used in Chapter 6 to estimate the cost-effectiveness of CT screening.

CHAPTER 6 - ESTIMATING THE COST-EFFECTIVENESS OF OPPORTUNISTIC CHLAMYDIA SCREENING

"£50M CAMPAIGN TO COMBAT RISE IN SEX DISEASES"

The Sunday Times, October 05, 2005

6.1 Aims

- To create a cost-effectiveness model that uses results of the dynamic model described in Chapter 5;

- To estimate the costs of acute infection, CT complications and screening costs (Chapter 4);

- To estimate the probability of progression to pelvic inflammatory disease;

- To estimate the cost-effectiveness of the NCSP and alternate screening strategies, and explore the sensitivity of model assumptions and uncertainty of the model.

6.2 Introduction

Questions remain regarding the cost-effectiveness of the NCSP and that of alternate screening strategies. Complications following PID and acute infection in men, women and neonates are important to estimate, due to their impact on the health of individuals and the potential associated use of resources to manage them. In this chapter these complications will be estimated using a cost-effectiveness model that will also estimate the costs of acute infection, clinical sequelae, and screening activities. These can then be combined to generate the possible effectiveness and cost-effectiveness of different opportunistic screening strategies.

The dynamic individual-based model developed by Turner *et al* (2006a) and parameterised in Chapter 5, was used to estimate the impact of CT screening in a model population with characteristics similar to those in the UK. The effectiveness of different screening strategies has been reported in Turner *et al* (2006b), and a summary of the results are presented here, which forms the basis for the cost-effectiveness analysis in this chapter.

6.2.1 Screening strategies

The model replicated screening strategies most likely to be employed in England, including the current NCSP strategy. These strategies were identified through discussions with colleagues in the NCSP and other scientists. Three opportunistic screening strategies were modelled, based on the likely options for screening, targeting different age groups (<20, <25, <30, <35, <40 years old):

Strategy 1 Offer an annual screen to women,

Strategy 2 Offer an annual screen to women and if they have changed their partner in the last 6 months. (This strategy extends screening eligibility based on sexual behaviour to target those at highest risk, based on evidence from a recent study indicating that women have a greater risk of infection and reinfection if they have acquired a new partner (LaMontagne DS, *et al.*, 2006))

Strategy 3 Offer an annual screen to women and men (NCSP strategy).

As mentioned in Chapter 2.3.2, a high proportion of young women and men visit their GP clinic annually (LaMontagne DS, *et al.*, 2006; Salisbury C, *et al.*, 2006). Based on this, it was assumed that 85% of the population attended a health care site annually (Turner KME, *et al.*, 2006b). The proportion screened is a combination of the proportion that are offered and that accept a screen, however there are no data on the proportion of individuals offered a screen in the NCSP. For simplicity in the model, it was assumed that all eligible individuals were offered a screen when they attend, and that a proportion (50% at baseline) accepts the screen, however this can be seen as some combination of the two elements (offer/acceptance). Thus, under ***Strategy 1*** the minimum interval between screens was one year (they cannot have more frequent screening). Once eligible, individuals attend approximately twice per year, but accept 50% of the time, hence the average time between screens was two years. Each subsequent screening offer was assumed to be independent of previous offers or acceptances. The assumptions about screening are given in Table 6.1.

Table 6.1 – Baseline screening parameter assumptions in the model.

Parameter	**Value**	**Reference**
Annual attendance rate at health care settings	0.85	LaMontagne *et al* (2006) Salisbury *et al* (2006)
Probability of accepting a screening offer	0.5	Macleod *et al* (2005b) Pimenta *et al* (2003b)
Proportion of PN	0.2	Chapter 5
Treatment efficacy	0.95	Chapter 2.2.5
Mean delay (in days) before PN	7	Assumption from Turner *et al* (2006b)

Note: Table adapted from Turner *et al* (2006b).

6.2.2 Effectiveness of screening

The impact on the prevalence of ***Strategies 1-3*** after 10 years of continuous screening is shown in Figure 6.1 (pre-screening prevalence is 3.2%). The biggest reductions in the prevalence are seen when the youngest age group is screened compared to no screening. Smaller reductions are seen as older age groups are included. While 100 runs of the model were performed to reduce the stochastic variability, there was still some uncertainty in the estimates of the prevalence reduction (Figure 6.2).

Figure 6.1 – The average prevalence of chlamydia (men and women) after 10 years of screening compared to no screening, for ***Strategies 1-3***, with ages screened.

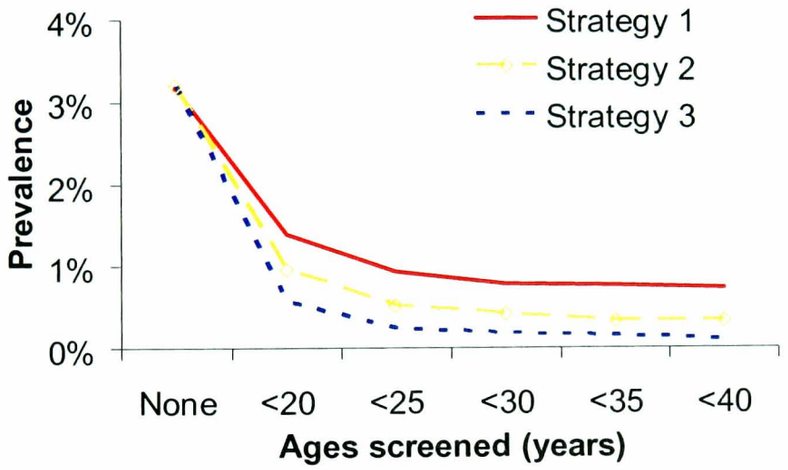
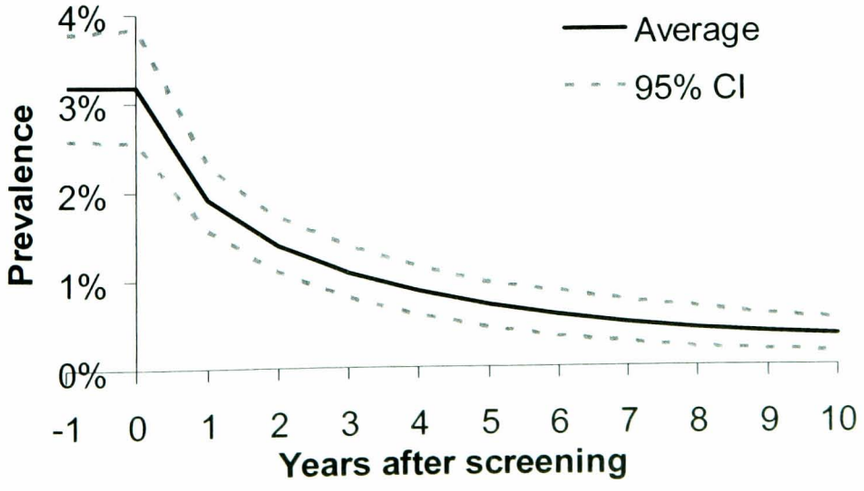


Figure 6.2 – The impact of the NCSP screening strategy (***Strategies 3,*** <25 year olds) on the overall prevalence in men and women (average and 95% CI from 100 runs).



The impact on the prevalence in men and women over time is given in Figure 6.5. For ***Strategies 1*** and ***2*** in which only women are screened, there is still an impact on the prevalence in men, due to PN. Similarly, these "knock on" effects of reductions in prevalence are also seen in those ages unscreened. If only women aged under 25 years are screened for ***Strategies 1-3***, there are reductions in those women screened (aged under 25) and also those unscreened (aged over 25 years).

Figure 6.3 – The impact of screening ***Strategies 1-3*** (screen <25 year olds) on chlamydia prevalence in men and women.

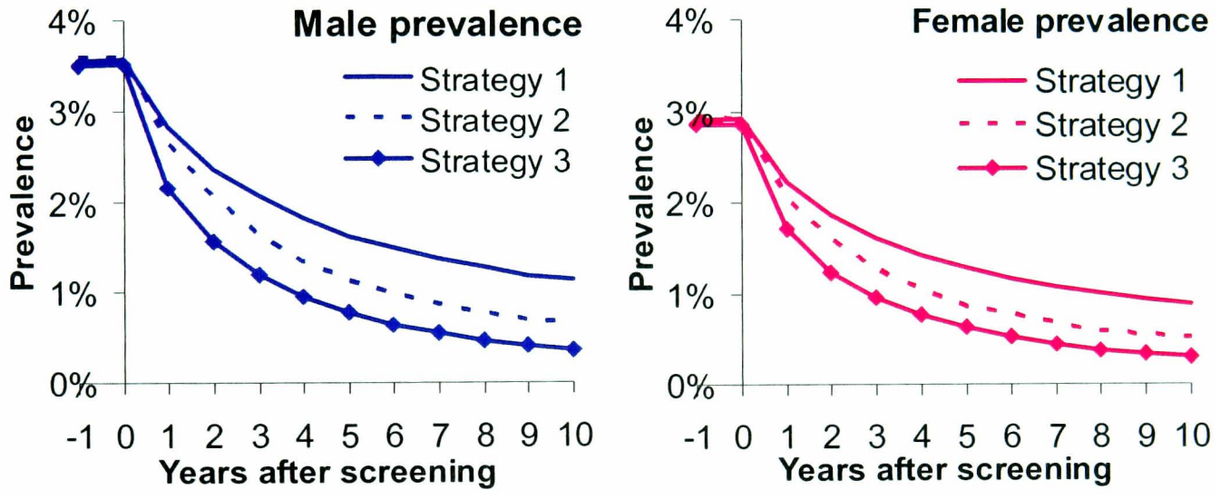
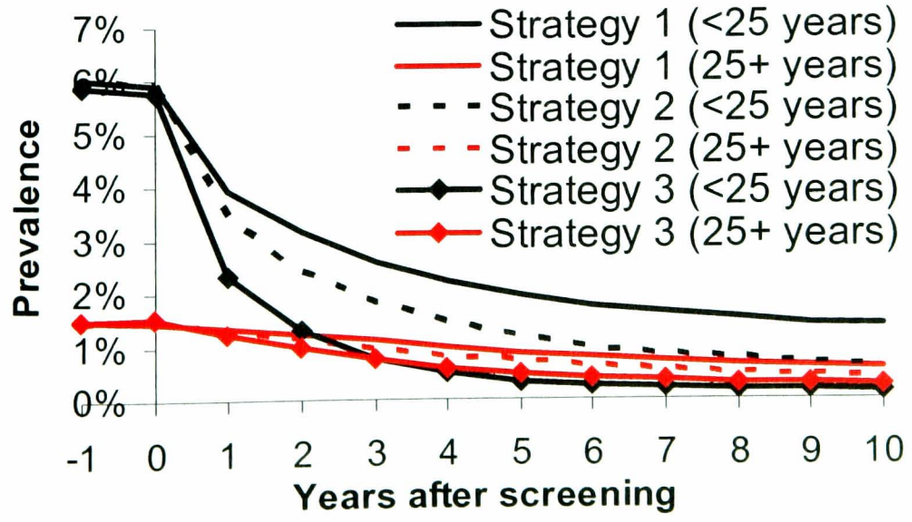


Figure 6.4 – The impact of ***Strategies 1-3*** (<25 year olds) on the prevalence in women aged under and over 25 years.



6.3 Methods

6.3.1 Approach

The dynamic model parameterised in Chapter 5 output the incident cases of symptomatic and asymptomatic chlamydial infection in men and women, and acute complications (PID in women and epididymitis in men), by year for each simulation. Owing to the complexity of the model and the logistics of running it, CT complications and the associated costs of infection, disease and screening were not incorporated in the dynamic model but in a separate cost-effectiveness (decision analytical) model instead. This was done mainly for pragmatic reasons, since the complications of infection (EP, TFI, etc.) are rare and may occur a long time after infection. Therefore, for these states to be incorporated into the dynamic model, it would have to be run on a much larger population size and over a much longer time period. Thus, the results of the individual based model were used to generate numbers of cases of infection and PID by age and time, which were inputted into the decision analytical model. Although the transmission model was individual based and stochastic, the progression and economic model was population based and deterministic. This approach of using two models to estimate the cost-effectiveness has been used previously, presumably for similar reasons (de Vries R, *et al.*, 2006; van Bergen JE, *et al.*, 2004; Welte R, *et al.*, 2000; Welte R, *et al.*, 2005).

6.3.2 Sensitivity of screening strategy assumptions

The NCSP recommendation of an annual screen for men and women aged under 25 years (***Strategy 3***) was chosen as the baseline screening strategy for sensitivity analyses (National Chlamydia Screening Programme, 2006), and the effectiveness reported (Turner KME, *et al.*, 2006b). The probability of accepting/being offered a screen was changed for both men and women from 50% (baseline) to 10%, 30% and 70%. An additional, pessimistic scenario of 10% of women and 1.4% of men accepting/being offered a screen was also modelled,

which roughly approximated the number of screens performed in men and women in the NCSP in 2004-2005 (National Chlamydia Screening Steering Group., 2005). The efficacy of PN with screening introduction was changed from 20% to 50% (applied to partners of those screened and those actively seeking treatment). A final scenario examined the cost-effectiveness if individuals only accepted a screen once, since evidence suggested that acceptance declines after the first screen acceptance (Hermann B, 2005).

6.3.3 Cost-effectiveness model

The cost-effectiveness model incorporated three elements: the costs of acute infection, the number of complications and their associated costs, and the costs of screening. Cases of PID in women were used to estimate the number of cases of EP, TFI, neonatal conjunctivitis and neonatal pneumonia, using the cost-effectiveness model. Because of the stochastic nature of infection within the dynamic model, each simulation of the dynamic model resulted in a different number of infections. Therefore the dynamic model was run 100 times for each screening scenario, and the average of these was inputted to get base case results.

6.3.3.1 Perspective

The model was constructed and parameterised from the perspective of the NHS in England, and included the direct costs of acute infection, complications and screening. Unit costs were derived from standard data sources (Chapter 2.5.2) and other published studies. Costs to the patient and wider society were not included in this analysis as recommended in the UK (National Institute for Clinical Excellence, 2004). Costs estimated in previous time periods were inflated to GB £2004 using the Hospital and Community Health Services Pay and Prices Index (Curtis L, *et al.*, 2004). All costs and complications were discounted at an annual rate of 3.5% in the base case as recommended by NICE (National Institute for Clinical Excellence, 2004). Sensitivity analyses were done using 0% and 6% for both costs and effects, and 3.5% for costs and no discounting for effects.

6.3.3.2 Effectiveness

The effectiveness of the model was the extent to which screening was able to reduce the prevalence of acute infection and associated complications. Results of the impact of screening on the reduction in prevalence are reported in Chapter 6.2.2 and Turner *et al* (2006b). This remainder of this chapter will present the impact of screening on the complications of acute CT infection and the associated heath gain or loss in economic terms.

6.3.3.3 Complications

The probabilities of developing complications are given in Table 6.2 and Figure 6.5 describes the set of equations used to estimate the total number of complications in the model. Supporting evidence is given in Chapter 2.2.2.

Table 6.2 – Risk of developing complications following acute chlamydial infection

Complication	**Probability (sample size)**	**Probability applied to:**	**Distrib. Type**	**Reference**
Symptomatic PID	1%, 10%, 30%	Asymptomatic CT	Scenario analysis*	Assumption
Ectopic pregnancy	7.6% (1309)[†]	Symptomatic PID	Beta	Weström *et al* (1992,1994)
Tubal factor infertility	10.8% (1309)[†]	Symptomatic PID but not EP	Beta	Weström *et al* (1992,1994)
Neonatal conjunctivitis	14.8% (1055)[‡]	Infected women giving birth vaginally	Beta	Rosenman *et al* (2003)
Neonatal pneumonia	7.0% (597)[‡]	Infected women giving birth vaginally	Beta	Rosenman *et al* (2003)
Epididymitis	2%	Asymptomatic CT	Fixed	Welte *et al* (2000)

Notes: *All screening strategies were run with all three probabilities; [†]Based on the number of women attempting pregnancy after a laparoscopically diagnosed PID case, PID cases was investigated based on clinical signs or symptoms of PID (Weström L, *et al.*, 1992); [‡]Based on the number of infants exposed at birth.

Figure 6.5 – Calculations used in the model to estimate the expected annual number of complications for all ages.

$$EP = p(EP) * \sum_{a_1=16}^{44}\left(PID_{a_1} * \sum_{i=a_2}^{44}\left(b(i)/(1+d)^{i-a_2}\right)\right)$$

$$TFI = p(TFI) * \sum_{a_1=16}^{44}\left(PID_{a_1} * \sum_{i=a_2}^{44}\left(b(i)/(1+d)^{i-a_2}\right)\right)$$

$$NC = p(NC) * \sum_{i=a_1}^{44}\left(CT_{a_1} * b(i)\right)$$

$$NP = p(NP) * \sum_{i=a_1}^{44}\left(CT_{a_1} * b(i)\right)$$

Where EP-ectopic pregnancy, TFI-tubal factor infertility, NC-neonatal conjunctivitis, NP-neonatal pneumonia, *p()* is the probability of the complication, a_1 *and* a_2 *are* age (see note below), *d* is the discount rate, *b(i)* is the age specific birth rate, and PID_a is the number of first PID cases by age, CT_a is the number of CT infections by age.
Note: the summation outside of the brackets (a_1) is to age 44 as the model ages correspond to the available data from Natsal 2000, while the summation inside the brackets (a_2) is to age 44 because the birth rate is virtually 0 after that age (Figure 6.6).

It was assumed that two percent of asymptomatic infections progress to epididymitis in men (Welte R, *et al.*, 2000) (Chapter 2.2.2.2). The model assumed that epididymitis occurred in the same year of infection. If re-infection occurred, the probability of developing epididymitis was assumed to be independent of previous episodes.

Three types of complications could have arisen from acute female infection: those directly affecting the immediate health of the females, those affecting her ability to reproduce, and complications affecting her newborn. The last two complications were assumed to be dependent on both the given probability that progression will occur and also on the age-specific pregnancy rates.

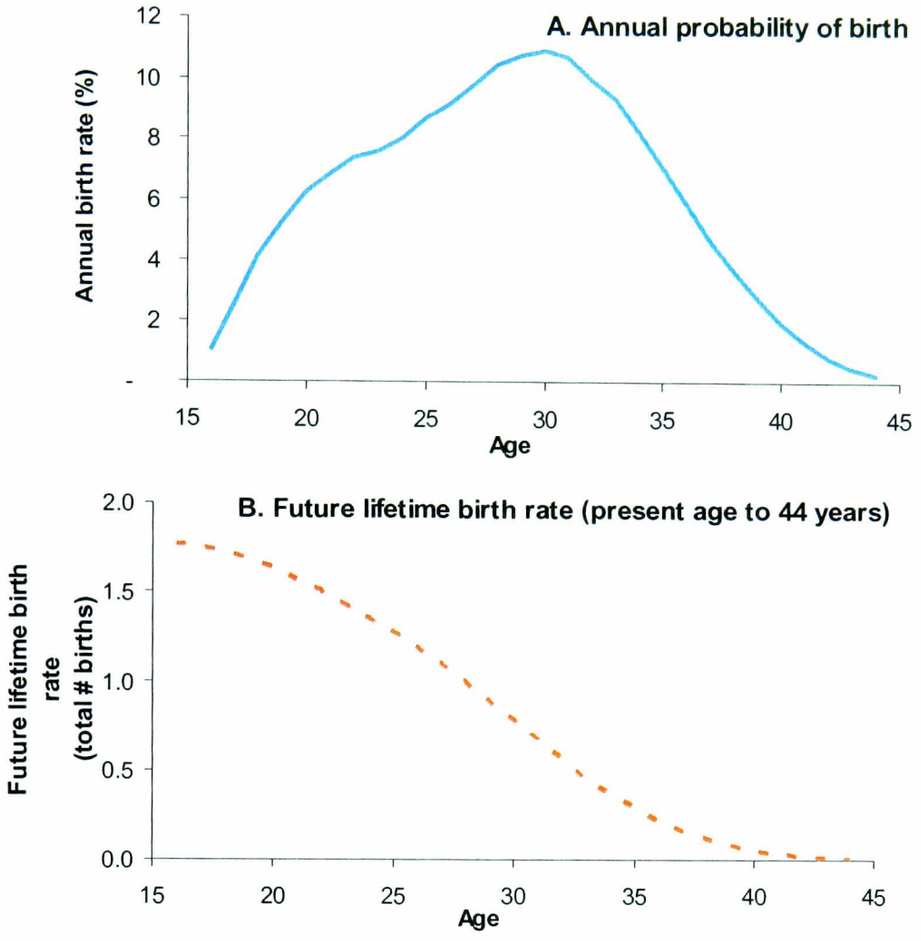
Only symptomatic PID was modelled, as there is evidence from Weström *et al* (1992, 1994) that the severity of PID symptoms is directly related to the probability of further complications such as EP and TFI, and also because the causal link between undetected

asymptomatic PID and TFI is weak (Chapter 2.2.2.1). There is conflicting evidence about the proportion of chlamydia cases that result in PID (Chapter 2.2.2.1). Therefore, three scenarios were run for no screening and each screening strategy with a PID progression probability of 1%, 10% and 30%. To determine which assumption may be closest to the actual value, the number of cases of PID estimated by the model when no screening occurred was compared to estimates of the incidence of PID in 16-44 year olds from a GP-based study (Hughes G, *et al.*, 2004). This was estimated to be between 1500 and 2400 per 100,000 women annually and included all clinical diagnoses of PID from any cause, and also potential misdiagnoses (cases were not confirmed laparoscopically).

To estimate pregnancy and neonatal complications, maternity rates for women in England and Wales for 2004 were used (Office for National Statistics, 2005a). These are rates for all women in the population, not just the sexually active women as is included in the model; however these data were used for simplicity. The maternity rate was used as a marker for the number of both births and desire for pregnancy (Figure 6.6). This will underestimate the actual number of females trying to conceive, as those not able to will therefore not be included in this dataset.

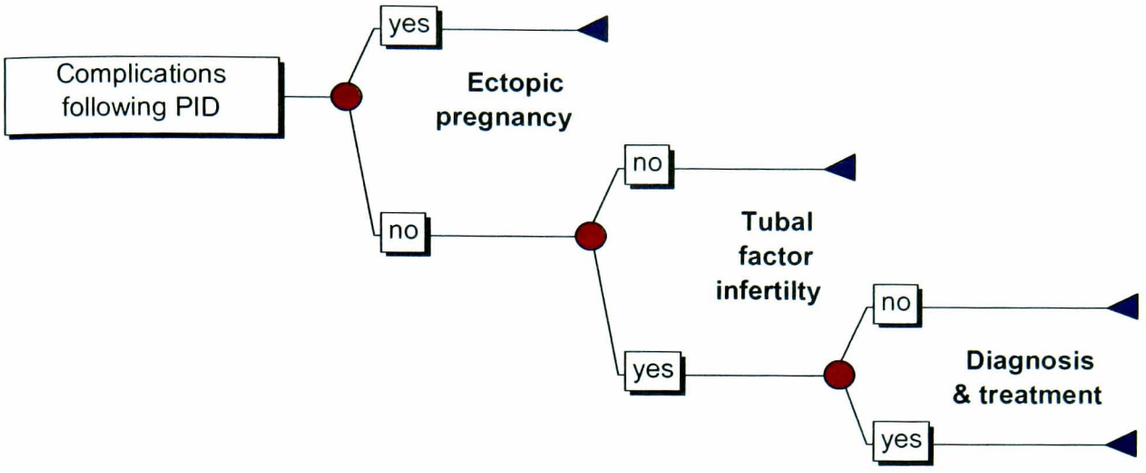
The annual age-specific maternity rate (Figure 6.6, A) was used to estimate the probability that an infected woman of a given age would give birth which may result in neonatal complications. The lifetime risk of developing EP and TFI depended on the age-specific future lifetime birth rate (this estimates the total number of future births for a woman of a given age, Figure 6.6, B). This was estimated by summing the future annual birth rate for each current age. For example, the future lifetime birth rate for a 30 year old would be the sum of her birth rate from 30-44 years.

Figure 6.6 – Age-specific maternity rate and future lifetime age-specific birth rate, for all women in England and Wales, 2004.



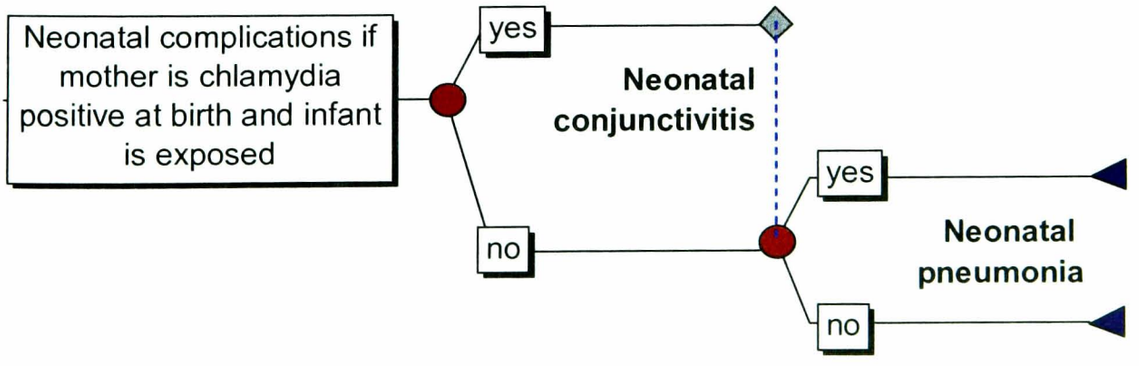
EP or TFI may occur when a pregnancy is attempted, perhaps due to tubal scarring or blocked fallopian tubes from a previous PID episode (Figure 2.1, Figure 6.7) (Cates W Jr, *et al.*, 1991). The lifetime risk for EP or TFI, based on the discounted lifetime risk of pregnancy for an infected woman of a given age (Figure 6.6), was only estimated once after initial PID. Weström *et al* (1992) reported the probability of EP for the first pregnancy following PID and confirmed TFI among those women attempting pregnancy to be 7.6% and 10.8%, respectively.

Figure 6.7 – Flow of complications in women with PID.



If a pregnant woman with acute infection exposed her infant to CT during birth (vaginal delivery), the probability of transmitting infection to her newborn, resulting in neonatal pneumonia was 7.0% and neonatal conjunctivitis was 14.8% (Figure 2.1 and Figure 6.8) (Rosenman MB, *et al.*, 2003). It was assumed that the probability of transmitting to an infant was irrespective of the presence of symptoms in the mother. Seventy-seven percent of women were assumed to have given birth vaginally (non-caesarean) (Department of Health, 2005). Since women can have more than one child during her lifetime, every new acute infection may result in neonatal complications.

Figure 6.8 – Flow of complications in neonates exposed at birth to infected mothers.



6.3.3.4 Costs

The probabilities of health care attendance and the component costs used to estimate the overall costs of acute infection and complications are given in Table 6.3 and Table 6.4, respectively.

Cost of acute infection

A proportion of symptomatic chlamydia cases were assumed to attend a GP clinic instead of a GUM clinic (Cassell JA, *et al.*, 2006). The costs were assumed to include a consultation with a clinician (average cost of GP clinic visit or 20 minute consultation with GUM consultant) and a full STI screen. This comprises testing for CT, gonorrhoea, trichomoniasis and bacterial vaginosis, including giving a sample, laboratory consumables and personnel costs, providing the results and a consultation for treatment and advice on partner notification (involves elicitation of current and recent partners, but does not include partner testing or treatment). The cost inputs are taken from earlier estimates (Chapter 4).

Cost of chlamydia complications

It was assumed that all men with epididymitis had a consultation in a community clinic (GP or GUM), and of these 10% were referred to hospital inpatient care. This estimate was based on records for epididymitis in the HES database (Chapter 2.3.3) (Department of Health, 2004a), assuming that half of all epididymitis cases in HES for men aged 16-44 were caused by chlamydia. For community settings, the average costs of a consultation, diagnosis (CT and gonorrhoea test) and treatment with Doxycycline (according to clinical guidelines (Walker PP, *et al.*, 2001)) were estimated. For hospital cases, the average cost per non-elective inpatient episode for scrotum testis/vas deferens disorders or scrotum open procedures (aged <70 years/without major complications) were estimated from the NHS Reference Costs, for Primary Care Trusts (Department of Health, 2005).

All PID cases were assumed to have had one GP clinic visit. These costs comprised the average cost of a GP consultation, cost of testing for CT and gonorrhoea and notifying of results, and the average cost of recommended PID treatment regimes (Joint Formulary Committee, 2004). It was assumed that 6.5% of PID cases were admitted to inpatient hospital care, based on the proportion of cases seen in HES compared to the midpoint estimate of incidence for those seen in GP surgeries (Department of Health, 2004a; Hughes G, *et al.*, 2004). An equal proportion (6.5%) was assumed to be treated as outpatient cases in hospital. The cost of an episode for an outpatient hospital gynaecology department and an inpatient episode of a non-elective, non-surgical treatment of a gynaecological condition were taken from the NHS Reference Costs (Department of Health, 2005).

It was assumed that all women with EP were admitted to inpatient hospital care for a termination, of which 60% were assumed to be medical (with a drug regime) and the rest surgical, based on the relative proportion of those reported as non-elective inpatients in the NHS Reference Costs (Department of Health, 2005).

It was assumed that half of women with TFI had an infertility investigation and treatment, either tubal surgery or in vitro fertilisation. The average cost of diagnosis and treatment was estimated to be the mean of that for mild and moderate TFI (£10,798 per live birth) (Philips Z, *et al.*, 2000). Women without an infertility investigation or treatment had no costs.

For neonatal conjunctivitis or pneumonia, it was assumed that there was a GP clinic visit, tests for CT and gonorrhoea, and treatment based on CDC guidelines (www.cdc.gov). A systematic review of the literature by Rosenman *et al* (Rosenman MB, *et al.*, 2003) found that 20% of cases of neonatal pneumonia were admitted to inpatient hospital care. It was estimated from HES data that these episodes lasted on average 8 days (SD 1) (Department of Health, 2004a) and it was assumed that they stayed in the special care baby unit (Curtis L, *et al.*, 2004).

Table 6.3 – Estimated probability of attending health care settings due to acute chlamydial infection and complications.

Condition	Baseline probability (Standard deviation)	Distrib.*	Reference
Symptomatically infected & actively seeking treatment			
GUM vs. GP clinic	Women: 77% (3%) Men: 95% (2%)	Beta	Cassell *et al* (2006)
Pelvic inflammatory disease			
Inpatient hospital admission	6.5% (0.6%)	Beta	Department of Health (2004a), Hughes *et al* (2004)
Outpatient hospital treatment	6.5% (0.6%)	Beta	Assumption
Epididymitis			
GP vs. GUM clinic	50% (25%)	Normal	Assumption
Inpatient hospital admission	10% (3%)	Normal	Department of Health (2004a)
Ectopic pregnancy			
Surgical vs. medical termination	60% (0.9%)	Beta	Department of Health (2005)
Tubal factor infertility			
Diagnosis & treatment	50% (25%)	Normal	Assumption
Neonatal pneumonia			
Inpatient hospital admission	20% (10%)	Beta	Rosenman *et al* (2003)

*Distributions: All normal distributions for probabilities were truncated at 0 and 1.

Table 6.4 – Estimated component costs of acute chlamydial infection and complications.

Condition	Baseline cost in £ (Standard deviation)	Reference
Symptomatically infected & actively seeking treatment (men/women)		
GP clinic visit	21 (2)	Curtis *et al* (2004)
GUM clinic visit	38 (2)	Curtis *et al* (2004)
Diagnosis	19 (1)	Adams *et al* (2004b)
Treatment	8 (1)	Adams *et al* (2004b), Clinical Effectiveness Group *et al* (2001), Joint Formulary Committee (2004)
Pelvic inflammatory disease		
Diagnosis	29 (5)	Adams *et al* (2004b)
Treatment	31 (8)	Joint Formulary Committee (2004)
Hospital inpatient episode	739 (394)	Department of Health (2005)
Hospital outpatient episode	123 (45)	Department of Health (2005)
Epididymitis		
Diagnosis	19 (2)	Adams *et al* (2004b)
Treatment	9 (1)	Joint Formulary Committee (2004), Walker *et al* (2001)
Hospital inpatient episode	854 (421)	Department of Health (2005)
Ectopic pregnancy		
Medical termination	684 (317)	Department of Health (2005)
Surgical termination	882 (407)	Department of Health (2005)
Tubal factor infertility		
Diagnosis & treatment	10,798 (4,279)	Philips *et al* (2000)
Neonatal conjunctivitis & pneumonia		
Diagnosis	18 (2)	Adams *et al* (2004b)
Treatment	2 (1)	Joint Formulary Committee (2004)
Daily hospital inpatient cost	357 (35)	Curtis *et al* (2004)

Note: All costs are normally distributed, truncated at 0, and rounded to the nearest £ for presentation.

Costs of screening and partner treatment

The costs of screening and PN were based on the analysis from Chapter 4 and associated input values. The average costs per positive and negative screen, and the cost of declining a screen were estimated. These were based on the overhead costs of a screening programme, the cost of accepting a test, giving a urine sample, LCR testing (including all consumables,

overheads and personnel costs) and notifying the patient of the result. All positive individuals were assumed to have a clinic visit for treatment with Azithromycin (National Chlamydia Screening Steering Group., 2005) and PN. The model was run 500 times with different input parameter values (specified from a given range of plausible values, distributed normally) and a normal distribution fitted to the results, similar to the analysis done in Chapter 4.3.5. The model gave an estimate of £20.04 (SD £1.69) and £31.14 (SD £1.70) for individuals screened who were negative and positive, respectively, and £6.41 (SD £1.16) for those who did not accept the screening offer. The cost of PN was based on a clinic visit, presumptive treatment with Azithromycin irrespective of infection status, with 80.6% of partners being tested for chlamydia (National Chlamydia Screening Steering Group., 2005), giving an estimate of £27.11 (SD £2.30).

6.3.3.5 Outcomes

Two outcomes were considered in the analysis: the number of major outcomes averted (MOA) and quality adjusted life year (QALY) gained. The MOAs included cases of epididymitis, PID, EP, TFI and neonatal conjunctivitis and neonatal pneumonia.

The average cost-effectiveness ratio (CER) was used to compare each strategy to no screening. The CER was calculated as: (difference in costs)/(difference in benefits), between screening and no screening, where the benefits are either MOAs or QALYs gained. However, as recommended by NICE, an incremental cost-effectiveness ratio (ICER) analysis was also done to assess the relative cost-effectiveness of alternate screening strategies (National Institute for Clinical Excellence, 2004). The ICER was calculated by ranking the programmes in order of net costs, and the additional benefits and additional costs of each programme compared with the previous strategy (excluding dominated ones) were estimated. Programmes were dominated if they cost more than the previous strategy and resulted in fewer benefits. Both the CER and ICER were estimated separately for each assumption about the progression to PID.

The time horizon for analysing the effects of screening was 10 years. Chronic complications in women (EP, TFI) and the associated costs that occurred until a woman was 44 years old were also included.

6.3.3.6 Quality adjusted life year estimates

The QALY losses from chlamydial infection and complications were estimated using quality of life weights (health utility index, HUI) taken from a study by the Institute of Medicine (IOM) (Institute of Medicine, 2000). These values were based on the consensus of an expert advisory panel. The duration of each condition was either based on the IOM estimate or from other sources (Table 6.5). The total QALY loss for each state = (1 - quality of life weight) * duration in each state. TFI was assumed to last longer than a year; therefore QALY loss from this condition was discounted in future years. Since the QALY estimates used in this analysis were based on expert opinion and the uncertainty around them is unknown (Institute of Medicine, 2000), a triangular distribution was assumed with the lower and upper estimates being 50% higher and lower than the average estimate.

Table 6.5 – Quality of life weight, duration of states, and estimated QALY loss from acute infection and complication states.

State	Quality weight	Duration (years)	QALY loss	Reference & note
Women				
Symptomatic acute infection	0.90	0.077	0.008	Institute of Medicine (2000), Turner *et al* (2006a)
Pelvic inflammatory disease (PID): overall			0.010	*Weighted for hospital care*
*PID - outpatient**	0.63	0.027	0.010	Institute of Medicine (2000)
*PID - inpatient**	0.57	0.005	0.002	Department of Health (2004a), Institute of Medicine (2000)
Ectopic pregnancy (EP): overall			0.032	*Weighted for hospital care*
*EP - inpatient**	0.23	0.008	0.006	Department of Health (2004a), Institute of Medicine (2000)
*EP - recuperation after inpatient**	0.66	0.077	0.026	Institute of Medicine (2000)
Tubal factor infertility	0.82	3.168	0.570	Collins *et al* (1997), Institute of Medicine (2000), Thurmond *et al* (1990)

(Continuation Table 6.5)

State	Quality weight	Duration (years)	QALY loss	Reference & note
Men				
Symptomatic acute infection	0.84	0.077	0.012	Institute of Medicine (2000), Turner *et al* (2006a)
Epididymitis - overall			0.011	*Weighted for hospital care*
*Epididymitis - outpatient**	0.46	0.019	0.010	Institute of Medicine (2000)
*Epididymitis - inpatient**	0.30	0.003	0.002	Department of Health (2004a), Institute of Medicine (2000)
Neonatal				
Neonatal conjunctivitis	0.97	0.042	0.001	Institute of Medicine (2000)
Neonatal pneumonia -overall			0.037	*Weighted for hospital care*
*Neonatal pneumonia - outpatient**	0.79	0.167	0.035	Institute of Medicine (2000)
*Neonatal pneumonia - inpatient**	0.55	0.022	0.010	Department of Health (2004a), Institute of Medicine (2000)

Note: *Inpatient refers to patients admitted to inpatient hospital care; outpatient is all other hospital and community care

6.3.3.7 Sensitivity analysis

A probabilistic multivariate sensitivity analysis was performed to assess the uncertainty of model assumptions using @Risk as in Chapter 4.3.5. For each dynamic model realisation (100 total for each screening strategy), the economic model was run 100 times, and for each realisation a different value for input parameters was randomly sampled from their distributions (using LHS). Details of the distributions are given in Table 6.2, Table 6.3 and Table 6.4. Average unit costs were assigned a normal distribution (with a given mean and standard deviation), truncated at 0. Where data on probabilities were available, a beta distribution was assigned. This included the probability of progressing to EP and TFI (Weström L, *et al.*, 1992), neonatal conjunctivitis and pneumonia (Rosenman MB, *et al.*, 2003), and the proportion with medical vs. surgical terminations (Department of Health, 2005). Where evidence was unavailable for probabilities, a normal distribution was assumed (mean and standard deviation, truncated at 0 and 1). For the multivariate sensitivity analysis, PID progression was assumed to be 10%. The ICER was estimated for the costs and benefits of no screening and the top four screening strategies.

6.4 Results

6.4.1 Costs

Estimates of the average costs of acute conditions, complications and interventions are given in Table 6.6.

Table 6.6 – Estimated average costs of acute infection, complications and interventions.

Condition	Baseline cost in £ (Standard Deviation)
Acute conditions	
Symptomatically infected & actively seeking treatment for CT infection	
Men	64 (6)
Women	61 (5)
Screened & infected (men/women)	31 (2)
Screened & NOT infected (men/women)	20 (2)
Do NOT accept screen offer (men/women)	6 (1)
Partner treatment	27 (2)
Complications	
Pelvic inflammatory disease	137 (46)
Epididymitis	142 (67)
Ectopic pregnancy	762 (329)
Tubal factor infertility	10,798 (4,279)
Neonatal conjunctivitis	41 (4)
Neonatal pneumonia	612 (555)

6.4.2 PID progression

The average annual incidence of PID per 100,000 women predicted by the model was 58 (PID = 1%), 581 (PID = 10%) and 1,750 (PID = 30%). A study of PID cases found 30% (42/140) of PID cases had evidence of ever being exposed to chlamydial infection (Simms I, *et al.*, 2006b). If that is applied to the numbers seen in GP surgeries, then an estimated *maximum* of between 450 and 720 cases of PID per 100,000 annually seen in GP surgeries

may be caused by chlamydia. This suggests an estimate of around 10% progression to PID is the most consistent with the data.

6.4.3 Cost–effectiveness

Under the baseline scenario without screening, in a model population of 40,000 sexually active individuals, there were on average 1,392 major outcomes and 65 QALYs lost over 10 years (assuming a PID progression probability of 10%). For different PID progression probabilities there were on average 393 (PID = 1%) and 3,529 (PID = 30%) MOs, corresponding to 10 and 156 QALYs lost, respectively.

The average cost-effectiveness of different screening strategies (screening versus no screening) is presented in Figure 6.9 (cost per MOA for all three screening strategies for individuals aged <25 years) and Figure 6.10 (cost per QALY gained for different ages, ***Strategy 1*** and ***3***). Table 6.7 presents results of all strategies and PID progression assumptions ranked according to increasing costs. ***Strategy 1*** was the least effective strategy, but most cost-effective (i.e. lowest average cost per MOA or QALY gained). ***Strategies 2*** and ***3*** yielded similar results and were less cost-effective than ***Strategy 1***. Extending a strategy to include older ages resulted in smaller increases in health than costs, thereby increasing the CER. The average CER of the NCSP strategy under baseline assumptions and 10% PID progression was £27,269. None of the screening programmes modelled were cost saving.

Figure 6.9 – The average cost per MOA of screening ***Strategies 1***, ***2*** and ***3*** for individuals aged under 25 years, given different assumptions about PID progression.

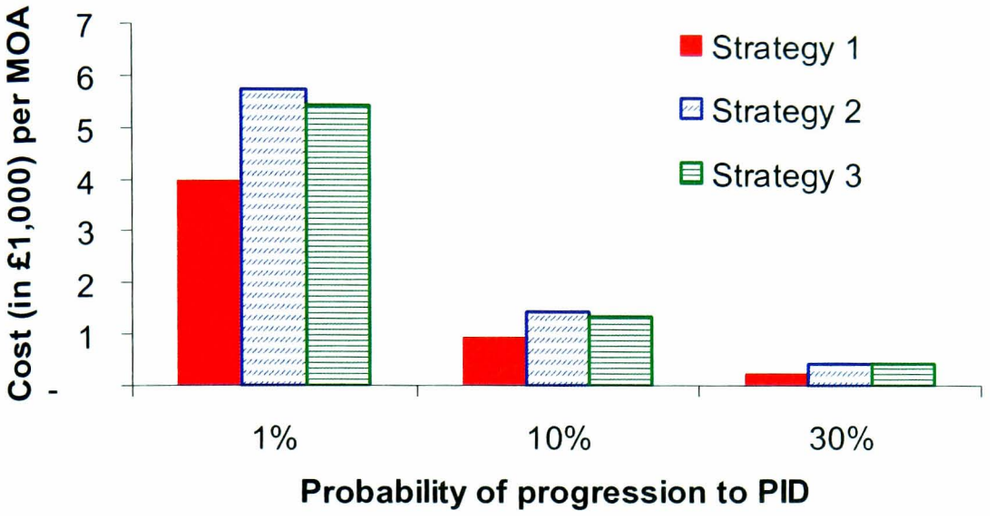
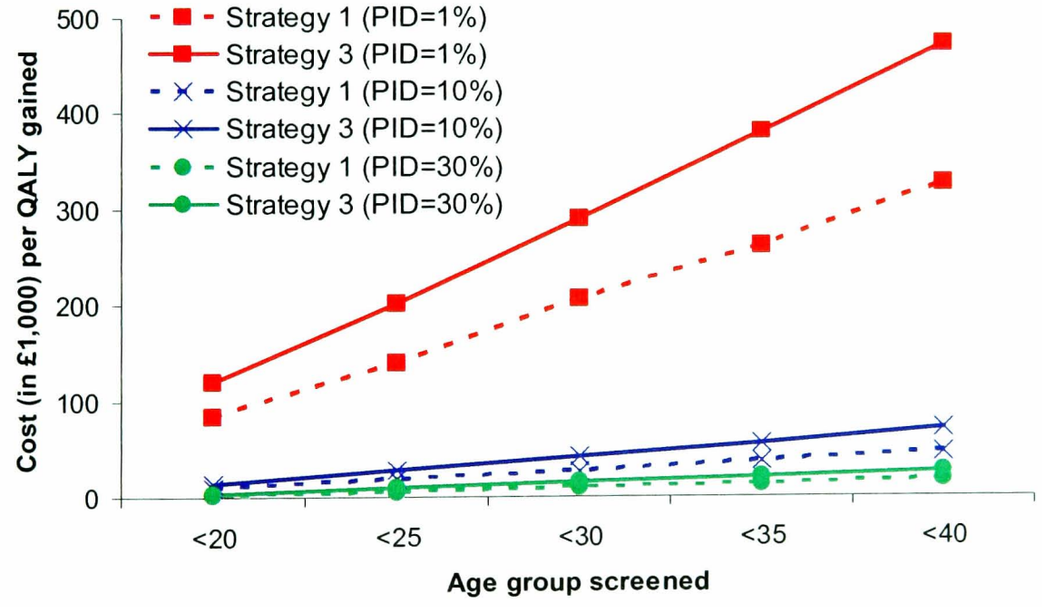


Figure 6.10 – The average cost-effectiveness (cost per QALY gained) of screening ***Strategies 1*** and ***3*** in different age groups compared to no screening, under different PID progression assumptions.



Results of the incremental cost-effectiveness analyses comparing alternate strategies are given in Table 6.7. A high ICER corresponds to a small increase in benefit over the screening programme above it but with a relatively large additional cost. The rank order of

screening scenarios was the same in the incremental analysis for all assumptions about PID progression. If PID progression were 1%, the ICER was very high (over £80,000 per QALY gained) for any screening programme compared to no screening. For PID progression of 10% or higher, the incremental cost per QALY gained when ***Strategies 1, 2,*** and ***3*** (aged under 20 years) were added was below £20,000 - £30,000 per QALY gained. However, adding screening of older age groups resulted in high ICERs (over £50,000). Several strategies showed extended dominance in Table 6.7, for all assumptions about PID progression. This occurs when the ICER for one screening strategy was higher than the one below it in the table. For example, examining the incremental cost per QALY gained in Table 6.7B (PID=10%), ***Strategy 2*** (<20) is extended dominated by ***Strategy 3*** (<20), and then both ***Strategy 3*** (<20), ***Strategy 1*** (<30) and ***Strategy 2*** (<25) are extended dominated by ***Strategy 3*** (<25). This means the strategies that are extended dominated could be excluded for consideration because there are others that yield a lower ICER. If the ICER is re-estimated and those strategies that are dominated or extended dominated are excluded, then the ICER (QALY gained) of the remaining strategies are ***Strategy 1*** (<20) is £9,204, ***Strategy 3*** (<20) is £28,062 and ***Strategy 3*** (<25) is £77,213. Given the NICE threshold, then ***Strategy 3*** (<20) would be acceptable but ***Strategy 3*** (<25) would not acceptable on cost-effectiveness grounds.

Table 6.7 – Cumulative major outcomes, QALYs lost and costs expected over 10 years, the incremental cost per outcome for each screening strategy, and the average cost per outcome (compared to no screening) for each assumption about pelvic inflammatory disease (PID) progression: A. PID = 1%, B- PID = 10%, C- PID = 30%.

PID = 1%

	Total MO	Total QALYs lost	Total cost (£)	Incremental cost (£)/MOA	Incremental cost (£)/QALY gained	Average cost (£)/MOA	Average cost (£)/QALY gained
Baseline - No screening	393	10	108,408	-	-		
Strategy 1 <20	256	6	430,991	2,364	84,337	2,364	84,337
Strategy 2 <20	222	5	670,680	7,118	241,271	3,305	116,693
Strategy 3 <20	201	5	739,267	3,125	149,745	3,284	119,562
Strategy 1 <25	215	5	811,689	Dominated	Dominated	3,960	139,219
Strategy 1 <30	203	5	1,196,464	Dominated	Dominated	5,754	207,198
Strategy 2 <25	171	4	1,378,328	21,573	736,387	5,728	206,685
Strategy 3 <25	137	3	1,494,862	3,474	157,304	5,432	201,371
Strategy 1 <35	189	4	1,577,516	Dominated	Dominated	7,204	262,845
Strategy 1 <40	185	4	1,959,279	Dominated	Dominated	8,905	326,900
Strategy 2 <30	149	3	2,088,871	Dominated	Dominated	8,122	296,053
Strategy 3 <30	114	3	2,253,126	32,374	1,544,567	7,696	290,770
Strategy 2 <35	140	3	2,799,862	Dominated	Dominated	10,657	389,895
Strategy 3 <35	104	2	3,015,808	75,208	3,161,809	10,067	381,688
Strategy 2 <40	133	3	3,517,839	Dominated	Dominated	13,157	485,712
Strategy 3 <40	94	2	3,773,363	76,841	6,909,379	12,271	474,314

B. PID = 10%

	Total MO	Total QALYs lost	Total cost (£)	Incremental cost (£)/MOA	Incremental cost (£)/QALY gained	Average cost (£)/MOA	Average cost (£)/QALY gained
Baseline - No screening	1,392	65	310,695		-		
Strategy 1 <20	883	39	553,352	477	9,204	477	9,204
Strategy 2 <20	736	31	771,367	1,484	29,416	703	13,640
Strategy 3 <20	673	29	832,498	959	24,103	726	14,371
Strategy 1 <25	739	32	918,213	Dominated	Dominated	930	18,476
Strategy 1 <30	645	28	1,283,628	16,415	978,039	1,303	26,459
Strategy 2 <25	584	24	1,462,494	2,928	44,109	1,426	28,212
Strategy 3 <25	468	19	1,556,572	807	19,352	1,348	27,269
Strategy 1 <35	633	28	1,666,599	Dominated	Dominated	1,788	36,849
Strategy 1 <40	610	28	2,048,769	Dominated	Dominated	2,224	46,404
Strategy 2 <30	491	20	2,157,585	Dominated	Dominated	2,051	41,470
Strategy 3 <30	400	17	2,308,023	11,059	302,328	2,013	41,461
Strategy 2 <35	460	20	2,869,275	Dominated	Dominated	2,745	56,481
Strategy 3 <35	363	16	3,064,432	20,479	747,964	2,676	55,987
Strategy 2 <40	444	20	3,582,115	Dominated	Dominated	3,453	71,953
Strategy 3 <40	343	15	3,828,432	39,230	1,938,410	3,355	70,952

C. PID = 30%

	Total MO	Total QALYs lost	Total cost (£)	Incremental cost (£)/MOA	Incremental cost (£)/QALY gained	Average cost (£)/MOA	Average cost (£)/QALY gained
Baseline - No screening	3,529	156	709,068	-	-		
Strategy 1 <20	2,216	92	796,042	66	1,364	66	1,364
Strategy 2 <20	1,878	75	974,854	529	10,402	161	3,283
Strategy 3 <20	1,676	66	1,008,678	168	3,845	162	3,338
Strategy 1 <25	1,799	75	1,110,924	Dominated	Dominated	232	4,960
Strategy 1 <30	1,641	70	1,466,413	13,279	Dominated	401	8,799
Strategy 2 <25	1,397	55	1,600,015	546	53,317	418	8,834
Strategy 3 <25	1,195	46	1,682,280	407	8,961	417	8,845
Strategy 1 <35	1,574	68	1,842,956	Dominated	Dominated	580	12,987
Strategy 1 <40	1,508	66	2,213,265	Dominated	Dominated	744	16,829
Strategy 2 <30	1,200	48	2,277,375	Dominated	Dominated	673	14,589
Strategy 3 <30	1,018	41	2,419,181	4,181	149,930	681	14,877
Strategy 2 <35	1,138	47	2,991,631	Dominated	Dominated	955	21,068
Strategy 3 <35	909	38	3,163,011	6,835	238,076	937	20,783
Strategy 2 <40	1,071	46	3,696,199	Dominated	Dominated	1,215	27,228
Strategy 3 <40	852	37	3,921,645	13,304	714,049	1,200	26,966

Note: all costs and outcomes are discounted at 3.5%. Results are presented in rank order of total costs, which include costs of infection, complications and programme costs. Dominated means that the MOA or QALYs gained is less than the non-dominated strategy above it in the Table.

6.4.4 Sensitivity analyses

The sensitivity of the estimated cost-effectiveness to the intervention assumptions given the NCSP strategy (***Strategy 3***, <25 years) are presented in Table 6.8. Low acceptance resulted in a higher CER compared to the baseline of 50% acceptance. Increasing the effective partner notification rate from 20% to 50% reduced the cost-effectiveness ratio by about 10%. Offering men and women aged under 25 years a single screening test was more cost-effective than continuous screening, mainly due to the much lower costs. The impact of changing the discount rate is given in Table 6.9.

Table 6.8 – Sensitivity of the estimated average cost-effectiveness of screening compared to no screening to the choice of intervention parameter.

PID rate	Scenario	Net MOA	Net QALY	Net costs (£)	Cost (£)/ MOA	Cost (£)/ QALY gained
1%	**Screening baseline**	**255**	**7**	**1,386,454**	**5,432**	**201,371**
	Acceptance=F-10%, M-1.4%	70	2	1,290,587	18,308	643,037
	Acceptance=10%	117	3	1,315,002	11,240	407,440
	Acceptance=30%	220	6	1,356,937	6,182	231,433
	Acceptance=70%	275	7	1,404,474	5,101	190,166
	PN = 50%	286	8	1,415,138	4,953	186,321
	Screen only once	187	5	530,449	2,830	104,007
10%	**Screening baseline**	**924**	**46**	**1,245,877**	**1,348**	**27,269**
	Acceptance=F-10%, M-1.4%	302	15	1,241,250	4,106	83,717
	Acceptance=10%	443	22	1,245,655	2,809	57,445
	Acceptance=30%	807	40	1,234,664	1,530	30,869
	Acceptance=70%	989	49	1,256,063	1,270	25,633
	PN = 50%	1,021	50	1,257,727	1,232	24,966
	Screen only once	677	34	429,762	635	12,814
30%	**Screening baseline**	**2,334**	**110**	**973,212**	**417**	**8,845**
	Acceptance=F-10%, M-1.4%	762	35	1,156,289	1,518	33,241
	Acceptance=10%	1,121	51	1,115,870	995	21,676
	Acceptance=30%	2,030	95	1,005,087	495	10,605
	Acceptance=70%	2,481	117	969,306	391	8,320
	PN = 50%	2,599	122	960,098	369	7,899
	Screen only once	1,735	81	227,799	131	2,826

Note: The baseline is the NSCP strategy (***Strategy 3*** - annual screen offer to men and women under 25 years old). Under baseline assumptions, screening acceptance is 50%, effective partner notification (PN) is 20% and screening is offered annually.

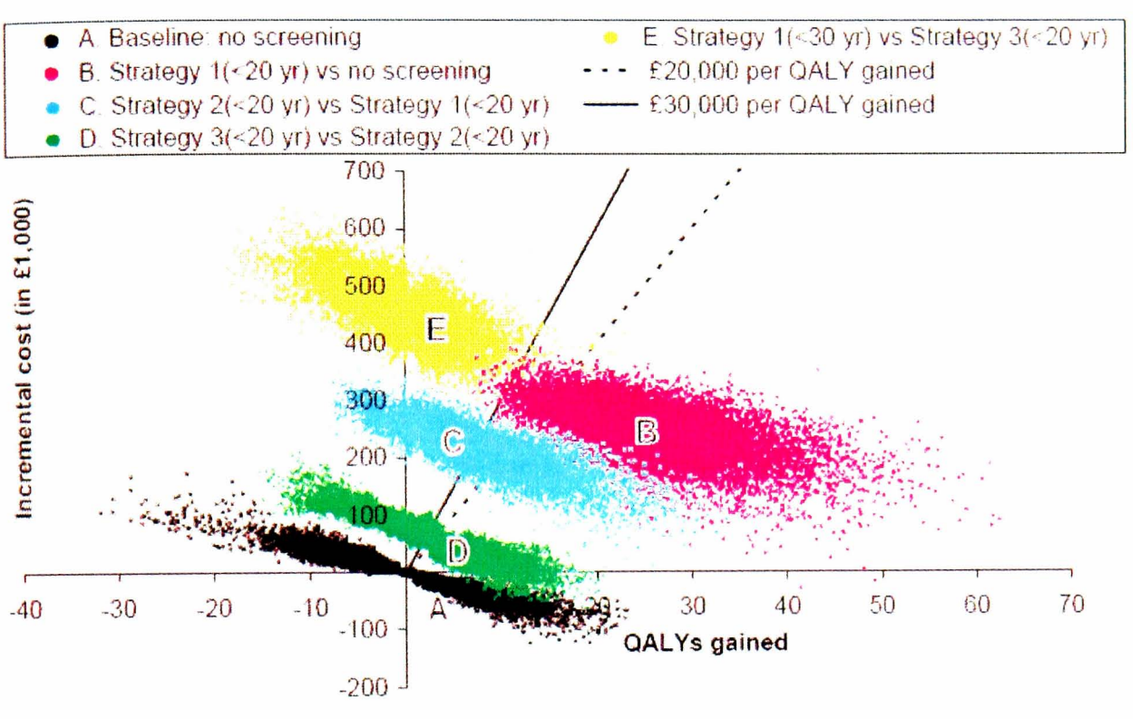
Table 6.9 – Sensitivity of the results to the discount rate for costs and complications, NCSP strategy (***Strategy 3*** - annual screening offer to men and women aged under 25 years compared with no screening).

PID rate	Discount rate-effects	Discount rate-costs	Net MOA	Net QALY	Net costs (£)	Cost (£) /MOA	Cost (£)/ QALY gained
1%	0%	0%	321	11	£1,644,897	£5,118	£144,924
	3.5%	3.5%	255	7	£1,386,454	£5,432	£201,371
	0.0%	3.5%	321	11	£1,383,644	£4,305	£121,907
	6%	6%	219	5	£1,236,641	£5,641	£243,833
10%	0%	0%	1,187	81	£1,406,086	£1,185	£17,265
	3.5%	3.5%	924	46	£1,245,877	£1,348	£27,269
	0.0%	3.5%	1,187	81	£1,220,846	£1,029	£14,991
	6%	6%	786	32	£1,131,554	£1,439	£35,620
30%	0%	0%	2,996	197	£959,671	£320	£4,872
	3.5%	3.5%	2,334	110	£973,212	£417	£8,845
	0.0%	3.5%	2,996	197	£911,004	£304	£4,625
	6%	6%	1,987	76	£922,869	£464	£12,081

6.4.5 Uncertainty analysis

Figure 6.11 illustrates the range of likely results from the probabilistic sensitivity analysis on the ICER (PID progression=10%). There is considerable uncertainty, even in the no-screening scenario, particularly in the QALYs lost from chlamydia (the spread in the horizontal axis is greater than in the vertical). It is clear from Figure 6.11 that ***Strategy 1*** (<20 years) results in large incremental QALY gains and has a high probability of falling below £20,000 per QALY gained (at 10% PID progression). Moving to ***Strategy 2*** (<20 years), results in almost half the points lying above the £30,000 per QALY gained line. Including men (***Strategy 3,***<20 years) results in small additions to the cost of the programme and small additional benefits over ***Strategy 2***, and about half of the simulations fall below £20,000 per QALY gained. Increasing the programme further (***Strategy 1***, <30 years), would result in large additional costs and few additional benefits, with nearly all results falling above £30,000 per QALY gained.

Figure 6.11 – Multivariate sensitivity analysis of the estimated incremental costs and QALYs gained for the most cost-effective strategies (PID progression is 10%).



6.5 Discussion

Estimates of the costs and cost-effectiveness of different chlamydia screening strategies including the current strategy recommended by the NCSP (***Strategy 3*** - annual screening offer to women and men aged under 25 years) are presented. None of the screening strategies modelled were cost-saving, but all resulted in better health and fewer major outcomes.

The most influential parameter was the probability of cases progressing to PID. Most other cost-effectiveness studies of chlamydia screening have used an estimate of around 25-30% progression to PID, which has included both symptomatic and asymptomatic PID (Table 2.4, Roberts *et al,* 2006). For example, Welte *et al* (2000) assumed that 25% of asymptomatic CT infections develop to PID, and that 40% of those are symptomatic PID requiring treatment. However, in their model all women with PID (symptomatic and asymptomatic) were assumed to be at risk for EP and TFI. This differs from our assumption that only women who have had symptomatic PID should have a risk on EP and TFI based on the work by Weström *et al* (1992). Recent studies indicate that the probability of asymptomatic CT progressing to PID may be much lower, by an order of magnitude (Chapter 2.2.2.1). If 30% of women with asymptomatic CT infection progressed to PID, we would expect a much higher reported incidence of PID in GP surgeries than is observed. Although some cases may be undiagnosed, the number of reported cases of PID in general practice are likely to be a reasonable upper bound on the number of cases due to CT infection, since this is PID from all causes including misdiagnosis (Hughes G, *et al.*, 2004). In fact the number of reported cases is inconsistent with progression greater than about 10%. This has major implications for the results of the cost-effectiveness analysis (Table 6.7).

If we were to consider solely the NCSP strategy (men and women <25 years) compared to no screening, the average cost-effectiveness ratio is about £27,000 when PID progression is 10%. NICE suggest that programmes with an ICER of greater than £20,000-£30,000 per

QALY gained are unlikely to be accepted on cost-effectiveness grounds (National Institute for Clinical Excellence, 2004). Therefore, the NCSP strategy appears to be within the range of acceptability on cost-effectiveness grounds if we ignore other screening strategies. However, NICE (2004) also recommend that the incremental cost-effectiveness ratio of alternate strategies is also explored. This indicates that the NCSP strategy involves a relatively high expected cost compared to the additional expected benefits. If PID progression were 10% or higher, then the full incremental analysis suggests that screening men and women under 20 should be recommended. If only 1% of infected women develop PID, then none of the screening strategies appeared to be acceptable on cost-effectiveness grounds.

The sensitivity analyses highlighted how the current strategy could be made more cost-effective. Increasing the proportion accepting or being offered a screen results in more favourable cost-effectiveness results compared to baseline (Table 6.8). The high CER for low acceptance occurs from the costs not only for those who accept screening but who also do *not* accept a screen (Chapter 4), in addition to the costs of sequelae. Efforts could be made to raise awareness about chlamydia and the benefits of regular screening to improve acceptance rates. Additionally, results from the third year of the NCSP indicate that 33% of partners were treated (National Chlamydia Screening Steering Group., 2006), which is higher than our baseline assumption of 20% and would make screening more cost-effective. Finally, the model used in this analysis was fitted to data from a review of CT prevalence studies in women (Chapter 3), but no equivalent data were available on male prevalence. New evidence from the NCSP and surveillance from STI clinics suggest that the peak prevalence is in men aged 20-25 (Table 2.3) (National Chlamydia Screening Steering Group., 2006; Health Protection Agency, 2006a). Future analyses could include new data to reflect these changes, which may in turn impact on the results.

Several papers have estimated the cost-effectiveness of CT screening using dynamic models; however, many more studies have used static models, which are incapable of including population-level effects (Chapter 2.5.3). Welte *et al* (2000, 2005) used a dynamic model similar to ours in two studies to examine the cost-effectiveness of chlamydia screening in the Netherlands. They estimated that screening might be cost saving after 10 years. The disparity in these results from ours is likely to be due to three key differences in their assumptions in both their dynamic and cost-effectiveness models. Firstly, they assumed a high proportion of individuals being treated as symptomatic cases before screening introduction (~40% compared with under 5% in our model, Chapter 5), thereby effectively removing them from developing complications. Secondly, they assumed a high probability of PID progression (25%). Thirdly, costs for most complications were much higher than those assumed in our model. For example, they assumed that 25% of PID cases will be admitted to hospital inpatient care, including an 11 day hospital stay, yielding an average estimated cost that was over 6 times higher than ours. The costs of other sequelae (EP, TFI, neonatal complications, epididymitis) were also higher than our estimates. Similarly, Townshend & Turner (2000) also estimated cost-savings after 10 years of screening, again with higher costs of complications and a higher probability of progression to PID than assumed in this analysis.

De Vries *et al* (2006) estimated that postal screening of men and women aged 15-29 years would be cost saving if the progression to PID was 25% or higher, but that if PID progression was 20%, it would cost £526 per MOA. If this is compared to ***Strategy 3*** for those aged under 30 years, if PID progression is 10% the cost/MOA is £2,013 and if PID is 30% the cost/MOA is £681. Therefore it is in the range of what is estimated in this analysis, although some of the underlying assumptions and the model structure differ. Anderson *et al* (2006) reported a similar result (£282/MOA) using Kretzschmar's model (Kretzschmar M, *et al.*, 2001) and updated values for the costs and screening inputs. Most recently, Low and colleagues (2007) also used a framework based on the model by Kretzschmar *et al* (2001), but used a much lower estimate of the progression to PID (3%). Their assumptions about the

high proportion of symptomatic infections being treated and low screening uptake meant that they did not see a large effect of screening on the prevalence, which consequently yielded a high cost per MOA (roughly £30,000 per MOA). Comparing that to ***Strategy 3*** (<25 years) for a PID progression of 1%, the results from this analysis were under £6,000/MOA, nearly five times lower than Low and colleagues estimated.

The maternity rates for all women in England and Wales were used to estimate neonatal and pregnancy complications. This may underestimate the true number of complications, since in the model, only those individuals that were sexually active were included. In Natsal 2000, roughly 25% of women reported first sex before 16, and the median age of first sex is 16 (14-19, 10^{th} and 90^{th} percentile) (Wellings *et al.*, 2001). Therefore, the values for the fertility rates (and hence the number of complications) would be expected to increase, especially in the youngest ages. This would increase the number of MOAs and QALY loss both in the baseline and screening strategies, which would probably make screening slightly more cost-effective, holding all other inputs constant. This can be explored in future work.

The screening costs in the current analysis were taken from the Chlamydia Pilot Study (Chapter 4). The initial set up costs of the NCSP are likely to include costs not modelled in this analysis, including training costs, computerisation costs, personnel, etc. Therefore this analysis may underestimate the true costs of a screening programme, thereby making screening appear more favourable than it may be. Additionally, in accordance with the NICE guidelines, in this study only the direct medical and screening costs were examined. Including additional costs, such as costs to those screened (Chapter 4.5) could be included in further analyses, along with other societal costs. Finally, costs associated with false positive or false negative tests were not considered in this analysis. False positive tests result in costs due to treatment and partner follow-up. If CT prevalence declines, the probability of false positive results increases. Individuals with false positive tests may incur psychological and social costs associated with disclosure of diagnosis to sex partners and stigma attached to

STIs (Duncan B, *et al.*, 2001) (Chapter 2.4.5), with no compensating benefit resulting from treatment gained by those infected.

In this analysis two outcomes were used: MOAs and QALYs gained. MOAs are an intermediate outcome, and it is difficult to compare results to other health interventions. Additionally, studies have also included different outcomes as major outcomes of CT (Chapter 2.5.3), which means that it is difficult to compare results of the cost per MOA even across CT screening studies. However, all but two cost-effectiveness studies (Walleser S, *et al.*, 2006; Hu D, *et al.*, 2004) have used MOAs or other intermediate outcomes such as cost per case treated (Chapter 2.5.3) including the cost-effectiveness analysis by the ClaSS study (Low N, *et al.*, 2007). Both Hu *et al* and Walleser *et al* used the IOM values to estimate the cost per QALY gained, as these are the only available estimates currently published. Additionally, only the QALY loss from CT complications were included, although there may be QALY loss from screening itself, such as the negative impact and stigmatisation of a positive test (Chapter 2.4.5, Chapter 7). The QALY estimates could be improved to gain a better understanding of the health loss from CT infection and complications, and should be an area of future work.

Ten years was chosen as the time period for analysis of the cost-effectiveness, to make these results comparable to what other studies have done. However, choosing a different time period would change the results of the CER and might possibly affect the decisions about screening. If the period is shortened, to one year in an extreme case, the cost-effectiveness ratio is very high and would be above the NICE thresholds for all screening strategies except screening the youngest ages with a PID progression of 30%. Increasing the time period to five years makes the CER more favourable, and as the time period approaches 10 years, the CER falls further and appears to stabilise. This is due to high costs in the first few years of screening with QALY gains building year on year, which makes the CER decrease over time. Additional sensitivity analyses could be done on this in the future.

6.6 Summary

This analysis used a dynamic individual-based model combined with a cost-effectiveness model, to estimate the likely cost-effectiveness of CT screening strategies. These can inform decisions about optimum screening strategies in the context of limited health-care resources. Offering an annual screen to men and women under 25 years of age results in ICERs above the normally accepted levels when compared with screening only those aged under 20 years (although the NCSP strategy may be deemed cost-effective when compared with no screening). Results suggest that increasing screening acceptance (and/or screen offers) and effective partner notification may yield a more favourable cost-effectiveness ratio due to greater benefits without a large relative increase in costs. Since one of the greatest uncertainties that impacts on the results is the probability of progression to PID, future work should focus on understanding the natural history of this condition. Monitoring the incidence of PID as screening is introduced nationally should be a research priority.

CHAPTER 7 - DISCUSSION

"SEX DISEASE TESTING 'MISSING TARGET'"

news.bbc.co.uk, June 10, 2003

7.1 Introduction

This thesis presents a set of analyses to estimate the cost-effectiveness of CT screening in England. It is the culmination of work involving a range of approaches and methods, selected according to the data available and the results needed. Methods included using economic models to estimate costs and probability of complications (Chapters 4 and 6), statistical models to analyse factors important to CT prevalence (Chapter 3), and individual-based stochastic transmission dynamic mathematical models to estimate the impact of screening on CT prevalence and ultimately the cost-effectiveness of screening (Chapter 6). The parameterised models used in this work are based on the best available data wherever possible, so that the results are relevant to public health decision makers. Each chapter in this thesis has already included a discussion specific to the analysis presented in it. This chapter will highlight key themes and present a general discussion about the findings in this thesis.

7.2 Overview

The goal of this thesis was to examine the cost-effectiveness of chlamydia screening in England. Six years after the work for this thesis began, the Department of Health's National Chlamydia Screening Programme is screening in 26 of the 85 programme areas in England (about 40% of primary care trusts), targeting men and women aged less than 25 years (Alireza Talebi, personal communication). They report a high positivity among both men and women tested, and have implemented screening across a range of health care and non-clinical settings (National Chlamydia Screening Steering Group., 2006).

The question posed in Chapter 2.5.1.1 of this thesis, "how much does CT screening cost and is it worth introducing?" can now be re-examined. The cost-effectiveness results suggest that screening is likely to be expensive but will result in additional health gained (Chapter 6). If the NCSP was scaled up for the population of England (16-44 year old men and women in England in 2005), and assuming that the progression to PID is 10%, then over 10 years the estimated net costs (total costs under screening minus costs under no screening) of the NCSP compared to no screening would be roughly £755 million, with roughly 44,000 QALYs gained. This includes the costs of acute infection, complications and screening and related activities. If there was no screening, the costs to the NHS would be roughly £167 million over 10 years. These are large sums of money, and any decisions about the future of the NCSP should perhaps consider the costs and health gains from screening estimated here. The outcomes depend on the assumptions made about the costs, progression to complications, and about how sexual behaviour, CT transmission and treatment seeking were modelled and parameterised. In particular, Chapter 6 highlights that the progression from acute CT infection to PID is a key influence on cost-effectiveness, and varying this from 1%-30% changes the results by more than an order of magnitude, and potentially the decision to screen. This has a large impact on the incremental cost per QALY, which is generally used to determine if a programme is "worth it". Interestingly, evaluating the target NCSP strategy

(including 50% acceptance/coverage in men and women) alongside several other strategies indicates that the NCSP strategy could be deemed as costing too much for the additional health gain, compared to a less inclusive programme such as screening just the youngest age group (i.e. those aged under 20 years). However the NCSP fits into the broader sexual health strategy of education and improving access to sexual health care, and decisions on screening may be taken in that wider context.

7.3 Evidence-based results

A goal of this thesis was to create a realistic model that could be used for public health decisions about CT screening. To do this, they needed to be based on the best evidence available. This was done by including results from the systematic review and analysis of studies reporting CT prevalence (Chapter 3), CT screening costs (directly estimated from the Chlamydia Pilot Study, Chapter 4), sexual behaviour and past treatment for CT data estimated directly from Natsal 2000 (Chapter 5), and then combining them with the best evidence about complications and costs in Chapter 6. When the data needed were incomplete, missing or not credible, assumptions were made and sensitivity analysis performed to assess how important they were to the results.

The decision to implement the NCSP was based on the best evidence available at the time (Chief Medical Officer's Expert Advisory Group, 1998; Townshend JRP, *et al.*, 2000). This thesis was meant to update and build on that knowledge and explore CT screening in more detail, using new data. In doing these analyses, gaps in the literature were identified where better evidence and data are needed and further empirical work is necessary. This includes information about health seeking behaviour, biological features of infection such as PID progression and duration of infection, CT prevalence in men, PN, and screening coverage and acceptance. Data from the NCSP could contribute to updated prevalence estimates (Chapter 3), costs of screening (Chapter 4) and new evidence in the models of transmission

and screening (Chapter 5), all of which can be used to continually assess the effectiveness and cost-effectiveness of CT screening in England. Information about people's treatment seeking behaviour would refine estimates of the costs and cost-effectiveness and answer questions such as: how often do men and women attend health care settings? Which clinics to do they attend? How often do they re-attend? How likely are they to (re)accept a test based on their perceived risk? How often do they seek testing/treatment if they think they have symptoms or are at risk?

7.4 Surveillance and monitoring for the NCSP

How do we know what impact the NCSP is having on CT epidemiology? How can we compare the results from the analyses here with what is happening "in the real world"? In order to assess the model predictions and the success of the NCSP, the prevalence of infection and complications needs to be monitored.

At present, the NCSP produces summary statistics of the programme, including the number of positive tests, numbers of partners treated, and treatment statistics (National Chlamydia Screening Steering Group., 2006). This information is useful and can be used in programme evaluation. However, additional information about the epidemiology of acute CT infection and CT complications should be monitored. A main rationale for CT screening is that it reduces complications and their associated costs. Features of the natural history of CT such as progression to PID are key to estimating the cost-effectiveness of screening, yet are poorly understood at present. The phased implementation of the NCSP makes it an ideal natural experiment to estimate the impact screening might have on PID and other complications of CT infection in specific geographical regions. Yet three years into the implementation, PID trends are not being monitored as part of the NCSP.

Various databases exist for measuring these complications in England. For example, the GPRD or other primary care databases could be used to monitor PID in GP clinics. HES

could be used to monitor PID seen in hospital (Chapter 2.3.3). Both datasets have historical data before screening was implemented, and results can be extracted by geographic area, to explore the differences in areas that are screening and those that are not. Based on the results from Chapter 6 and the effectiveness of screening reported in Turner *et al* (2006b), the prevalence and complications would be expected to decline immediately following screening implementation, given high screening coverage and acceptance.

Another aspect of surveillance is monitoring the tests used for diagnosis. If CT screening does in fact reduce prevalence, then the PPV of the current tests (provided they do not change in specificity) will decrease as prevalence declines (Chapter 2.2.4). This means that increasing numbers of false positives will occur and people will be told they are infected when in reality they are not. There are negative psychological implications for this, as being diagnosed with CT often results in feelings of stigmatisation and feeling down (Pavlin NL, *et al.*, 2006; Duncan B, *et al.*, 2001; Mills N, *et al.*, 2006; Santer M, 1997). Therefore test performance should be continually monitored in the laboratories, and new tests and methods should be evaluated, as testing methods have changed very quickly in recent years. If "point of care" tests can improve sensitivity and specificity (they are not currently recommended for wide scale CT screening in England), they might prove to be useful especially among positive individuals that may not return for treatment or transmit to a partner before treatment (Vickerman P, *et al.*, 2003).

As screening and treatment of CT is implemented nationally with high coverage, some individuals may have treatment failure and there will be presumptive treatment for partners (both with and without infection). This widespread use of a single therapy (Azithromycin is mainly used in the NCSP) may exert selective pressure for the evolution of antibiotic resistance. There is no strong evidence from other countries that resistance may develop with screening introduction (Clarke J, 2006), however it remains a possibility (Wang SA, *et al.*,

2005). CT antibiotic resistance is not currently monitored in the UK, but there are plans to explore resistance testing further (Catherine Ison, personal communication).

An important component of the costs and the cost-effectiveness result (Chapter 4 and 6) is the uptake of screening. In Chapter 4 results from the Chlamydia Pilot Study indicated acceptance was around 65%, and in Chapter 6 it was assumed that there was universal coverage and a base case acceptance of 50%. However results from the first three years of the NCSP indicate that in the settings currently screening a much lower proportion of the target population is being screened, indicated by the low levels of reported testing (LaMontagne DS, *et al.*, 2004; National Chlamydia Screening Steering Group., 2005; National Chlamydia Screening Steering Group., 2006). Modelling results indicated that reducing the proportion screened (by lower acceptance/coverage) reduces the average cost of screening, reduces the effectiveness of screening (smaller impact on the prevalence, see Turner *et al*, 2006b), and makes screening less cost-effectiveness. That is, low acceptance means there are fewer people tested and treated which reduces the average cost per test, *but* screening becomes less effective and less cost-effective as the decrease in benefits is greater than the decrease in costs (Chapter 6). Therefore, increasing the number of people screened should be a priority. This may be done through education for both young adults and clinicians about the benefits of screening, or emphasis in health care setting on continuously offering the screening test. In the current structure of the NCSP, the number of screening offers are not being monitored, only the total number of screens done. Therefore, there is no way to assess if it is low test acceptance or low numbers of test offers, to target ways to improve this.

7.5 Methodological issues

This thesis adds to the current body of evidence about the prevalence, costs, biological features of CT infection and the cost-effectiveness of CT screening. In particular, it has used rigorous parameterisation methods to create a more realistic model of CT transmission and screening than previously done (Chapter 5), and is an improvement over existing models. In the most recent publication about CT screening from the ClaSS study, Low *et al* (2007) report on the cost-effectiveness of screening using a model that was calibrated to the data. No fitting method was used except a visual comparison of model results to the data. Low and colleagues have been critical of the NCSP implementation as they claim there is not enough evidence to support it (Low N, *et al.*, 2002; Low N, *et al.*, 2005; Macleod J, *et al.*, 2005a), however they have not used the available evidence optimally to create a realistic model. They adapted their model from Kretzschmar *et al* (2001), and used many of her original assumptions without incorporating new data. For example, they used 30% and 75% symptomatic infection in women and men respectively based on Kretzschmar's initial assumptions, although the evidence from Natsal 2000 has emerged that suggests that far fewer individuals have symptomatic infection warranting treatment seeking than previously thought (Chapter 5). Comparison modelling work found that if Kretzschmar's values are used in the model presented here, then before screening is implemented, nearly half of 25 year olds would have reported being treated (Turner KME, *et al.*, 2006a), which is not supported by the data (Chapter 5). The implications of this are that if many people have symptoms and get treatment early, then screening will have a much smaller impact and will be less cost-effective, which their study indicates (Low N, *et al.*, 2007). In essence, they underestimate the impact of screening, and we perhaps overestimate it.

As mentioned in Chapter 5, this model is being used and adapted for additional STI modelling in the HPA, and despite a rigorous fitting process, the work done for this thesis highlighted areas where additional improvements could be made. For example, the youngest

ages (and women) have more partners in the model than in the data (Chapter 5). Further modelling work may involve changing the model structure or by using additional data to improve the fit to behaviour. The subsequent impact on the biological parameter estimates could be assessed. The parameterisation routines found that very few individuals with infection seek treatment (0% for men and 4.5% for women). This is different from what other studies have assumed by an order of magnitude (around half of infections are symptomatic are treated). In fact, there are men who do seek treatment. The truth probably lies somewhere in between, although the data do suggest that it is closer to our estimates than those from other models, and further exploration is needed. While the work presented here is an improvement on what has been done before, we do not yet have a definitive answer about modelling sexual behaviour or CT epidemiology. There is ongoing work to compare the ClaSS and Kretzschmar models to our model, and results are forthcoming. Results from this thesis highlight the importance of rigorous model testing to understand the underlying behaviour and dynamics of infection, to create a useful public health tool.

Modelling is an abstraction of reality, and will never be able to simulate exactly what is happening. There is always uncertainty in the models, both in the assumptions we make about the model structure and the parameter estimates. Sensitivity analyses can improve our understanding about how much variation there may be in model and parameter assumptions, explore how wide the range of possible answers are, assess which factors are most important or have the biggest impact on the output or simulate different strategic options. Some of the different ways the uncertainty was handled in this thesis were: defining distributions for input parameters based on the available evidence, making the models stochastic to account for random variation and chance events, modelling different types of programmes, doing multiple runs to estimate the behavioural and biological parameters for the dynamic model, discounting the costs and effects, doing "what-if" scenarios, and combining the uncertainty from the dynamic model with the uncertainty in the economic model. Undoubtedly

uncertainty will remain, and the extent to which it affects the overall outcomes and estimates of the cost-effectiveness is unknown, but may be explored in future work.

The individual-based dynamic model used in Chapter 5 and 6 took a long time to run because of its complexity and the number of events it simulated at every time step. This meant that parameterising it was a difficult and lengthy task. It was a challenge deciding how to fit to problematic data, i.e. Natsal 2000 data in which there were discrepancies in the male and female data. There were also many different ways in which the model could have been structured and parameterised, the approach chosen was based on the best available evidence and data. As data become available in particular from the NCSP, the model could be refined or additional fitting done.

Another thing that could have been done differently and that could be done in the future is to incorporate all aspects of CT screening into the individual-based dynamic model, instead of feeding the results from this model into a separate economic model. Other models have also chosen the approach we took, by using both an individual-based dynamic component and a population-based static component (Chapter 2.5.3), because of the challenges mentioned. Incorporating all costs and outcomes into one model would allow for aspects of infection to be better modelled. For example, this might include an increased or decreased risk of infection based on previous infection (to simulate a risk factor for infection or immunity) or account for events that are rare and stochastic in the population (i.e. PID or TFI). It would also allow for better estimates of the timing of events that happen in the future (EP or TFI).

7.6 Conclusions

Screening for chlamydia appears to have a place in the array of health interventions funded by the Department of Health in England. Based on modelling work and the best evidence currently available, there is a high prevalence of CT in the UK, the costs of screening are reasonable and modelling work indicates where cost savings could be made, and CT screening may be deemed "worth it", although the results suggest a less inclusive target group may be more acceptable on cost-effective grounds. However, a conclusive answer about the cost-effectiveness of CT screening cannot be made until the progression to PID (and other CT-related complications) is better understood as it impacts the results by an order of magnitude, and is vital to estimating the health effects of CT infection. The results presented here may be controversial, as they suggest that the NCSP strategy may not be the most cost-effective method of gaining health. However there are many other reasons for screening which this analysis did not incorporate (for instance to raise awareness of issues around sexual health). It is hoped that the evidence presented here and published elsewhere can help shape decisions in the future.

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APPENDICES

Appendix 1. Publications arising from this thesis or from work related to this thesis.

Appendix 2. Full results of the systematic review from Chapter 3.

ORIGINAL ARTICLE

Chlamydia trachomatis in the United Kingdom: a systematic review and analysis of prevalence studies

E J Adams, A Charlett, W J Edmunds, G Hughes

Sex Transm Infect 2004;**80**:354–362. doi: 10.1136/sti.2003.005454

Objectives: To undertake a systematic review to obtain estimates of genital *Chlamydia trachomatis* prevalence in various populations in the United Kingdom and Ireland; to determine which populations have the highest rates of infection; and to explore the most important determinants of infection.
Methods: Electronic databases were searched using the keywords "chlamydia" and "England," "Wales," "UK," "Scotland," "Ireland," or "Britain." Additional unpublished data and references were solicited from experts. Studies were included in the analysis if *C trachomatis* prevalence was reported, and if they met inclusion criteria. Nine variables identified as potentially important descriptors of chlamydia prevalence were extracted from each study and analysed using various logistic regression models. Only studies reporting prevalence in female populations were included in the models, because there were few data from males.
Results: 357 studies were identified using the search methods, 90 of which met inclusion criteria, and 19 of which contributed to the final model. The most influential variables on prevalence were age and setting of the population tested. In general practice surgeries, the under 20 year old age group had an estimated prevalence of 8.1% (95% CI 6.5 to 9.9), 20–24 year olds 5.2% (95% CI 4.3 to 6.3), 25–29 year olds 2.6% (95% CI 2.0 to 3.3), decreasing to 1.4% (95% CI 1.0 to 1.9) in those aged over 30 years. Overall, healthcare settings had higher prevalence estimates than population based studies. For example, among under 20 year olds, estimates were 17.3% (95% CI 13.6 to 21.8) in genitourinary medicine clinics, 12.6% (95% CI 6.4 to 23.2) in antenatal clinics, 12.3% (95% CI 9.8 to 15.3) in termination of pregnancy clinics, 10.7% (95% CI 8.3 to 13.8) in youth clinics, 10.0% (95% CI 8.7 to 11.5) in family planning clinics, and 8.1% (95% CI 6.5 to 9.9) in general practice, compared to 5.0% (95% CI 3.2 to 7.6) in population based studies. The type of test, specimen used, date, and location of test were not strongly associated with chlamydia prevalence.
Conclusion: The chlamydia prevalence estimates by age and setting from the model may be used to inform chlamydia screening strategies. The systematic review revealed much heterogeneity in the studies identified, but with clear patterns of prevalence. It also indicated gaps in the knowledge about chlamydia prevalence in certain subgroups such as men and the general population.

See end of article for authors' affiliations

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Chlamydia trachomatis is the most common sexually transmitted infection diagnosed in genitourinary medicine (GUM) clinics in the United Kingdom.[1] Most acute infections in males and particularly females are asymptomatic but, if untreated, the infection may progress to severe complications. The National Strategy for Sexual Health and HIV for England has highlighted the need to screen and treat asymptomatic infection.[2] A chlamydia screening programme is being implemented in phases across England offering opportunistic chlamydia testing in select healthcare settings.[3] Robust estimates of chlamydia prevalence are essential to help determine which population subgroups should be screened to maximise screening effectiveness as the programme is rolled out nationally. Estimates of chlamydia prevalence from studies conducted throughout the United Kingdom vary considerably.[4 5] There has been no comprehensive systematic review of chlamydia prevalence ever undertaken in the United Kingdom, although a recent article on chlamydia prevalence in asymptomatic women in Europe has been published.[6] The most recent comparisons of data and overviews of chlamydia prevalence in the United Kingdom were published in 1998 or earlier,[7 8] were not done systematically, have excluded the largest, most recent studies, or have focused on prevalence in limited settings.[9–11]

Of the various chlamydia prevalence studies done in the United Kingdom, there has been considerable heterogeneity in methodologies used, making interpretation and comparison difficult. However, statistical methods are available to explore these differences. Some of the factors that might influence the overall prevalence include test setting and date, geographical location, type of diagnostic test and specimen, the age group and sex of those tested, sexual behaviour, and presence of symptoms. This study aimed to identify all studies on chlamydia prevalence in the United Kingdom including unpublished studies, explore which factors are the most important factors affecting prevalence estimates, estimate the prevalence for various populations, and explore which populations have the highest rates of infection.

METHODS

Study identification

Electronic databases (Medline via PubMed (from 1966), EMBase (from 1980), Web of Science–Science Citation Index and Social Sciences Citation Index (from 1981), SIGLE—System for Information on Grey Literature in Europe (from 1980) and HMIC: DH Data, Health Management Database) were searched using the keyword "chlamydia" with one of the following: "England," "Wales," "UK," "Scotland," "Ireland," or "Britain" for studies published up to July 2002.

Abbreviations: FPC, family planning clinic; GP, general practice; GUM, genitourinary medicine; TOP, termination of pregnancy

References from chlamydia reviews were also searched. To reduce the effects of publication bias, a letter was sent to a selection of experts in the field who had published recently on chlamydia prevalence, requesting additional published or unpublished data, and names of researchers who might have additional information. Thirty letters were sent in total, with 22 responses with information received (73% response rate).

Exclusion criteria

Studies were included in the systematic review if a specific UK population was tested for *C trachomatis*, and if the number of people tested and positive was reported. A study was excluded from the analysis if it:

- reported on prevalence in neonatal or prepubescent populations
- selected populations of chlamydia positive individuals (that is, for follow up, diagnostic comparability or treatment outcomes, etc)
- reported only prevalence among partners
- recruited only individuals with symptoms (urethral/vaginal discharge, abdominal pain, etc)
- estimated chlamydia prevalence in individuals with another infection
- used serology for diagnosis.

Data extraction

Nine variables were extracted from each study. These were (coded categories in parentheses): date of testing (before 1985, 1985–90, 1990–5, 1995–2000, after 2000, other, unknown), diagnostic test (nucleic acid amplification (LCR/PCR/TMA), antigen (EIA/ELISA/DFA/MIF), culture, mixture of tests/other, unknown), specimen collected (urine, cervical/endocervical swab, urethral swab, mixture of specimens, other, unknown), sex (female, male, both, unknown), age (<20 years old, 20–24 years old, 25–29 years old, 30+ years old, other, unknown), setting of test (general practice (GP) surgery/community clinic, family planning clinic (FPC), termination of pregnancy (TOP) clinic, GUM clinic, population based/postal survey, youth clinic, antenatal clinic, other, unknown), number of individuals tested, number of positive individuals, and study ID. If a study reported disaggregate results (that is, prevalence in males and females, multiple age groups, various settings, etc), these were reported as separate "observations," each one comprising a population with the same characteristics of extracted variables. These observations were then expanded to give individual records, each representing a person within each combination of age group, sex, setting, etc. These patient level data were treated as such in the regression analyses. When a variable did not fit into one of the specified groups, it was coded as "other." Data from many studies were collected over several years, and longitudinal studies were coded in the appropriate band when possible. Similarly, there was no way of standardising age data in the studies extracted. Age classes were defined to include the greatest number of studies, while providing meaningful results on the difference in prevalence by age. Classification by the age bands listed was chosen instead of computing the mean or median age, as the age stratification was unknown for most studies. The setting of attendance/testing (and not reason for attending) was recorded.

Geographical location was extracted from each study and is included in the appendix (see *STI* website, www.stijournal.com). However, it was dropped from the regression analysis, but did not appear to be associated with *C trachomatis* positivity. Information on patient selection and the proportion who accepted a test offer was also extracted (appendix), but not used in the model. The proportion of individuals tested with symptoms might influence the prevalence, since symptomatic individuals may be more likely to appear in clinical settings. It was extracted from the studies but was not included in the analysis because of problems comparing this variable across studies. Similarly, sexual behaviour is also thought to be an important determinant of prevalence, but very few studies included this information and it was not included in the data extraction or analysis.

After applying exclusion criteria to the studies identified in the systematic review, there was still variation in the completeness and quality of the extractable data from the remaining studies. While some studies included details about selection of study participants or population sampled, others did not. Papers were not graded for quality, and it was not used as an exclusion criterion per se if all other criteria were met.

Statistical analysis

The data were analysed using Stata version 8. The prevalence and 95% confidence interval (CI) of each observation was computed using an exact binomial method.[12] A weighted average of prevalence by setting for all studies was computed.

Logistic regression methods were used to explore the effect of the explanatory variables on prevalence. In the regression models, observations and their extracted patient level data were included if all of the variables were specified—that is, if there was no coding of "unknown" or "other." For the analysis, data from females and males were explored separately, as these were considered to be separate populations with separate indicators of prevalence. Since there were few data from men, a separate regression analysis was not performed, but the prevalence (and 95% CI) was computed.

For females, logistic regression analysis was used to assess the association between each explanatory variable (setting, test, specimen, age group, date, location, sex) and the outcome, observed prevalence. A mixed effects model was fitted via Gauss-Hermite quadrature using the *xtlogit* command in Stata, which treated all variables as fixed except for study ID, which was treated as a random effect. While it is well recognised that variable selection can introduce biases into the analysis, a backwards elimination of those explanatory variables that were apparently unimportant variables ($p>0.05$ likelihood ratio test) was performed in order to maximise the number of observations in the model. The *quadchk* command was used to check the stability of the likelihood and parameter estimates. Interactions between the explanatory variables were explored.

A random effects meta-analysis was also performed. An arcsine square root transformation of the prevalence of each subgroup was performed which had an approximate Gaussian distribution with a standard deviation of $1/(2^*(n^{0.5}))$. This was used as an estimate of the within study standard deviation in the *meta* command within Stata. The meta-analysis was done for females by age group and setting. Estimates of the prevalence and 95% CIs for the different subgroups were obtained from the mixed effects model and the meta-analysis. Results from the meta-analysis were back-transformed to provide an estimated prevalence and 95% CI. A sensitivity analysis was done to assess the impact of the larger studies. Observations with populations of over 1000 individuals were dropped from the data and the mixed effects model rerun. However, age and setting remained the only explanatory variables that were associated with the prevalence.

RESULTS

Study identification

A total of 357 studies were identified in the literature search for consideration in the analysis; 90 (27%) met the inclusion

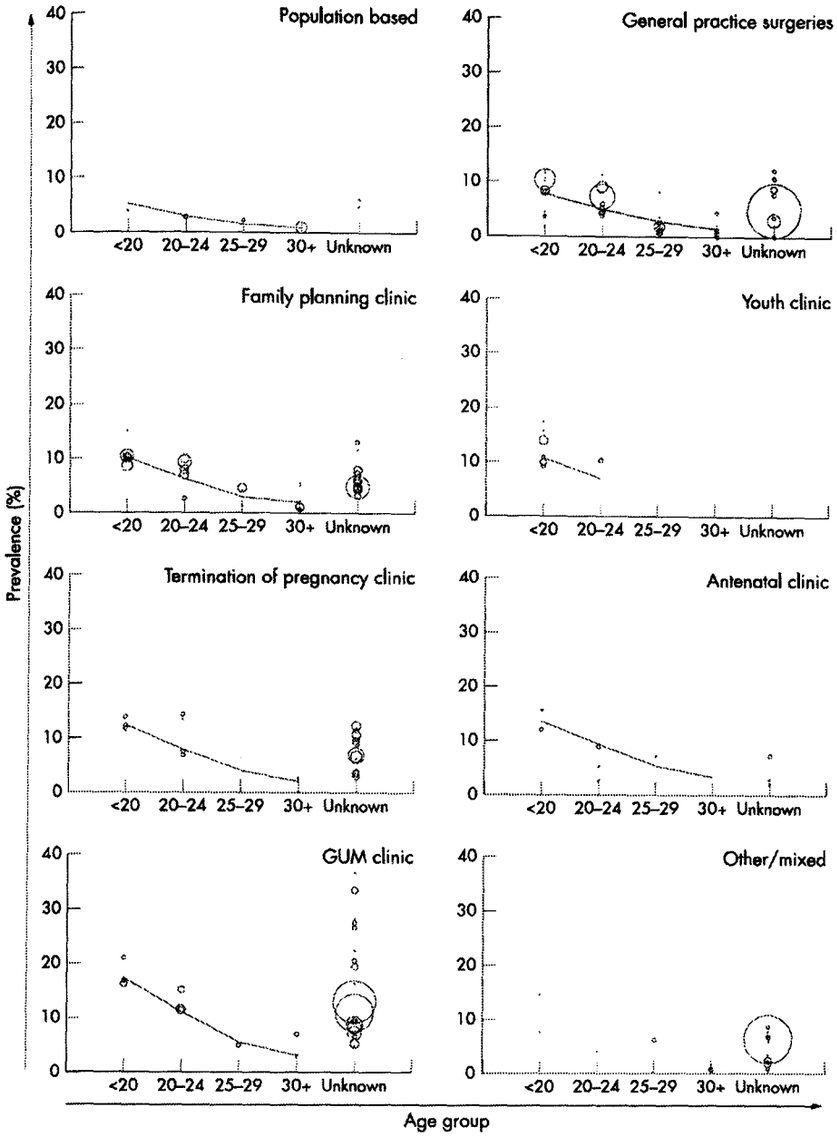

Figure 1 Reported and estimated chlamydia prevalence in females. Reported prevalence (clear bubbles) from all studies meeting the systematic review inclusion criteria, by setting and age group (irrespective of diagnostic test, specimen and date). Bubble size represents the size of the population tested (each population has a specific set of characteristics—for example, test, specimen, etc). Lines show the prevalence predictions from the final mixed model for the two significant predictors of prevalence, age group, and setting (%, 95% CI).

criteria and were included in the analysis, one of which was unpublished (see appendix for a description of the studies and extracted variables). The included studies comprised a total of 149 430 individuals tested for chlamydia, subdivided into 255 observations (that is, different combinations of age, sex, setting, etc).

Description of included studies

Selected studies varied and included those that investigated the prevalence in one specific population, changes in prevalence over time, differences in prevalence by age, prevalence comparisons among different geographical regions, large multicentre screening studies, and any combination thereof. Figure 1 shows reported prevalence in females from all studies, by setting and age group. Trends in prevalence by age group were consistent across settings, with those aged <20 years old having the highest prevalence in each setting. Many of the studies had missing data for one or more of the variables extracted, and nearly half of the studies had no usable information on patient age.

The majority of studies (84, 93%) were conducted in healthcare settings, the rest were postal surveys,[13–16] door to door interviews,[4] or in military recruits.[17] Among the healthcare settings, most individuals (70%) were tested in general practice (GP) surgeries, FPC, or GUM clinics, and 6% of individuals were tested in TOP clinics (table 1 for a summary of observations and individuals included in the analysis). Studies were based on tests done between 1973 and 2002, with over half of the observations (63% of individuals) tested from 1995 to the present. Half of the individuals were tested using nucleic acid amplification tests and nearly a quarter with antigen tests.

The number of individuals tested in each study varied considerably, ranging between 20[18] and 42 944[19] individuals, with a mean of 593 and median of 180 people tested. Over 80% of the prevalence estimates were from females and about 11% from males (the others were unknown or mixed populations). The age groups were chosen to ensure that the maximum number of individuals tested in each study could be included in the analysis and that their results were

Table 1 Descriptive statistics of the studies identified in the literature search meeting inclusion criteria. Results are listed as number and percentage of the total, at both the study level and extracted patient level

	Study level		Individual level	
	No of observations	% of total	No of individuals	% of total
Sex				
Female	205	80.3	121 152	81.1
Male	38	14.9	16 178	10.8
Both	6	2.4	8946	6.0
Unknown	6	2.4	3154	2.1
Date of testing				
Before 1985	8	3.1	2377	1.6
1985–90	28	11.0	26 419	17.7
1990–5	36	14.1	15 264	10.2
1995–2000	81	31.8	68 494	45.8
After 2000	51	20.0	25 224	16.9
Other	5	2.0	1175	0.8
Unknown	46	18.0	10 477	7.0
Diagnostic test				
Nucleic acid amplification	84	32.9	73 368	49.1
Antigen	89	34.9	34 936	23.4
Culture	27	10.5	18 163	12.1
Mixture	20	7.8	11 433	7.7
Unknown	35	13.7	11 530	7.7
Specimen				
Urine	75	29.4	31 064	20.8
Cervical/endocervical swab	99	38.8	36 090	24.2
Urethral swab	8	3.1	3036	2.0
Mixture	31	12.2	49 573	33.2
Other	2	0.8	3963	2.6
Unknown	40	15.7	25 704	17.2
Age group				
<20 years	54	21.2	13 397	9.0
20–24 years	35	13.7	14 218	9.5
25–29 years	20	7.8	4120	2.7
30+ years	38	14.9	6917	4.6
Other	56	22.0	61 794	41.4
Unknown	52	20.4	48 984	32.8
Setting				
GP surgery/community clinic	58	22.7	45 262	30.3
FPC	40	15.7	17 825	11.9
TOP clinic	34	13.3	9120	6.1
GUM clinic	45	17.7	40 001	26.8
Population based	16	6.3	4963	3.3
Youth clinic	8	3.1	1996	1.3
Antenatal clinic	12	4.7	1256	0.8
Other/mixed	42	16.5	29 007	19.5
Total	**255**		**149 430**	

informative. However, the majority of individuals tested did not fit into a distinct category or the age group was unknown (74% of individuals). Of the remaining 26% that fell into one of the age groups, 36% were aged less than 20 years, 37% were aged 20–24 years, 11% were aged 25–29 years, and 16% were over 30 years old.

Forty two per cent of studies reported information on the presence of symptoms among individuals tested. Studies reported excluding individuals with symptoms,[20–22] the proportion of chlamydia positive individuals with symptoms,[13 17 23–36] aggregate information on proportion of all patients with symptoms,[37–39] and information on symptoms in both chlamydia positive and chlamydia negative individuals.[23 40 53]

There were 25 studies that reported the prevalence from males (table 2, fig 2). A total of 16 178 males were tested across all settings (population based, GP surgery, FPC, GUM and other settings). The ages of individuals tested were mainly unknown in GUM clinics, but varied in the other settings. Prevalence estimates ranged from 0% to 33%, and the crude mean prevalence estimate by setting was similar for that in females.

Regression models and prevalence estimates

In the final mixed effects and meta-analysis models with age and setting (female data only), 19 studies (21%) representing 32 188 individuals (22%) were included, comprising the studies in which all variables were known and coded. All of the population based data were from the NATSAL 2000 study,[4] and 56% of the other settings were comprised of individual data from the Department of Health chlamydia pilot study.[5]

In the single variable analysis, all variables were associated with prevalence ($p<0.05$), (table 3). In the mixed effects model, where confounding effects of the other explanatory variables were accounted for, only age group and setting exhibited a strong association with prevalence ($p<0.0001$ and $p = 0.002$, respectively). The diagnostic test, specimen type, and date of testing did not exhibit an association with prevalence ($p = 0.5$, $p = 0.09$, $p = 0.9$ respectively). Table 3 gives the adjusted odds ratios and 95% CIs for all variables considered. In each setting, the females in the youngest age group (aged <20 years) had the highest prevalence, with the prevalence decreasing in each subsequent age group (table 4 and fig 1). For example, in GP surgeries, the prevalence

Table 2 Male prevalence estimates. Extracted data and prevalence estimates (95% CI), by setting and age group

Setting	Author/ref	Age group	Prevalence % (95% CI)
Population based	Fenton *et al*[4]	18–19	2.0 (0.2 to 6.9)
		20–24	2.8 (1.2 to 5.4)
		25–29	4.8 (2.7 to 7.6)
		30–44	1.1 (0.6 to 1.9)
	Macleod *et al*[14]	18–45	1.9 (0.0 to 10.3)
	Pierpoint *et al*[13]	18–24	1.5 (0.2 to 5.4)
		25–29	0.0 (0.0 to 3.4)
		30–35	3.9 (1.6 to 7.9)
	Rogstad *et al*[16]	19–21	1.2 (0.5 to 2.2)
	Stephenson *et al*[15]	18–35	2.5 (0.3 to 8.7)
GP surgery/ community clinic	Ainsworth *et al*[54]	<40	14.8 (4.2–33.7)
	Berry *et al*[24]	18–34	2.6 (0.3 to 9.1)
	Kudesia *et al*[55]	<30	15.2 (8.7 to 23.8)
		30–40	3.4 (0.4 to 11.7)
		>40	0.7 (0.0 to 4.1)
FPC	Harvey *et al*[52]	<20	5.7 (1.2 to 15.7)
GUM clinic	Butt *et al*[53]	Unknown	15.5 (10.1 to 22.4)
	Caul *et al*[54]	Unknown	33.3 (25.1 to 42.4)
	Crowley *et al*[44]	Unknown	24.6 (20.5 to 29.1)
	Dixon *et al*[56]	Unknown	14.6 (13.2 to 16.0)
	Evans *et al*[57]	>13	18.3 (13.0 to 24.8)
	Harry *et al*[25]	17–46	6.8 (5.5 to 8.3)
	Higgins *et al*[58]	Unknown	14.9 (11.5 to 18.8)
	Hunter *et al*[52]	Unknown	16.0 (12.9 to 19.6)
	Matthews and Wise[59]	Unknown	16.1 (12.7 to 20.0)
	Mohanty[22]	Unknown	3.5 (1.5 to 6.8)
		Unknown	5.3 (2.9 to 8.8)
	Paul *et al*[48]	Unknown	16.7 (13.9 to 19.9)
	Young *et al*[60]	Unknown	12.6 (8.4 to 17.7)
	Zelin *et al*[43]	17–77	9.6 (6.7 to 13.1)
Other	Madge *et al*[61]	Unknown	0.5 (0.0 to 2.5)
	McKay *et al*[17]	16–19	9.3 (6.9 to 12.1)
		20–24	11.0 (7.4 to 15.6)
		>25	8.7 (1.1 to 28.0)
	Pierpoint *et al*[13]	18–24	0.0 (0.0 to 2.1)
		25–29	2.2 (0.6 to 5.6)
		30–35	2.6 (1.0 to 5.6)
	Scoular *et al*[19]	15–44	9.7 (8.7 to 10.7)

estimates were 8.1% (95% CI 6.5 to 9.9) for <20 year olds, 5.2% (95% CI 4.3 to 6.3) for 20–24 year olds, 2.6% (95% CI 2.0 to 3.3) for 25–30 year olds, and 1.4% (95% CI 1.0 to 1.9) for >30 year olds. By setting the prevalence estimates also varied. For instance, among <20 year olds, estimates were 17.3% (95% CI 13.6 to 21.8) for GUM clinics, 12.6% (95% CI 6.4 to 23.2) for antenatal clinics, 12.3% (95% CI 9.8 to 15.3) for TOP clinics, 10.7% (95% CI 8.3 to 13.8) for youth clinics,

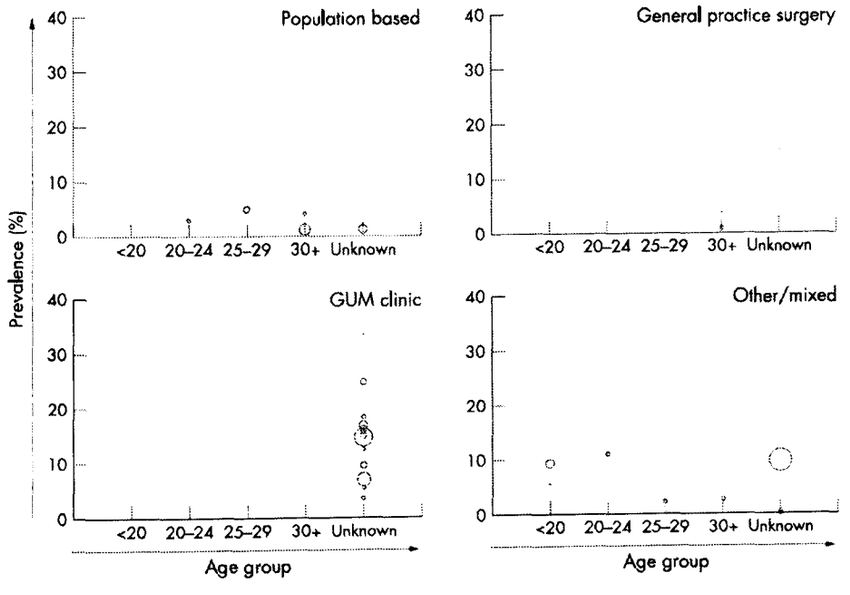

Figure 2 Reported and estimated chlamydia prevalence in males. Reported prevalence (clear bubbles) from all studies meeting the systematic review inclusion criteria, by setting and age group (irrespective of diagnostic test, specimen and date). Bubble size represents the size of the population tested (each population has a specific set of characteristics—for example, test, specimen, etc).

Table 3 Crude and adjusted odds ratios (OR) and 95% CI for the single and multiple variable models, for females only

	Crude (single variable)			Adjusted (multiple variable)		
Risk factor	**Estimated OR**	**95% CI**	**p Value**	**Estimated OR**	**95% CI**	**p Value**
Age group						
<20	Reference		<0.0001	Reference		<0.0001
20–24	0.57	0.47 to 0.67		0.62	0.52 to 0.75	
25–29	0.28	0.22 to 0.35		0.30	0.23 to 0.39	
30+	0.14	0.11 to 0.19		0.16	0.12 to 0.22	
Setting						
GP surgery/community clinic	Reference		<0.0001	Reference		0.002
FPC	1.24	0.92 to 1.67		1.27	1.00 to 1.62	
TOP clinic	1.61	1.23 to 2.10		1.60	0.20 to 2.14	
GUM clinic	3.08	2.37 to 4.00		2.39	0.72 to 3.33	
Population based	0.56	0.26 to 1.19		0.60	0.37 to 0.95	
Youth clinic	2.72	1.92 to 3.84		1.37	0.95 to 1.98	
Antenatal clinic	1.06	0.58 to 1.94		1.64	0.79 to 3.43	
Date						
Before 1985	Reference		<0.0001	NE		0.09
1985–1989	0.42	0.33 to 0.54		Reference		
1990–4	0.30	0.24 to 0.36		0.88	0.40 to 1.96	
1995–9	0.25	0.20 to 0.30		0.78	0.43 to 1.40	
After 2000	0.32	0.27 to 0.37		1.27	0.62 to 2.59	
Diagnostic test						
Nucleic acid amplification	Reference		0.04	Reference		0.5
Antigen	1.06	0.83 to 1.34		1.09	0.82 to 1.45	
Culture	1.57	1.08 to 2.29		NE		
Specimen tested						
Urine	Reference		0.0005	Reference		0.09
Cervical/endocervical swab	0.86	0.78 to 0.93		1.37	0.96 to 1.95	

The multivariate logistic regression model contained age and setting as the two predictors of prevalence; NE, not estimable as either age or setting missing in category.

and 10.0% (95% CI 8.7 to 11.5) for FPC. However, studies performed in GP surgeries also had an overall high chlamydia prevalence of 8.1% (95% CI 6.5 to 9.9) compared with 5.0% in population based studies (95% CI 3.2 to 7.6). Sensitivity analysis from the quadrature check of the final mixed model showed that the maximum relative difference in the parameters was 1.0×10^{-10} and all of the other parameters were less than that (meaning that the number of quadrature points chosen does not affect the reliability of the estimate). A global test for interactions of age and setting gave no strong evidence for an interaction ($p = 0.44$). The results from the meta-analysis for females only were similar to the logistic regression model results and are given in table 4.

The prevalence estimates from the final model appear to be a reasonable fit to the extracted data (including those that were not used to predict the model), for all settings except for population based studies. This setting did not appear to have such strong decreasing prevalence trends with age (figs 1 and 2), although there was not enough evidence with the available data to explore an age-setting interaction. Therefore, the model results (and 95% CIs) of 4.9% (3.2 to 7.6), 3.2% (2.1 to 4.9), 1.5% (1.0 to 2.5), and 0.8% (0.5 to 1.3) for females aged <20 years, 20–24 years, 25–29 years, and 30+ years respectively, are slight overestimates for those aged under 25 years, and slight underestimates for those aged over 25 years compared to the NATSAL data (3.8% (1.0 to 9.5), 2.7% (1.1 to 5.5), 2.2% (0.9 to 4.5), and 0.9% (0.4 to 1.6) in the respective age groups). However, the 95% confidence estimates from the NATSAL raw data are very wide and overlapping with the 95% CI from the model. The crude prevalence estimates by setting for just those studies included in the mixed effects model (table 4) were similar to the estimates from the literature review of all female studies in certain settings: population based, youth clinic, TOP and antenatal clinics, but slightly higher for GP surgeries, FPC, and GUM (appendix). Therefore, excluding studies with incomplete data appeared to slightly affect certain estimates, but not all.

DISCUSSION

Review of findings

This is the first systematic review of chlamydia prevalence in the United Kingdom. It has revealed a large degree of heterogeneity in the sampling and testing methods used in chlamydia prevalence studies. The regression methods gave insight into the most important variables predicting chlamydia prevalence in these studies, and provided estimates of chlamydia prevalence for females among different groups. The results highlight the high prevalence in younger age groups and certain clinical settings, regardless of other factors, and also the few data available on the prevalence of chlamydia in men.

Many variables appeared to have little impact on overall prevalence estimates. Neither diagnostic test nor specimen were apparently associated with the estimated female prevalence. While high test sensitivity and specificity are important to minimise false positive and false negative test outcomes, testing methodology does not appear to have a large impact on overall chlamydia prevalence estimated here. However, the test and specimen were the same (nucleic acid amplification, urine) within all studies, except for one, included in the regression analyses.

The majority of studies included in the analysis were conducted in health care settings. This is often the most practical and feasible way to obtain prevalence estimates because test acceptability is generally high among individuals presenting for other health related reasons, especially when offered a non-invasive urine test,[7] and testing is facilitated within the existing clinic infrastructure. Of the 30% of studies that reported the proportion of individuals that accepted chlamydia testing, a higher proportion of individuals accepted testing in GP surgeries compared to population based studies (crude mean of 82% (range 45%–99%) and 46% (range 29%–71%) respectively). This suggests that there may have been less participation bias in reported estimates from GP surgeries than in the general population surveys. However, it is unknown if the individuals who accepted testing were representative of individuals from those

Table 4 Results from the random effects model and the meta-analysis, for females only, by age group and setting (%, 95% CI), and the crude overall mean and references from data included in each setting

	Logistic regression model				Meta-analysis						
	Age group				Age group						
Setting	<20 years	20–24 years	25–29 years	30+ years	<20 years	20–24 years	25–29 years	30+ years	Crude overall mean	No ind in model	References
Population based	4.8 (3.2 to 7.6)	3.2 (2.1 to 4.9)	1.5 (1.0 to 2.5)	0.8 (0.5 to 1.3)	3.8 (1.0 to 8.3)	2.7 (1.1 to 5.0)	2.2 (0.9 to 4.1)	0.9 (0.4 to 1.5)	1.6 (1.0 to 2.3)	1725	4
GP surgery	8.1 (6.5 to 9.9)	5.2 (4.3 to 6.3)	2.6 (2.0 to 3.3)	1.4 (1.0 to 1.9)	8.6 (6.6 to 10.9)	5.9 (4.7 to 7.2)	2.9 (1.2 to 5.2)	1.1 (0.2 to 2.7)	7.1 (6.7 to 7.6)	13 207	5, 13, 40, 50, 62–64
FPC	10.0 (8.7 to 11.5)	6.5 (5.5 to 7.8)	3.2 (2.5 to 4.2)	1.8 (1.3 to 2.4)	10.0 (9.1 to 10.9)	7.4 (5.7 to 9.4)	3.8 (2.2 to 6.0)	1.5 (0.5 to 2.8)	8.1 (7.6 to 8.7)	9512	5, 32, 51, 65–68
Youth clinic	10.7 (8.3 to 13.8)	7.0 (5.1 to 9.6)	-	-	12.3 (10.0 to 14.9)	10.1 (7.0 to 13.6)	-	-	12.2 (10.8 to 13.7)	1996	5, 41
Antenatal clinic	12.6 (6.4 to 23.2)	8.3 (4.2 to 15.7)	4.1 (2.0 to 8.2)	2.2 (1.1 to 4.6)	13.5 (9.5 to 19.1)	6.5 (3.5 to 10.4)	7.2 (2.4 to 14.2)	0.0 (1.2 to 1.2)	8.5 (6.6 to 10.6)	803	5, 67
TOP clinic	12.3 (9.8 to 15.3)	8.1 (6.4 to 10.1)	4.0 (3.0 to 5.4)	2.2 (1.6 to 3.1)	13.6 (10.6 to 16.8)	9.7 (6.5 to 13.3)	2.0 (0.3 to 5.1)	1.2 (0.2 to 2.9)	8.5 (7.4 to 9.8)	2114	5, 30, 67, 69, 70
GUM clinic	17.3 (13.6 to 21.8)	11.6 (8.9 to 14.9)	5.9 (4.3 to 8.1)	3.2 (2.2 to 4.7)	17.3 (13.6 to 21.3)	12.4 (10.3 to 14.7)	4.9 (2.6 to 8.0)	5.1 (2.7 to 8.3)	12.7 (11.5 to 14.0)	2831	5, 71, 72

populations, or if they were different, and therefore the extent of any selection bias.

Notwithstanding, these results indicate that prevalence in healthcare settings is, in general, higher than in population based studies. This difference may be due to individuals at a higher risk of infection attending healthcare settings. For example, in a recent chlamydia screening pilot study nearly 40% of females who accepted opportunistic screening listed contraception as the main reason for attendance at a variety of healthcare settings.[73] Therefore, this might represent a more sexually active population than those tested in non-healthcare settings. Sexual behaviour data were not available from most studies and were not included in the analyses, but might be a good marker of infection as indicated by the NATSAL data.[3]

The presence of genital symptoms may be another reason for higher chlamydia prevalence among healthcare setting attendees. For example, in the pilot screening study 8% of individuals tested listed genital tract symptoms as the primary reason for attending the clinic.[73] This information was not consistently reported among the studies identified in the literature search, and in those included in the regression model only four studies included the proportion of positive and negative individuals with symptoms.[40 41 50 51] However, this information might be a potentially useful means of comparing the groups and may be a factor affecting the differences in prevalence, especially in non-healthcare settings.

Implications of these results

Results from these models can help inform policy on chlamydia screening. As chlamydia screening is rolled out to more sites across England as proposed in the National Sexual Health and HIV Strategy for England,[2 3] the results from this analysis strongly support the need for high coverage in younger age groups. However, this study also highlights particularly high prevalence among attenders agreeing to be screened in GP surgeries, a setting that has not been given a high priority in the current screening policy.[74] Since the GP is the first point of contact with the health system for most individuals, with 70% of males and 90% of females under 35 years old in England attending a GP surgery each year,[75] screening in this setting would be an effective way of identifying and treating large numbers of chlamydia positive individuals. The results of this study suggest that testing in FPC, TOP clinics, youth clinics, and GUM clinics would yield many positive individuals.

This analysis did not include male data. Figure 2 shows that there are very few studies reporting prevalence data in males, and the studies that are included generally have a small sample size and are not stratified by age. However, from the crude overall prevalence based on the available data in limited settings, the prevalence may be as high as that in females, although the peak in prevalence may occur at a later age.[1] The current approach is to identify infected males through partner notification of positive females. However, this might not be occurring effectively enough in practice and screening males might need to be considered for a national chlamydia screening programme.[76] This review highlights the scarcity of male prevalence data. Further studies on prevalence in males may help elucidate the burden of infection in this group, and help inform the current debate on screening men.

Estimating the effectiveness of a chlamydia screening strategy will rely heavily on prevalence in the general population and specific subpopulations. Likewise, with limited resources in a government funded intervention, modelling the cost effectiveness of various screening strategies requires

Key messages

- This study presents the first systematic review and analysis of chlamydia prevalence studies in the United Kingdom. It explores the important determinants of chlamydial infection, and provides estimates of the prevalence for various populations
- The results highlight the high prevalence among younger age groups and in clinical settings. The choice of test and specimen, and the date of testing were not strongly associated with chlamydia prevalence. There is also a paucity of data on prevalence in males and in the general population in the United Kingdom
- These prevalence estimates can be used to inform chlamydia screening strategies

prevalence estimates and confidence intervals, which can be exploited further in sensitivity analyses.

Methodology issues and further research

The approach we used allows the associations between predictors and prevalence to be explored. The estimations from this analysis are based purely on reported studies, and there may be some bias from the initial literature review from oversampling in certain populations. In particular, as with prevalence in males, there is a paucity of prevalence data from the general population as well. The results of another large ongoing chlamydia screening study (ClaSS, funded by the NHS Health Technology Assessment Programme)[25] were unavailable to include in this analysis, but are due to provide more data on chlamydia prevalence in the general population when they are published.

The results from the meta-analysis were very similar to those of the logistic regression model, as would be expected. Unlike the meta-analysis techniques used for randomised controlled trials in which stringent inclusion criteria can be defined based on study methodology, it is difficult to do this with observational studies such as the ones presented in this analysis. Since the estimates obtained are from such studies, they may be prone to biases. While all studies reported on the test setting, other variables were often missing, and therefore contribute to uncertainty in the interpretation of results.

One of our implicit inclusion criteria for the final model was that a study must have extractable data for age group and setting. While much information was lacking, 19 studies (21% of the total identified in the systematic review) still had sufficient data to include them in the logistic regression model and meta-analysis. More data might contribute additional information and be added to models (for example data from males and the general population). Ideally, these would be from well designed studies with specific information about the individuals tested (and those not tested), and information about age, screening methodology, presence of symptoms, and sexual behaviour.

A large amount of methodological heterogeneity was revealed in chlamydia prevalence studies from the United Kingdom. There are few data from specific populations such as men and the general population. A model based on extracted data from the studies identified in the literature review provided prevalence estimates that may be used to inform chlamydia screening strategies. Results indicate clear trends of a high prevalence in younger age groups that decreases with increasing age across settings, and prevalence differences by setting.

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CONTRIBUTORS

EJA, WJE, and GH participated in the study planning and design; EJA conducted the systematic review and data extraction; AC and EJA planned the analysis; and AC and EJA conducted the statistical analysis; EJA was the lead writer; and all authors provided revision and commented on the paper.

See *STI* website (www.stijournal.com) for appendix containing all studies that met the systematic review inclusion criteria, with references.

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ORIGINAL ARTICLE

Modelling the healthcare costs of an opportunistic chlamydia screening programme

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Objectives: To estimate the average cost per screening offer, cost per testing episode and cost per chlamydia positive episode for an opportunistic chlamydia screening programme (including partner management), and to explore the uncertainty of parameter assumptions, based on the costs to the healthcare system.

Methods: A decision tree was constructed and parameterised using empirical data from a chlamydia screening pilot study and other sources. The model was run using baseline data from the pilot, and univariate and multivariate sensitivity analyses were conducted.

Results: The total estimated cost for offering screening over 12 months to 33 215 females aged 16–24 was £493 412. The average cost (with partner management) was £14.88 per screening offer (90% credibility interval (CI) 10.34 to 18.56), £21.83 per testing episode (90% CI 18.16 to 24.20), and £38.36 per positive episode (90% CI 33.97 to 42.25). The proportion of individuals accepting screening, the clinician (general practitioner/nurse) time and their relative involvement in discussing screening, the test cost, the time to notify patients of their results, and the receptionist time recruiting patients had the greatest impact on the outcomes in both the univariate and multivariate sensitivity analyses.

Conclusions: Results from this costing study may be used to inform resource allocation for current and future chlamydia screening programme implementation.

Genital *Chlamydia trachomatis* infection is the most common sexually transmitted infection (STI) diagnosed in genitourinary medicine (GUM) clinics in the United Kingdom.[1] It is mainly asymptomatic and may lead to pelvic inflammatory disease (PID) in a proportion of untreated cases, which in turn may cause ectopic pregnancy and infertility in women.[2] Asymptomatically infected individuals may not have adequate opportunity or seek to be tested, leaving a reservoir of hidden infections and risk of sequelae. Therefore, screening at-risk populations can identify and treat asymptomatic infection, reduce sequelae, and perhaps impact the associated long term healthcare costs.[3 4]

The decision to implement opportunistic chlamydia screening may be based in part upon results from economic analysis, which have been undertaken using various screening assumptions.[5 6] A review of other cost effectiveness studies by Honey *et al*[7] found that depending on the model assumptions, screening females for chlamydial infection can be cost effective under various baseline prevalence estimates, especially when age is used to select women and DNA testing methods are used. In England, chlamydia screening is currently being implemented in phases across the country.[8] It is, therefore, timely to assess the cost of such a screening programme and examine in detail the relative contribution of the cost elements, using a combination of data such as the time involvement of personnel, variable costs, and overhead costs. As screening encompasses more sites across the country, information from this study may be particularly useful as it directly feeds back into programme implementation, and may help other sites that are planning and undertaking screening programmes elsewhere.

In this study, a decision analytical model was used to estimate the average cost per test offer, cost per testing episode, and cost per chlamydia positive episode, based on the costs incurred by the healthcare system. The model structure gives the ability to change the model assumptions and run a series of "what if" scenarios (for example, what if the role of practice nurses is emphasised over doctors' roles in discussing screening). It also allows for detailed analyses of uncertainty on how patients move through the screening process for both patient flow and the costs of the programme. The results from this analysis may help to advise on appropriate resource allocation to minimise screening costs and improve the efficiency of future screening programmes in the United Kingdom and elsewhere.

METHODS

Screening methodology

Data on patient flow came from a pilot study funded by the Department of Health (England) to evaluate the costs, acceptability, and feasibility of opportunisitic chlamydia screening; these methods have been fully described elsewhere.[9 10] This analysis included 16–24 year old females who were offered screening when attending GUM clinics, family planning clinics, antenatal clinics, termination of pregnancy clinics, and general practitioner (GP) surgeries. The study was undertaken between 1 September 1999 and 31 August 2000 in Portsmouth and Wirral, England. Although some men were also offered screening opportunistically at GUM and youth clinics those data are not included here. In the pilot study, research nurses were responsible for managing patients and their partners. In this analysis, we have estimated the costs of a health adviser who would have a similar role with patient and partner management. Women who accepted a test offer were asked to submit a urine sample for ligase chain reaction (LCR) testing (LCx *Chlamydia trachomatis* assay, Abbott Laboratories Diagnostic Division). Patients in the pilot study with an insufficient diagnosis were advised to get another test, and patients with an equivocal result were given the option to be treated or retested. The

Abbreviations: CI, credibility interval; GP, general practitioner; GUM, genitourinary medicine; LCR, ligase chain reaction; PID, pelvic inflammatory disease; STI, sexually transmitted infection

model used in this analysis assumed that patients with a final diagnosis of positive, insufficient, or equivocal were asked to attend for treatment (azithromycin or doxycycline; alternative regimen used for pregnant women). The positive patients were also asked to report any sexual partners from the past 3 months. For the reported partners, contact was attempted (either by the patient or the health adviser), and the partner(s) was asked to attend, receive prophylactic treatment, and give a urine sample for LCR testing. A small subset of partners was tested using other methods (n = 20); these were not included in this analysis.

Decision analysis model

Two linked decision trees (Precision Tree, version 1.0.4, Palisade Corporation) were constructed to simulate the flow of female screening episodes from initial test offer to patient treatment and partner reporting (fig 1A), and contacting partners and partner management (prophylaxis and testing) (fig 1B). Two of the nodes have branches with the same outcomes (or next steps), which are linked in the model (that is, all insufficient/equivocal diagnoses are treated as positives and go to the treatment node, and individuals may have reported partners without receiving treatment). Each node of the model returns the number of patient episodes and the expected average value of the model at that point.

Patient data extraction

In the pilot screening model, patient testing and management spanned across various healthcare settings. The methodology of the pilot study stated that patients would be tested in a variety of settings but treatment and partner notification would be undertaken in GUM clinics, by health advisers or at the site of testing. This analysis combined the number of patient episodes through each step of the tree across healthcare settings, instead of using individuals as the unit of measurement. Since some women were tested more than once and in various clinical settings,[9] each time they were offered a test they would have been included in the total number of patient episodes. This was thought to better estimate the true costs to the screening programme. However, this may contribute to a different acceptance rate than if the results were estimated based on the number of women who accepted testing, instead of counting each occasion they were offered a test. Data were also combined from Portsmouth and Wirral to give an average estimate of the value of such a screening strategy.

Two researchers (DSL, ARJ) extracted the data for each branch of the decision tree using different methods to check for accuracy (Stata, version 8.2, Stata Corporation, and SPSS, version 11.0, SPSS Inc). In both methods, screening episodes from men, women aged <16 years or >24 years and any test of cure episodes were excluded from the analysis. For both extraction methods, a stepwise approach was used following the decision trees (figs 1A, B) with the test records filtered at each node.

Costs

The overall healthcare costs of screening were estimated from direct costs from the pilot study (preliminary invoiced expense forms supplied by the Department of Health, Economics and Operational Research Division) and additional costs borne by the healthcare system (that is, clinicians involved in screening who did not receive remuneration from the screening programme, etc). Incorporating both types of

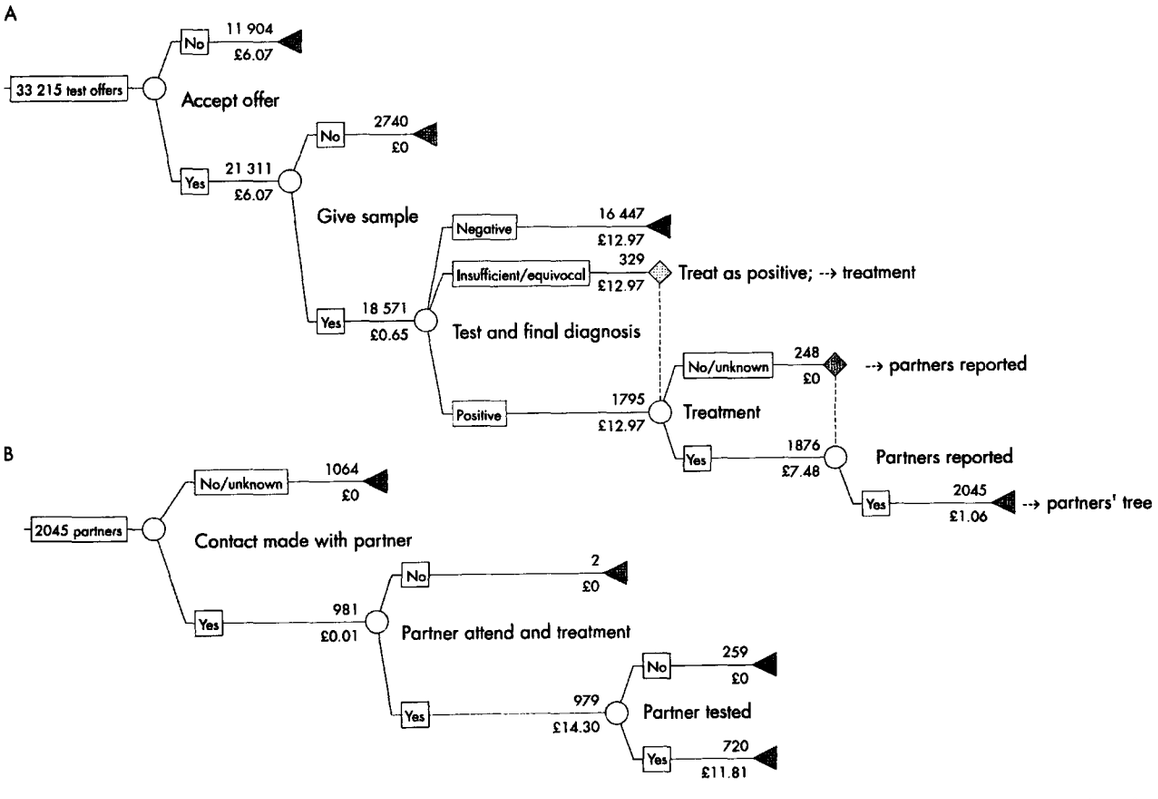

Figure 1 Schematic diagram of the screening trees used in the analysis. (A) Patient tree; (B) partner tree. For each branch option, the number who flowed through that branch is given above the line, and the baseline cost is below. Triangles indicate a branch termination, and broken lines indicate a flow to another node.

Table 1 Total annual overhead costs used in the analysis based on invoiced expenses from the chlamydia screening pilot study

Item	Cost (£)*
Total personnel overheads	**36 974**
Programme administrator	11 138
Consultant coordinator	14 362
Administration and clerical	11 474
Total capital overheads	**17 164**
Refrigerators	4421
Computers and printers	4851
Office furnishings	2621
Accommodation: rent/alterations	5271
Total running overheads	**22 329**
Travel and transportation	1244
Telephone and fax	323
Stationery and postage	12 178
Advertising	671
Other costs	7913

Source: Preliminary cost data provided by the Department of Health, Economics and Operational Research Division, and data from the questionnaire on time and patient flow.
*Costs inflated to £UK at 2001 rates.

costs was thought to more closely estimate the true costs of a chlamydia screening programme, by taking on the wider healthcare costs (but excluding the social costs and costs to the patient). The included costs were not all paid for directly by the screening study itself, and therefore would not necessarily be funded in a nationally implemented programme.

The planning and set-up costs of the screening programme were included and were based on the pilot invoiced expenses. Costs deemed to be associated with the research side of the pilot screening programme were excluded from the analysis (that is, personnel costs for analysis relating to the study evaluation, since the pilot was a research study to evaluate the feasibility and effectiveness of chlamydia screening). Recruitment of staff and laboratory upgrade costs (from EIA to NAAT testing) were also excluded.

In the pilot, a fee was paid to the clinicians for each chlamydia test initiated. However, this cost was excluded from the analysis, as it is unlikely to continue in the phased implementation of the national programme. Instead, their time costs have been accounted for in the analysis by estimating the cost of a consultation with a healthcare clinician to offer screening to a potential patient (see below).

All costs were inflated to reflect 2001 prices (£ sterling), using the Hospital and Community Health Services inflation indices for either prices or pay.[11] The adjusted costs included all overhead costs and some of the unit costs (noted in tables 1 and 2).

Overheads

There was an overhead fixed cost for the screening infrastructure, personnel and running the programme (table 1). These costs were taken from the expenditure reports and include one off and recurring costs.

While the patient flow data were taken over a 12 month period, the screening study and associated costs were incurred roughly over 2 years. Therefore, the total costs were annualised to allow for comparison with the study period data. One-off costs, including refrigerators, computers, and office furnishings, were assigned an estimated lifespan of 5 years, and an annual cost per item was estimated[12] using a discount rate of 3.5%.[11] Only one of the sites supplied these one-off costs, so these total annualised costs were doubled to account for both sites. The personnel (that is, administrators, screening coordinator, etc) and running (that is, telephones, travel/transport, etc) overhead costs from both the Portsmouth and Wirral sites (including set up and pilot costs) were halved to estimate an annual cost per item. An overhead cost per patient screening episode was estimated from the total overhead costs.

Costs at each branch

Variable costs were added at each step in the decision tree (table 2). To estimate these, costs of materials and personnel were summed (derived from the mean Portsmouth and Wirral costs when data were available). Personnel costs were derived from the estimated salary of a typical healthcare worker who would see a patient or partner (receptionists, GPs, practice nurses/health advisers, and GUM consultants), and included qualification costs, ongoing training and other additional costs such as overhead costs, to estimate the actual opportunity costs.[11 13] In the pilot, women were screened at various clinical settings and would have spoken to various healthcare personnel. This analysis assumed that the salary of a practice nurse or health adviser (both assumed to be a grade F nurse in the NHS pay scale[13]) would give a lower cost estimate, and that of a GP clinician an upper estimate. The relative involvement of both clinicians was assumed to be 50%, but was allowed to vary in the sensitivity analysis (see below). These annual costs were used to derive the cost per patient related minute (except for receptionist, which was just a cost per minute), using data on the average number of weeks worked per year, and the average number of hours per week.[11]

These data were then combined with estimates of the time spent on different screening and related activities. To obtain this, a questionnaire was sent to the primary research nurses involved in the original chlamydia screening pilot in both sites, asking about the time spent on specific activities during the screening process. These estimates were not directly measured while the pilot was conducted, and therefore are based on retrospective accounts. The baseline estimates represent an average when data from both sites were available.

The total cost of a patient (or partner) flowing through various parts of the tree (with different outcomes) will simply be the sum of the branch costs through which she or he flows.

Outcome: estimated average cost of screening

Three main outcomes were estimated: the average cost per screening offer; cost per testing episode (giving a urine sample and testing, regardless of the outcome), and cost per positive episode. The cost estimates are additive, such that the cost per testing episode includes the cost per screening offer and the cost per positive episode includes the cost per testing episode. These are simply the weighted average of all possible outcomes (and associated costs) for that decision node and all subsequent nodes. For example, the cost per offer is the weighted average of the cost of all the occasions a test offer was not accepted and the cost of all occasions a test was accepted and all of their subsequent downstream costs. Likewise, the cost per testing episode is the weighted average of those testing negative and those with a diagnosis of positive, insufficient, or equivocal. For all outcomes, these costs include those of accepting a test, the laboratory costs of testing, and the costs of notifying them of their results, and also include the weighted costs of those testing positive that may include the additional costs of treatment and partner notification for a proportion of positives.

All outcomes included the costs of partner management (contacting, treatment, and testing) as these are all part of the screening structure and contribute to the cost of the outcomes. These outcomes were assessed from the healthcare

Table 2 Total variable costs at each node of the decision tree (in bold) and their constituent inputs

Item	Baseline	Unit	Minimum	Maximum	Distribution*	Source†	Comment
Overall: personnel							
Receptionist	0.13	£/Minute				Assumption	
GP	1.01	£/Minute‡				Ref 11	
Practice nurse/health adviser§	0.42	£/Minute‡				Ref 11, 14	
Medical GUM Consultant	1.40	£/Minute‡				Ref 11, 14	
(1) Accepting the test	**3.77**	**£/Episode**	**1.50**	**5.42**			
Information leaflet	0.31	£/Item				A	Cost inflated to £UK at 2001 rates
Receptionist time	1.8	Minute	0.5	3	Uniform	A	Screening selection and invitation
GP/nurse time to discuss screening	4.5	Minute	2	7	Triangular	A	Depends on setting/clinician
% GP time compared to nurse time	50	%	0	100	Uniform	Assumption	
(2) Giving a sample	**0.65**	**£/Episode**					
Sample container	0.50	£/Item				B	Cost inflated to £UK at 2001 rates
Request form	0.15	£/Item				B	Cost inflated to £UK at 2001 rates
(3) Testing and final diagnosis	**12.97**	**£/Episode**	**10.71**	**15.25**			Cost inflated to £UK at 2001 rates
LCR test materials and personnel	11.81	£/Item	10.49	13.14	Uniform	B	Average of both sites, cost inflated to £UK at 2001 rates
Health adviser time to notify patient	2.8	Minute	0.5	5	Uniform	A	
(4) Treatment	**7.46**	**£/Episode**					
Azithromycin	7.33	£/Treatment				Ref 17	Recommended dosage[17]
Doxycycline	4.98	£/Treatment				Ref 17	Recommended dosage[17]
Health adviser time for treatment	5	Minute				A	Partner notification not included
% receiving azithromycin compared to doxycycline	15.6	%	0	100	Triangular	C	
(5) Partners reported	**1.06**	**£/Episode**	**0.85**	**1.27**			
Health adviser time for eliciting partner information	2.5	Minute	2	3	Uniform	A	
(6) Partners contacted	**0.01**	**£/Partner episode**	**0.00**	**0.13**			
Health adviser time to contact partner	1	Minute	0	10	Triangular	A	
% partners contacted by health adviser compared to patient contacted	3	%				C	
(7) Partner attendance and treatment	**14.30**	**£/Partner episode**	**7.16**	**10.74**			
Time for partner clinic visit	12.5	Minute	10	15	Uniform	A	
% partners seen by health adviser compared to GUM consultant	70	%	40	100	Uniform	Assumption	
(8) Partner tested	**11.81**	**£/Partner episode**	**10.49**	**13.14**	**Uniform**	**B**	See No 3 above.

*Distributions used in the sensitivity analysis. Uniform distributions were used to represent a large degree of uncertainty (any value over the range selected randomly); triangular distributions were used when the most likely value was known (the value drawn for each simulation was more likely to be closer to the mean value).
†A, data from interview with primary research nurses in Portsmouth and Wirral; B, preliminary pilot expenses provided by the Department of Health, Economics and Operational Research Division; C, pilot database.
‡Patient related minute.
§Mid-scale grade F nurse.

provider perspective, incorporating the costs of the screening programme and the associated wider healthcare costs. The baseline costs were used in the primary analysis.

Sensitivity analyses

Sensitivity analyses were undertaken to assess which costs and patient flow values were most important to the outcomes, and to explore the range of possible outcomes (given some parameter uncertainty) for this screening programme. The costs of such a screening programme are variable and may depend on the personnel involved in counselling and testing (that is, whether a general practitioner, health adviser, or GUM consultant discusses screening with a patient), the cost of the LCR test (which often varies between laboratories), and the numbers of patients and their partners who flow through the screening and partner decision trees.

Parameter values were drawn from specified distributions. The patient flow through the model was based on data from the pilot and was binomially distributed (proportion at each branch and the total number). The cost and the time components were mainly drawn from uniform distributions to represent a large degree of uncertainty (with any value randomly drawn from the range). Triangular distributions were assigned when there was considerable evidence that the mean closely approximated the baseline value. Then, the value used for each simulation was more likely to be drawn from a value closer to the mean. The baseline and maximum and minimum values used are given in table 2 along with the assigned distribution.

The screening programme modelled here is just one of many possible options. Therefore, univariate sensitivity analyses were performed, which varied one of the model assumptions at a time, and we then compared results to the baseline model outcomes. The input parameters were varied between the minimum and maximum values given in table 2. Additionally, several other "what if" scenarios were tested, in which one or two of the parameters were changed. This included (a) changing the relative time a receptionist rather than GP spent with a patient during screening recruitment (that is, if a receptionist spends 3 minutes recruiting each patient then a GP spends only 3 minutes per patient; or no receptionist involvement then 10 minutes of GP time per patient), (b) excluding the cost of a consultation with a clinician for non-test acceptors, (c) varying the test acceptance rate from 34% to 94% (roughly a 50% change from the baseline of 64%), (d) including a lower LCR test cost estimate of £9, thought to be more realistic of the test costs for a larger scale screening programme, and (e) changing the chlamydia prevalence of tested patients. The prevalence range was based on a lower estimate of 3% found in 18–24 year old females in a population based survey,[15] and on an upper estimate of 18%

found in females aged 16–24 attending GUM clinics.[10] The estimate for prevalence was driven by data from the decision analysis model, and it was assumed that positivity was an approximate estimate for prevalence.[16] It was estimated by: (positive + equivocal + insufficient tests)/total tests. In this analysis the baseline prevalence was estimated to be 11.4%, based on the above equation and data on screening episodes, and differed slightly from the estimated prevalence in the pilot study.[10]

A probabilistic multivariate sensitivity analysis was also performed using @risk (version 4.0.5, Palisade Corporation) running within Excel (version 2000, Microsoft). The analysis was run 1000 times, and at each simulation parameter values were randomly drawn using Latin Hypercube sampling. The parameters that varied were the input costs and times with ranges given in table 2, the distribution of individuals flowing through the tree (drawn from binomial distributions described above), and the acceptance rate (triangular distribution: minimum 34%, mean 64%, maximum 94%). Distributions for the outcome variables (cost/offer, cost/tested, cost/positive) were generated along with non-parametric 90% credibility intervals (CIs)—that is, 90% of the model simulations fell within the upper and lower CI.

RESULTS

The estimated overall annual cost of the opportunistic screening programme based on offering screening to 33 215 women aged 16–24 was £493 412. Of these costs, 80% (£394 429) were the variable patient costs, 5% (£22 515) were associated with partner management costs, and 15% (£76,468) were overhead costs for running the programme. Thirty nine per cent of the costs were personnel costs (including overheads and variable costs). About a third (37%) of the total costs were associated with the test kit cost (excluding testing personnel). These estimates are specific to the number of screening episodes examined in this analysis.

The estimated average cost per test offer given the flow of individual testing episodes in the pilot was £14.88 (90% CI 10.34 to 18.56), which included all of the downstream costs of testing, notifying patients of results, treatment and partner notification for positives, and all of the partner management costs. The average cost per testing episode was £21.83 (90% CI 18.16 to 24.20) including all downstream costs and partner management. The estimated average cost per positive episode was £38.36 (90% CI 33.97 to 42.25), which included a proportion of positive episodes having treatment and partner management. If the partner management costs were ignored, the average cost per screening offer, testing episode, and positive episode were reduced to £14.18 (90% CI 10.01 to 17.80), £20.57 (90% CI 17.18 to 22.63), and £27.35 (90% CI 24.29 to 29.98), respectively. If the partner tree was examined alone, the expected average cost per partner contact was £11.01 (90% CI 9.12 to 13.23), a weighted average of the costs of contact made with a proportion of partners, and partner treatment and testing for a proportion of partners.

Sensitivity analyses

In the univariate sensitivity analysis, varying the proportion accepting the test offer had the greatest expected impact on the cost per screening offer compared to the baseline result (fig 2). As the test acceptance increased, so did the cost per offer, and vice versa as the acceptance decreased (£18.98 for 94% acceptance; £10.74 for 34% acceptance). The relative role of the receptionist in explaining screening (compared to GP involvement) also had a large impact (25% difference from baseline) on the cost per offer. As the receptionist spent more time explaining screening and the clinicians spent less time, the average cost per offer declined from £18.59 to £13.98. Similarly, as the time associated with primary care clinicians (doctors or nurses) explaining screening to patients decreased, so did the average cost per offer.

Several of the parameters had a moderate impact on the outcomes (12% or less change from the baseline results). These included the relative involvement of GP versus practice nurse explaining screening to patients, excluding the healthcare worker consultation for non-test accepter, the test cost, and the prevalence of chlamydial infection. A two way analysis of the prevalence and the proportion accepting a test indicated that the prevalence had little impact on the outcomes, compared to the proportion accepting a test that had a large impact on the cost per test offer (fig 3).

The distribution of the results from the multivariate sensitivity analysis is shown in figure 4. The estimated average cost per positive individual was less certain (had a wider range of possible values) than the cost per offer and cost per individual tested. The multivariate sensitivity analysis results indicated that the parameters that impacted most on the outcomes were (in order of importance): the proportion accepting a screening offer, the relative importance of GP versus nurse involvement in discussing screening and patient recruitment, the GP/nurse time to discuss screening before test acceptance, the total laboratory test cost, the time to notify patients of their results, and the receptionist time spent selecting and recruiting patients.

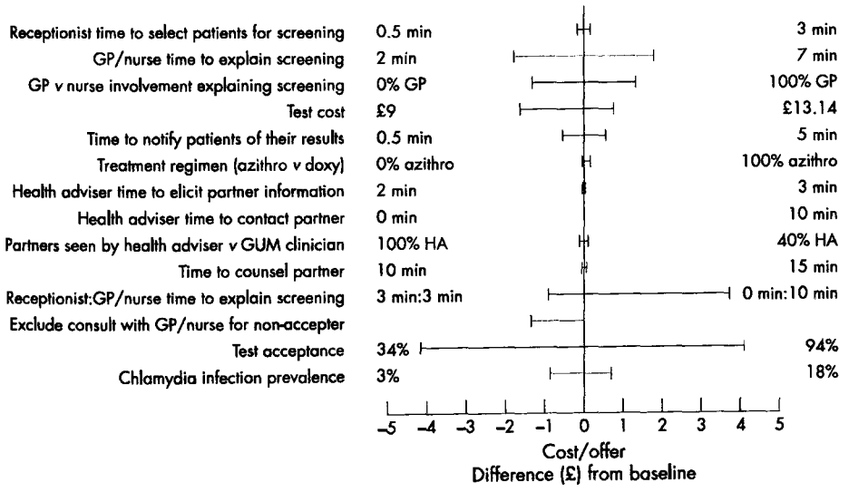

Figure 2 Results from the univariate sensitivity analysis. The difference (£) from the baseline cost per test offer for various parameters tested individually from their minimum to maximum values. A negative difference denotes a cost savings from the baseline.

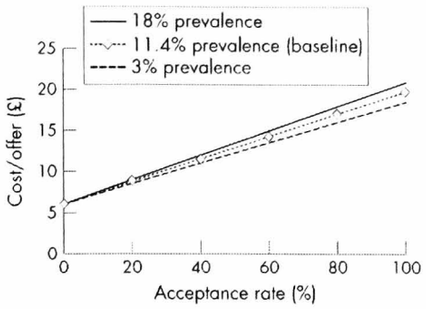

Figure 3 Results from the two way sensitivity analysis of prevalence and acceptance rate; change in the cost (£)/offer.

DISCUSSION

This analysis provides estimates of the average cost of screening from the healthcare perspective. The average cost per screening offer was about £15 including partner management. It was an additional estimated £7 more (£21 total) per person tested, and £16 more than that per person positive (total about £38).

Varying the proportion that accepted a test had the largest effect on the cost per offer, since the participants largely drive the overall costs of the screening programme. While a high test acceptance rate accounts for higher costs, it may help identify the greatest number of infections if the correct population is tested. Identifying cases through screening with the aim to reduce transmission and prevent sequelae may save money in the longer term. This is an area of ongoing research, and can be better addressed with cost effectiveness studies.

Since the laboratory test cost was important in the sensitivity analysis (in part because more than one third of the total screening cost came from LCR testing), determining the most accurate value for this variable will provide a better estimate of the overall costs of screening. Variations in laboratory cost may be explained by differences in the LCR test kit cost and laboratory personnel, and some local variation is expected. There are also various laboratory options, for the testing process including leasing equipment, buying equipment, and renting reagents, that can be examined to see if test costs can be reduced to drive down the overall laboratory costs.

Partner management contributed only 5% of the overall costs, yet it is an important part of a screening programme. While screening females will detect their infection, partner notification will identify male partners at risk who may not otherwise be tested, and treating partners may prevent both re-infection and onward transmission of chlamydia. The costs of partner management were included in the screening model, and it does not appear to make a difference to the cost per screening offer or cost per testing episode if it is included or not, although it does impact the cost per positive episode.

The infrastructure in place for screening may remain (for example the overheads), irrespective of the numbers being tested and treated, at least in the short run. Roughly 25% of the overhead costs were one-off costs such as capital items (refrigerators, office furnishings, computer equipment) that would probably not need to be spent again if more tests were done. These costs would, however, be necessary if a new site were to implement a screening programme. Screening start-up costs may be used for these capital costs, unless they could be accommodated and streamlined within the current healthcare infrastructure. This could be explored in future analyses.

Results from the multivariate and univariate sensitivity analyses highlight areas of uncertainty in the data that influence the costs of screening. For example, the time spent by clinicians explaining screening had a large impact on the costs because of its high variability and impact on all screening offers. Refining this and other estimates may give more precise estimates of the costs involved. However, some of the costs incurred in the pilot study, such as clinician time explaining screening, may not be incurred in future screening paradigms[8] because patients will be expected to self select for screening and there would be minimal involvement of staff for recruitment. Time and motion studies can be conducted to better understand the flow of people through screening and the costs involved in each step. This information can be used to streamline the process and reduce costs within the existing infrastructure.

The costs and resources will be dictated at a local level to a certain extent, so variation in the outcomes would be

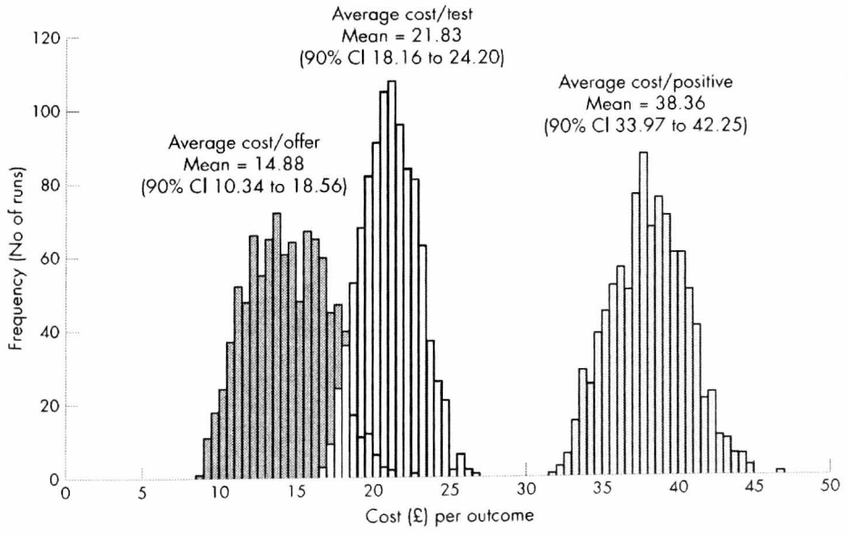

Figure 4 Results from the multivariate sensitivity analysis; frequency distribution of outcomes for 1000 runs, including partner management costs.

expected if this analysis were done for other sites. However, the results from this analysis may also provide a point of reference for evaluating future screening proposals.

There are several reasons why this analysis adds greatly to the information about the cost of genital chlamydia screening. Firstly, the model input data on the patient and partner flow were taken directly from the pilot study. Secondly, much of the cost data also came directly from the pilot invoiced expenses, so is thought to accurately represent the current costs of a screening programme. Thirdly, the individual patient data allow direct estimates of the mean and variance in proportions at each node. This, combined with the flexible model structure and ability to simulate alternative scenarios, provides a powerful tool to explore the average costs of screening, the uncertainty in these estimates, and the cost under different scenarios.

Cost effectiveness studies of chlamydia screening address a different issue from the one in this analysis, but they require similar screening costs. In this analysis, the detailed costs at each step of the tree are examined, and include costs from the wider healthcare system such as personnel who have contact with potential patients in settings where screening is offered (receptionists, nurses, general practitioners), overhead costs of running a screening programme, screening set-up costs, and partner management costs. These may be included in other studies estimating the cost effectiveness of screening, depending on the assumptions about the infrastructure and organisation of the screening programme. Some studies have estimated the time and relative involvement of healthcare workers for different outcomes (PID, ectopic pregnancy, infertility),[6 18 19] but this is the only recent analysis to explicitly estimate the time and costs at each step of a screening programme. The method presented here provides a more precise estimate of the cost of patients with a specific outcome flowing through the screening tree.

This analysis was done from the health provider perspective. It included screening costs and also those of other healthcare personnel involved in the screening process. However, there are other costs that are not included, such as patient costs and the wider societal costs. For example, there may be costs to a positive patient in terms of time lost from work to travel to a clinic to receive treatment, and similar costs for a partner. Another large chlamydia screening study is collecting patient costs as part of their study, which should provide more information when the results are published.[20]

Only the screening costs were included in this analysis, and none of the averted costs from preventing infection and sequelae were estimated. For example, preventing PID or ectopic pregnancy may be a result of screening and treating asymptomatic infection through a screening programme. Other costs and modelling studies have included these sequelae and the estimated costs saving from averting infection and/or complications.[3 6 21 22] Results from this analysis combined with the identified costs of sequelae will be used in further modelling and economic studies.

This analysis provided the average expected cost of screening, based on detailed data, and provides a novel framework for estimating the costs and uncertainty of a screening programme. The uncertainty analyses provided information about the relative importance of different components of the screening model that may direct what information should be collected in future studies. Results may help advise in the phased chlamydia screening implementation planned for future areas in England, and for screening programmes elsewhere.

Key messages

- This study estimates the healthcare costs of opportunistic chlamydia screening in clinical settings in England. It is based on empirical data from a recently completed chlamydia screening pilot study and uses decision analytical modelling techniques to explore the uncertainty of results and the impact of changing key assumptions in the screening paradigm.
- The average cost per screening offer is approximately £15 (under baseline assumptions); these are costs incurred by both the screening programme and the healthcare system in which screening occurs. Sensitivity analyses highlight the elements of screening where costs could be targeted for reduction, including lowering the laboratory test costs and reducing clinician involvement in screening.

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CONTRIBUTORS

EJA contributed to designing and planning the study, created the decision tree model, collected and analysed the costs and related data, conducted interviews with the research nurses, conducted the cost and sensitivity analyses, interpreted results and prepared the manuscript as the lead writer; DSL and ARJ helped develop the decision tree model, extracted and analysed the empirical data from the pilot study and were involved in the data analysis and interpretation; JMP helped develop the decision tree model, was a primary investigator of the pilot study, and helped with interpretation of the data and results; KAF contributed to the study development and helped with interpretation of the analysis; WJE helped conceive and design the study, contributed to the model design, cost estimates and interpretation of data, and all authors read and provided comments on the manuscript and approved the final paper.

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COMMENTARY

How much does chlamydia screening cost and is it worth introducing? That is, will the savings from future disease averted offset the screening costs (will it be cost saving?), and if it will not, is the extra health "bought" by screening worth it, in terms of alternative uses of the same resources? Here, Roberts *et al*[1] provide a valuable critique of the literature on the cost effectiveness of chlamydia screening. Despite a large body of published work, their paper highlights the lack of appropriate methods used in the majority of previous studies.

To correctly model the full effects of screening for an infectious disease like chlamydia (including the "knock-on" effects of reduced prevalence, re-infection, and partner treatment), a well parameterised dynamic model should be used.[2 3] Only two out of 59 studies assessed in detail by Roberts *et al*[1] included a dynamic model.[4 5] The studies using static models are unlikely to have been able to accurately estimate the cost effectiveness of screening.[6]

Once the appropriate model structure is chosen, dynamic models also need to be properly parameterised to reflect both sexual behaviour and the epidemiology of chlamydia.[7] Given the significant uncertainty in parameter estimates, this is a difficult but necessary process if the model is to be of public health use. Roberts *et al*[1] show that many key assumptions in the models were not investigated with sensitivity analyses, and some of the parameter values chosen should be updated as new data have come to light. For example, the progression to pelvic inflammatory disease (PID) is the most important contributor to the estimated number of sequelae and costs, and therefore it is critical that this is accurately quantified. Cost effectiveness studies have generally assumed that 25%–30% of chlamydial infections result in PID, and only one study reviewed by Roberts *et al*[1] performed a thorough sensitivity analysis on this and other progression probability assumptions. However, recent evidence suggests that the proportion of women developing PID may be significantly lower, perhaps even around 1%.[8 9] This means that many of the previous studies may have overestimated the likely benefits (that is, prevented cases of PID and other sequelae) and cost effectiveness of screening.

As chlamydia screening is being implemented nationally across England[10] and other countries, it is an appropriate time to reassess its effectiveness and cost effectiveness. New studies using more appropriate methods and better parameter estimates are urgently needed to assess the most effective way to implement screening. There is no excuse for continuing to publish cost effectiveness results using inappropriate methods or parameter estimates (for example, Ward *et al*[11]). As screening is introduced in phases across England, there is a window of opportunity to collect data on the incidence of PID in populations screened and unscreened and to explore how the incidence of PID may change with early treatment of acute chlamydial infection. Other data—for example, from the National Chlamydia Screening Programme (including chlamydia prevalence, effective partner notification rates, and costs of treatment), could also be used to update models. As with other public health interventions, chlamydia screening should be closely monitored and the effectiveness and cost effectiveness evaluated over time so that public funds can be spent wisely.

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Developing a realistic sexual network model of chlamydia transmission in Britain

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Abstract

Background: A national chlamydia screening programme is currently being rolled out in the UK and other countries. However, much of the epidemiology remains poorly understood. In this paper we present a stochastic, individual based, dynamic sexual network model of chlamydia transmission and its parameterisation. Mathematical models provide a theoretical framework for understanding the key epidemiological features of chlamydia: sexual behaviour, health care seeking and transmission dynamics.

Results: The model parameters were estimated either directly or by systematic fitting to a variety of appropriate data sources. The fitted model was representative of sexual behaviour, chlamydia epidemiology and health care use in England. We were able to recapture the observed age distribution of chlamydia prevalence.

Conclusion: Estimating parameters for models of sexual behaviour and transmission of chlamydia is complex. Most of the parameter values are highly correlated, highly variable and there is little empirical evidence to inform estimates. We used a novel approach to estimate the rate of active treatment seeking, by combining data sources, which improved the credibility of the model results. The model structure is flexible and is broadly applicable to other developed world settings and provides a practical tool for public health decision makers.

Background

Chlamydia is a very common, curable sexually transmitted infection (STI) caused by the *Chlamydia trachomatis* bacteria. Chlamydia prevalence in young women attending general practice in Britain was estimated to be 8.1% in those under 20 and 5.2% in those aged 20–24 [1], and is similar in other developed countries. Many infections are asymptomatic, resulting in a large reservoir of undetected, untreated infections [2]. Untreated chlamydia infection may result in long-term sequelae in women including pelvic inflammatory disease (PID) and ectopic pregnancy [3]. Detection of chlamydia has become easier with the recent introduction of rapid, sensitive, affordable, and non-invasive DNA tests [4]. Treatment is also straightfor-

ward and inexpensive with doxycycline or azithromycin [5]. Chlamydia screening therefore, has been or is being implemented in various developed countries including USA, Sweden, Netherlands, and UK [6-9]. However much of the epidemiology of chlamydia remains poorly understood [10] and there are many questions regarding the long term impact of interventions, such as how much PID is attributable to chlamydia infection and what are the economic and health costs and benefits of chlamydia screening? Appropriate mathematical models are required to address these questions adequately. Models are able to compare a variety of "what if" scenarios and inform estimates of biological and epidemiological parameters which are difficult to measure in practice e.g. transmission rate or the proportion of symptomatic cases seeking treatment.

Population-based deterministic models were first used to illustrate the importance of the contact structure and dynamic aspects of infection [11-13]. However population-based models fail to capture important individual level effects in the sexual network. For example, re-infection is dependent on the infection and treatment status of current partners, not the average level of infection in the community. Individual based models of STI transmission with dynamic sexual partnerships have been developed which can incorporate such effects [14,15]. Ghani *et al* developed an individual-based, dynamic sexual network model of gonorrhoea transmission within a highly active "core-group" population [15]. Individuals and their partnerships are explicitly represented, enabling detailed analysis of the network structure. Partnerships form according to mixing preferences based on sexual activity level and dissolve dynamically.

There is a growing public health need for a realistic, dynamic model of chlamydia transmission to inform and interpret the potential effect of interventions such as screening programmes and partner notification [16] To this end it was necessary to extend Ghani's model. The distribution of chlamydia is more widespread and less focussed in core groups than gonorrhoea, so a population model was developed [17]. The US Add Health study found a ten-fold higher prevalence of chlamydia (4.19%) compared with gonorrhoea (0.43%) in a probability sample of 18–26 year olds [2]. In the UK there were 104,155 chlamydia diagnoses in GUM clinics in 2004, compared with 22,335 of gonorrhoea [18] To be realistic, the model also requires age-structure, because chlamydia prevalence declines with increasing age [1], and at the population level sexual behaviour and partner choice are strongly age-dependent [19,20]. Therefore, we extended the model to incorporate age-structured sexual behaviour and partnership preferences in the general population. The final model is a realistic representation of sexual behaviour and chlamydia epidemiology in England, but is also broadly applicable in other developed world settings.

The purpose of this paper is to describe the model parameterisation method and to present the values of selected parameters that will be used in future applications to explore chlamydia screening interventions.

Method

Model description

The model is a stochastic, individual based network model based on that described by Ghani *et al* [15]. It is exclusively heterosexual and includes dynamic partnership choice, formation and dissolution, disease transmission, and recovery. The model has a Susceptible-Infected-Susceptible (SIS) structure. Susceptible individuals are infected, then either seek care or remain untreated, returning to a susceptible state following spontaneous recovery or treatment. The extended model also incorporates age-structured sexual behaviour and mixing, screening, and partner treatment. The resulting complex model can simulate a range of sexual behaviour, disease transmission and control programmes. The model simulates sexual behaviour, chlamydia transmission and interventions in Britain.

The parameterisation of sexual behaviour was primarily informed by the National Survey of Sexual Behaviour and Lifestyles (Natsal) 2000 [19,21,22], a stratified, nationally representative, probability sample survey of men and women in Britain aged 16–44. Over 12,000 individuals in the core sample, including an ethnic minority boost sample, were asked about their sexual behaviour via face-to-face interview and computer assisted self-interview ('CASI') [23]. The response rate was 65.4% in the core sample and 63.0% in the ethnic minority boost sample.

Sexual behaviour

Individuals are explicitly represented in the model by age, gender, preferred number of partners, preferred duration of partnerships, identity of current and past partners, infection status (and whether actively seeking treatment or not), and other clinical characteristics such as number of screens and results. For ease of analysis, behavioural data equivalent to Natsal 2000 [19,21,22]questionnaire responses (including partners in the last year and new partners in the last year) were also stored for each individual.

The rate of sexual partner change for an individual is determined by the rate of new partnership formation, the availability of suitable partners, the rate at which partnerships dissolve, and the gap between partnerships. Individuals are available to form a new partnership if their current number of partnerships is less than their desired

Table 1: Fixed model parameters

Parameter	Best fit or estimated value	Source
Behavioural parameters		
Population size (Female = 20,000, Male = 20,000)	40,000	-
Age range in years (uniform distribution)	16–44	Natsal 2000 [19]
Preferred number of concurrent partners		Natsal 2000 [19]
<35 years old	1 or 2	
35+ years old	1	
Proportion wanting 2 partners (< 35 years old)	0.05	Assumption based on Kretzschmar model [24]
Mean duration of short partnerships (days)	14	Assumption based on Natsal 2000 [19]
Number of sex acts per day		Assumption based on Kretzschmar model [24]
Short partnerships	1	
Long partnerships	0.25	
Mean gap in days between partnerships (dispersion)*	14 (2)	Assumption
Infection parameters		
Duration (in days)		Assumption based on Golden [10], Korenromp [30]
No treatment seeking	180	
Treatment seeking	30	
Mean refractory period (in days) following treatment (dispersion)*	7 (10)	Assumption based on CEG guidelines [5]
Health care parameters		
Attendance rate at health care setting (proportion who report attending a health care setting in the last 12 months)	0.85	Chlamydia Recall Study [26,27]
Treatment efficacy (in those partner notified or screened)	0.95	Treatment guidelines [37]
Mean delay (in days) before partner treatment (dispersion)*	7 (10)	Assumption based on unpublished Recall study
Probability of accepting screen	0.5	Assumption based on screening studies [38,39]

*Parameters drawn from a negative binomial distribution, mean and dispersion.

number of partnerships (either 1 or 2). Potential pairs are selected at random from the pool of available candidates and the partnership forms stochastically according to probabilities assigned in age mixing matrices for men and women (derived from Natsal 2000 data). Most partnerships form between people of the same age and men have a tendency to form partnerships with women somewhat younger than themselves (age difference mode = 0 years, mean = 2) [19]. The duration of partnerships is assumed to be exponentially distributed, giving a constant per time-step probability of a partnership dissolving of 1/(average duration of partnership). Long and short partnerships have different mean durations (Table 1). When a new partnership forms in the model, one person from the pair is selected at random and that person's preferred duration (long or short) is assigned to the new partnership. This means that those who prefer long partnerships sometimes have short partnerships, and vice versa. There is a gap between partnerships, during which time an individual cannot form any new partnerships, plus an additional period of time when an individual cannot form a partnership with their most recent partner to prevent the same partnership reforming immediately the pair become available.

The level of concurrency is defined as the proportion of the population that prefer 2 partners until they reach 35 years of age, fixed at 5% in these simulations (Table 1). After age 35, all persons prefer one sex partner [24], although existing partnerships are not ended. If either partner has an existing partner when the partnership forms, the concurrent partnership is always assigned as short.

Age dependent processes

Age is an important determinant of sexual behaviour and chlamydia risk [19-21]. The model population is aged 16–44, as in Natsal 2000. Aging occurs deterministically once per year for all individuals in the population. The preferences for new partnerships (but not existing partnerships) are adjusted annually. When an individual reaches age 45, they are removed from the population and a new 16 year old enters (gender maintained). Existing partnerships are not ended, but are flagged as external to the population, so that individuals <45 year of age in a stable partnership do not become prematurely available for new partnerships when their partner passes 45 years of age.

In the model, sexual partnerships form stochastically according to age mixing preferences. Individuals generally form fewer new partnerships as they age. This is implemented by a fraction of the population who prefer short partnerships switching to long, all those who prefer long partnerships increasing the average duration of partner-

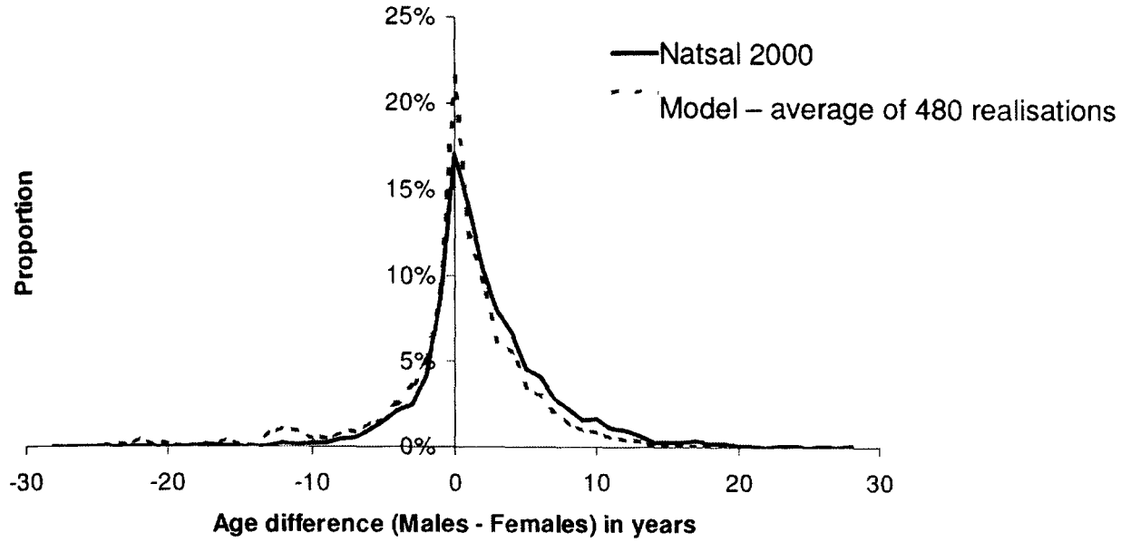

Figure 1
Frequency of age differences between sexual partners (males compared to females, aged 16–44) observed in Natsal 2000 and in the model.

ships (i.e. decreasing the chance of the partnership dissolving) and shifting the preference for partners of different ages according to the age mixing matrices.

Infection processes

Transmission of chlamydia occurs stochastically between an infected index case and uninfected current partner, with a per sex act probability, assuming one sex act per day in partnerships which have lasted less than one month and 0.25 per day in longer partnerships.

There is a constant per day probability of recovery of (1/average duration of infection). A fraction of newly infected individuals are assumed to actively seek treatment and to recover at a faster rate than those not seeking treatment. The recovery rate of those not seeking care is influenced by the level of screening and partner notification. After treatment for any reason, individuals enter a variable refractory period during which re-infection cannot occur, to simulate patients following advice to abstain for a week and until partners have been treated (British Association of Sexual Health and HIV (BASHH) guidelines) [5].

Partner notification and screening

Partner notification is implemented by examining partnerships within the last 3 months (as per BASHH guidelines) [5]. For each partner there is a probability of being contacted. Notified partners are treated after a variable delay following treatment of the index case, with certain efficacy. Individuals may be partner notified as a result of the index seeking treatment due to symptoms or screening. For individuals treated via partner notification, their partners are not traced.

Various screening programmes can be implemented in the model, some of which are explored in Turner *et al* (Turner KME, Adams EJ, LaMontagne DS, Emmett L, Baster K, Edmunds WJ. **Modelling the effectiveness of chlamydia screening in England** (*submitted*). Available upon request).

Model parameterisation

For many of the model parameters few data are available (e.g. fraction of individuals who seek treatment for infections), the value is highly variable (e.g. duration of untreated infection [10,25]) or the parameter of interest cannot be measured directly (e.g. sexual behaviour is usually collected retrospectively and cross-sectionally as number of partners over a given time period, but is implemented prospectively as desired partner formation and dissolution rates). Therefore, some of the parameters are estimated by fitting the model to data.

Behavioural parameters were informed principally by Natsal 2000 [19,21,22].Infection and treatment parameters were fitted using Natsal 2000 and other available data sources [1,21,26,27].

Table 2: Fitted model parameters

Parameter	Best fit or estimated value	Limits of 95% CI	Range (increment)	Source
Behavioural parameters				
Proportion that switch from desiring short to long partnerships per year				Fitted to Natsal 2000 [19]
Men	0.04	0.02–0.06	0.0–0.08	
Women	0.08	0.06–0.08	0.04–0.12 (0.02)	
Initial proportion of 16 year olds desiring short partnerships				Fitted to Natsal 2000 [19]
Men	0.6	0.5–0.7	0.4–0.8	
Women	0.5	0.4–0.6	0.3–0.7 (0.1)	
Mean duration in days of long partnerships (16 year olds)	900			Based on exploratory fitting to Natsal 2000 [19]
Increase in partnership duration per year, in days	200			Based on exploratory fitting to Natsal 2000 [19]
Infection parameters				
Transmission probability per sex act	0.0375	0.035–0.04	0.035–0.05 (0.0025)	Fitted to Natsal 2000 [19] & Adams *et al* [1]
Proportion seeking treatment				Fitted to Natsal 2000 [19] & Adams *et al* [1]
Men	0.0	0.04–0.05	0–0.05	
Women	0.045	0–0.005	0–0.055 (0.005)	
Health care parameters				
Proportion of partners notified	0.2	0.1–0.25	0.0–0.5 (0.05)	Fitted to Natsal 2000 [21] & Adams *et al* [1]

Note: Fitted parameters are presented with the limits of the 95% confidence intervals (meaning that the 95% CI lies within those limits, further refinement was not done). The range tested in the fitting routines and the increment used is also shown.

Behavioural parameter estimation

Estimation of behavioural parameters was done in two stages: an exploratory stage, to assess the impact of different parameters on model behaviour and to refine parameter ranges, followed by a second phase of fitting using maximum likelihood. Several parameters were unknown:

- the proportion of individuals desiring short partnerships (males (M) and females (F))
- the proportion of individuals changing from wanting short partnerships to long partnership each year (M, F)
- the average duration of long partnerships (M, F)
- the annual increase in preferred partnership duration (M, F)
- the duration of the average gap between partnerships.

Sexual behaviour stabilised after running the model for 10 years, and a population of 6000 (3000 males and females) was sufficient to generate the range of behaviour observed in larger model populations. Latin hypercube sampling (LHS) was used to generate more than 800 parameter sets in the exploratory phase. The average of 5 model realisations was used to maximise efficiency. There was high correlation between the parameters in determining the fit of the model.

The model outputs were grouped by age, sex and sexual activity and were compared to Natsal 2000 data. Sexual activity groups were defined on the basis of number of partners (0–1, 2–3, 4–7, 8+) and were populated with either the number of individuals reporting that activity level (i.e. frequency) or the number of partnerships contributed by individuals within that group (weighted frequency).

In the Natsal 2000 survey, there was inconsistency between genders in reported behaviour: men reported on average 1.5 times as many partners as women, in common with other such surveys [19,28]. During the exploratory phase, male and female data were therefore fitted separately, using least squares. Fitting to the male reported data generated higher rates of partner change than fitting to female data. Fitting to data on the number of partnerships generated higher rates of partner change than fitting to the number of individuals observed with different levels of activity.

For the second phase, the model was fitted using maximum likelihood to male partnerships in the last year only. This best replicated the variability and range of observed

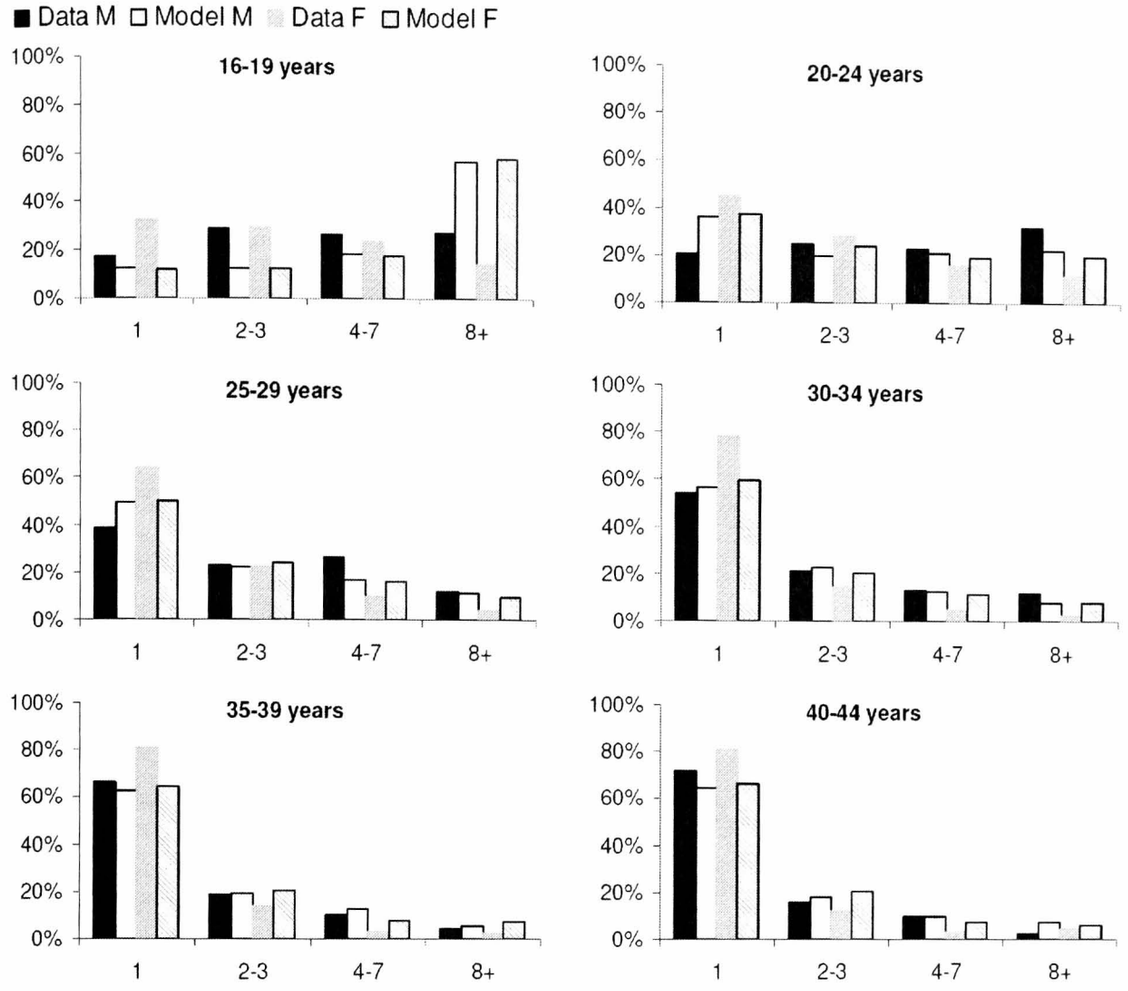

Figure 2
Proportion of partnerships contributed by different activity groups for the best fitting model (fitted to male partnerships), model output compared with Natsal 2000 data by age group and gender.

behaviour, giving a longer tail to the distribution (i.e. including a few individuals with many partners). It has also been suggested that male reporting may be more reliable than females [29].

Results from the exploratory runs showed that varying as few as four population parameters was sufficient to generate a range of sexual behaviour comparable with the empirical data. The proportion of short partnerships (M, F) at recruitment into the sexually active population and the proportion that change from preferring short to long partnerships (M, F) were therefore varied in the second phase. The remaining parameters were fixed (Table 1): average duration of long partnerships in 16 year olds, the annual increase in desired partnership duration, duration of short partnerships and the duration of the gap between partnerships. All fixed parameters were assumed to be the same for men and women. The log likelihood, saturated log likelihood and deviance were calculated (Appendix). Behavioural parameters and their best fit values are given in Table 2. A matrix of probabilities of partnership formation by age was derived from the age differences between

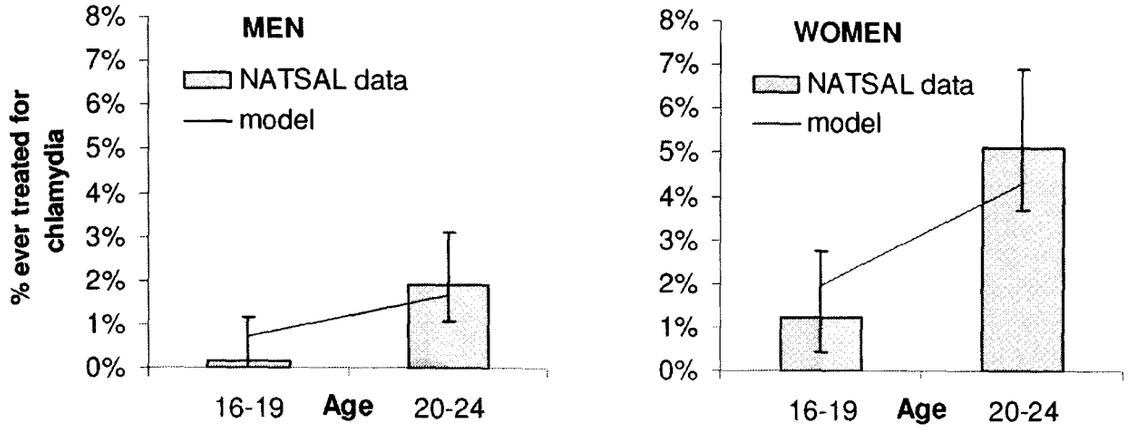

Figure 3
Baseline results for the proportion of males (a) and females (b) by age group ever treated for chlamydia, Natsal 2000 compared to the model.

sexual partners observed in Natsal 2000 data and used in the model. The age differences observed in the model are compared with Natsal 2000 in Figure 1.

Infection parameter fitting

Chlamydia prevalence in the model depends on the transmission probability, duration of infection in those cases seeking treatment and not seeking treatment, the proportion seeking treatment, and the level of partner notification. Estimates for the duration of chlamydial infection vary greatly [10,30]. Further, the duration and transmission probability are highly correlated in determining chlamydia prevalence. We therefore chose to fix the average duration of infection in men and women at one month for those seeking treatment and six months for those not seeking treatment. The transmission probability, the proportion seeking treatment (M/F), and the level of partner notification were allowed to vary. Infection was introduced into the population and run for 15 years to reach a stable equilibrium, before calculating the model fit.

The model was fitted to data on chlamydia prevalence in women and the proportion of individuals who have reported ever having been diagnosed with chlamydia (and presumed treated), by age and gender [1,21]. Chlamydia prevalence estimates were taken from a systematic review of chlamydia prevalence in general practice (GP) clinic attendees [1]. These were estimated for various factors using a random effects regression model. Numerators and denominators were generated to ensure the prevalence and their 95% confidence intervals (CI) were the same as those in the systematic review [1]. Data on previous chlamydia diagnoses were obtained from the Natsal 2000 survey. Those older than 25 years reported less past treatment for chlamydia than younger women, which may reflect recent changes in testing, treatment, prevalence, or recall bias. Therefore data on previous diagnosis for males and females aged <25 years only and chlamydia prevalence in all age groups were used to fit the model. The binomial log likelihood, saturated log likelihood and deviance for each subgroup were calculated and then summed (Appendix).

Exploratory runs of the model were performed to predict the likely range of values for the varied parameters (each parameter set was averaged over 15 simulations). This

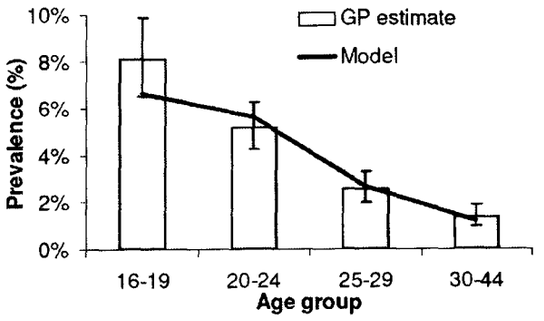

Figure 4
Baseline model chlamydia prevalence by age compared with estimated prevalence in general practice attendees (Adams *et al*, 2004) [1].

range was then further refined by systematically combining parameters (proportion seeking treatment (M/F), transmission probability, and partner notification), by fixing two parameters and allowing the others to vary. Once a local best fit was found (lowest deviance), the other parameters were varied to search for a better fit. Thirty realisations were performed for each parameter set for the final fitting routines. Univariate sensitivity analysis was performed for each of the five parameters, and the 95% CI was estimated by finding those parameter values that lie within 3.84 of the deviance estimate.

Results

The results of fitting the model to behavioural data are shown in Figure 2 for male and female partnerships in the last year. The best fit parameter values, and the values that gave fits within 95% confidence limits are presented in Table 2. The model fits better to the male data than the female data, due to the choice of fitting procedure (i.e., the model was fitted to male behavioural data). In both males and females, the model overestimates the number of partners of the youngest age groups, and slightly underestimates in older age groups. The fitted model has a higher rate of partner change in females than observed in the data. The discrepancy between data and model is greatest in the youngest women

Given the set of behavioural parameters, the estimated biological parameters (and 95% confidence intervals) that produced the best fit are shown in Table 2. The best fitting model suggests a partner notification efficacy of 20%, per sex act transmission probability of 0.0375 and that a small fraction of cases are treated as a result of active treatment seeking (less than 5% of new female and 0.05% of new male cases). The best fitting model results are shown in comparison with the proportion reporting chlamydia treatment (Figure 3) and the prevalence of chlamydia in women (Figure 4).

Discussion

The aim of this study was to develop a flexible, credible model of chlamydia transmission in Britain to address public health questions regarding chlamydia epidemiology and interventions including screening. We extended the model of Ghani *et al* to incorporate relevant features such as age-dependent sexual behaviour [15]. We used multiple data sources and an iterative process of parameter fitting and refinement to estimate sexual behaviour and biological parameters representative of current chlamydia epidemiology in Britain.

The distribution of sexual behaviour in the fitted model is broadly similar to that observed in Britain (Figure 2). In the model the total number of partnerships contributed by men and women are equal, because it is a closed population and partnerships can be counted perfectly. However, the model was fitted to male partnership data from Natsal 2000, which found that men report more partnerships than women [19,28]. Data available to validate and parameterise the model are based on retrospective accounts of individual's sexual behaviour, which are subject to various biases [31,32]. The reasons for the observed discrepancy are not fully understood, but could include male over-reporting, female under-reporting or gender differences in the distribution of partners. An Australian study compared reports of sexual behaviour under different survey conditions and found that males' reports were more consistent than females', and that females tended to report fewer partners when they believed the responses were not anonymous compared with when they believed lies would be detected, suggesting a bias towards underreporting [29]. Others have suggested that the difference between men and women primarily lies in the tail of the distribution and that female sex workers, who are likely to be poorly represented in population-based surveys, may supply the extra partnerships reported by men [33,34]. The true situation is probably a combination of these. We chose to fit the model to behaviour reported by men, as this may be more reliable. However, the sexual activity of women in the model is then higher than that reported in the data. The difference is greatest in the youngest women. If we had fitted to either women or some average of both, the model would have fitted neither data set well, although the overall model behaviour would be roughly similar and the fitted infection parameters would be slightly different.

The distribution of chlamydia by age and the number of people treated for infection follows that observed in young women [1,21]. Chlamydia prevalence is highest in the youngest age groups and lowest in the oldest. While surveillance data from genitourinary medicine clinics suggest that male prevalence may be highest in the 20–24 year old ages [18], a recent review does not suggest a difference in male and female prevalence, therefore we fitted to female data only. More data on the prevalence and incidence of chlamydia in men are needed to improve the parameter estimates [1].

The estimates of transmission probability are highly dependent on the values of the duration of infection chosen, but there are few reliable data on the timing of treatment or recovery under different scenarios of symptoms, contact tracing and screening. If the average duration of all infections were shorter than we modelled, the transmission probability would need to be higher to fit to the same overall prevalence. The level of partner notification (that is partners of contacts are known to have been tested and treated) predicted by the best fitting model was 20%. Data from the Chlamydia Recall Study suggested that partner

notification might be as high as 50% in a study setting [26]. There are problems in interpreting the estimate of 20% as it is also correlated with the other infection parameter estimates and was fitted to the observed low rate of treatment. However the efficacy in a non-study setting is likely to be lower and the importance of maintaining and improving partner notification is crucial to the long-term success and effectiveness of interventions.

The proportion seeking treatment is low compared with other estimates of the proportion symptomatic [3,24,35]. This is due to several reasons. Firstly, active treatment seeking is not directly analogous to symptomaticity, which is an assumption in our model. A modelling study has suggested that the proportion of time an infection shows symptoms may be less frequent and also intermittent [30], and therefore may not prompt an individual to seek treatment if his/her symptoms disappear. In a recent US Add Health study, 4.19% of 18–26 year olds were infected with chlamydia, and more than 95% of infections were asymptomatic [2]. In the model, those who have reported treatment for chlamydia may have done so from either seeking treatment or through partner notification. In reality, treatment may be more frequent (with or without confirmed diagnosis) due to co-treatment of gonorrhoea cases or syndromic management of urethritis in men [36]. Secondly, we fitted to very low rates of treatment observed in the population, particularly among men, based on retrospective data collected by Natsal 2000. Recent data from the Health Protection Agency show that chlamydia diagnoses (and presumably treatment) have increased since 2000, from both a real increase in chlamydia prevalence and increased testing and diagnoses through education and screening [18]. We compared our estimates of treatment seeking to those in the model by Kretzschmar *et al* [24], which is the most thorough study published to date and is broadly comparable to ours in terms of structure and dynamics. We ran our model using the infection parameters from their published model, including a higher proportion of symptomatic infection (higher treatment rate). The model chlamydia prevalence was similar to that observed using our values, but the proportion of 20–24 year olds ever treated was over 45%. This compares with 4.5% in the fitted model and 5.1% (3.7–6.9%, 95% CI) of 20–24 year old women ever treated for chlamydia reported in Natsal 2000. Similarly, the Chlamydia Recall Study found that 8% of women aged 20–24 reported past treatment for chlamydia [26]. We believe that, although the true rate of treatment seeking maybe higher than we estimated, the novel use of data on reported rates of treatment to parameterise the model has led to a more credible model and is justified by the fit to data.

The model is complex and there are many interactions between the parameters. Therefore the values presented here should be considered as a best fitting set of parameters, rather than taken individually. There are limitations to the model structure, e.g. there may be more individual variability between individuals during their sexual life histories than we were able to simulate. There is a trade-off between model complexity and the ability to validate the model with data. More data are needed on sexual life histories as well as further analysis of the sensitivity and robustness of the model assumptions. The advantages of this individual based model over other possible choices are that the history of individuals can be tracked over time, e.g. exposure to infection, previous partners or number of screens. Infection and reinfection events occur within explicitly defined partnerships, which enables partner notification. Finally the model structure is very flexible and additional screening or partner notification strategies and other behavioural patterns or infections can be added.

Conclusion

The model is applicable to other developed world settings. It is being used to investigate the effectiveness of interventions such as chlamydia screening in England (Turner et al, *submitted*). Modelling is underway to improve understanding of the natural history of pelvic inflammatory disease and estimate the cost-effectiveness of interventions designed to prevent it. The model fitting was as systematic as possible given the limitations of computing time and data. A strength is the use of novel data on past treatment to improve parameter estimates. We therefore believe this model to be a significant improvement in providing a realistic model for use in public health decision-making.

Abbreviations

Natsal 2000 – National Survey of Sexual Attitudes and Lifestyles 2000

BASHH – British Association of Sexual Health and HIV

GP – General practice

STI – Sexually Transmitted Infection

Competing interests

The author(s) declare that they have no competing interests.

Appendix

The proportion of males in each sexual activity group (defined by the number of partnerships in the last year) by age group is assumed to follow a multinomial distribu-

tion. The log-likelihood (L_{beh}) of the model given the data and the saturated log-likelihood (L_{beh}*) are given by:

$$L_{beh} = \sum_a \sum_p Q_{ap} * \log(y_{ap})$$

$$L_{beh}* = \sum_a \sum_p Q_{ap} * \log(z_{ap})$$

where Q_{ap} is the number of males (female results not used for final fitting), age group a (16–19, 20–24, 25–29, 30–34, 35–39, 40–44) and sexual activity group p with a given number of partners (1, 2–3, 4–7, 8+) observed from Natsal, and y_{ap} *and* z_{ap} are the proportion of males, age group a with p number of partners, from the Natsal 2000 data and observed in the model, respectively. The deviance is given by:

$$Dev_{beh} = (-2*(L_{ap} - L_{ap}*))$$

which was minimised to find the best fitting set of behavioural parameters.

The biological parameters were also fitted using maximum likelihood. As the data are binomial the model log likelihood (L_{bio}) and saturated log likelihood (L_{bio} *) are given by:

$$L_{bio} = L_{bio\_prev} + L_{bio\_prop}$$

$$L_{bio}* = L_{bio\_prev}* + L_{bio\_prop}*$$

The formula is illustrated for L_{bio_prev} and is the same for L_{bio_prop}:

$$L_{bio\_prev} = \sum_g \sum_a \left(I_{ga} * \log x_{ga} \right) + \left(S_{ga} * \log(1 - x_{ga}) \right)$$

$$L_{bio\_prev}* = \sum_g \sum_a \left(I_{ga} * \log\left(\frac{I_{ga}}{S_{ga} + I_{ga}} \right) \right) + \left(S_{ga} * \log\left(\frac{S_{ga}}{S_{ga} + I_{ga}} \right) \right)$$

where I_{ga} is the observed number of infected, S_{ga} the observed number of susceptibles, and x_{ga} is the model estimate of the proportion of infected, by gender g and age group a. For prevalence, g (females), by four age groups a (16–19, 20–24, 25–29, 30–44) and for the proportion ever treated, g (males, females) by two age groups (16–19, 20–24) and the values summed.

The deviance was calculated and minimised in the fitting routine:

$$Dev_{beh} = (-2*(L_{ap} - L_{ap}*)).$$

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CHLAMYDIA SCREENING

Modelling the effectiveness of chlamydia screening in England

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Background: Several developed countries have initiated chlamydia screening programmes. Screening for a sexually transmitted infection has both direct individual and indirect population-wide effects. Mathematical models can incorporate these non-linear effects and estimate the likely impact of different screening programmes and identify areas where more data are needed.

Methods: A stochastic, individual based dynamic network model, parameterised from UK screening studies and data on sexual behaviour and chlamydia epidemiology, was used to investigate the likely impact of opportunistic screening on chlamydia prevalence. Three main strategies were considered for <25 year olds: (1) annual offer to women; (2) annual offer to women or if changed partner within last 6 months; (3) annual offer to men and women. Sensitivity analyses were performed for key screening parameters including uptake rate, targeted age range, percentage of partners notified, and screening interval.

Results: Under strategy 1, continuous opportunistic screening of women <25 years of age is expected to reduce the population prevalence by over 50% after 5 years. Prevalence is also expected to decrease in unscreened older women and in men. For all three strategies screening those aged over 25 results in small additional reductions in prevalence. Including men led to a faster and greater reduction in overall prevalence, but involved approximately twice as many tests as strategy 1 and 10% more than strategy 2. The frequency of attendance at healthcare sites limits the number of opportunities to screen and the effect of changing the screening interval.

Conclusions: The model suggests that continuous opportunistic screening at high uptake rates could significantly reduced chlamydia prevalence within a few years. Opportunistic programmes depend on regular attendance at healthcare providers, but there is a lack of high quality data on patterns of attendance. Inequalities in coverage may result in a less efficient and less equitable outcome.

Genital chlamydia infection is a prevalent bacterial sexually transmitted infection (STI) internationally and a leading cause of preventable infertility.[1 2] *Chlamydia trachomatis* infection is most common in young, sexually active adults.[3] In the United Kingdom, approximately 3–10% of women aged under 25 years are infected.[4] Treatment with antimicrobials is simple and cheap; however, chlamydia is often asymptomatic.[5] If left untreated, infection may result in long term sequelae such as pelvic inflammatory disease (PID), ectopic pregnancy, and infertility.[6] In England in 2002, the National Chlamydia Screening Programme (NCSP) began opportunistic screening in clinical and non-clinical settings, including primary care.[7] Eligible attendees are offered a chlamydia test, irrespective of reason for attending. Several other countries have chlamydia screening programmes, including the United States, Sweden, and the Netherlands.[8–10]

Screening and treating those infected with chlamydia not only benefits the individuals identified by the programme, but also confers indirect benefits on the wider population, by preventing onward transmission. However, these dynamic, non-linear effects are difficult to predict and field studies of chlamydia screening are necessarily restricted in duration and the range of scenarios that can be investigated. Mathematical models offer a means to estimate the direct and population level effects of different interventions.[11–14] Programmatic questions can also be addressed—for example, what is the effect of screening men as well as women?

We use a transmission dynamic mathematical model (as this is the appropriate method to evaluate interventions against infectious diseases[11 15 16]) extensively parameterised to represent current sexual behaviour and chlamydia transmission dynamics in England.[14] Different screening strategies were simulated to investigate the potential impact of opportunistic screening on population prevalence. The insights obtained are widely applicable to countries considering chlamydia screening.

METHODS

We used an individual based, stochastic dynamic sexual network model of chlamydial infection, extended from that of Ghani *et al*,[13] to include age structure, age dependent sex partner preferences, partner notification, and opportunistic screening.[14] A detailed description of the model and its parameterisation are given elsewhere[14]; a brief summary is presented.

The model population consists of 40 000 individuals (20 000 men and 20 000 women) aged 16–44 who form and break sexual partnerships according to age dependent sexual behaviour and mixing patterns. The model has a **S**usceptible-**I**nfected-**S**usceptible (SIS) structure, in which susceptible individuals are infected by an infected partner. Infected individuals return to a susceptible state, either through natural resolution of infection, actively seeking treatment, partner notification or screening (fig 1).

Parameters were obtained directly from appropriate data and literature or were estimated by fitting the model to UK data on sexual behaviour, chlamydia epidemiology and

Abbreviations: Natsal, National Survey of Sexual Attitudes and Lifestyles; NCSP, National Chlamydia Screening Programme; PID, pelvic inflammatory disease; SIS, Susceptible-Infected-Susceptible

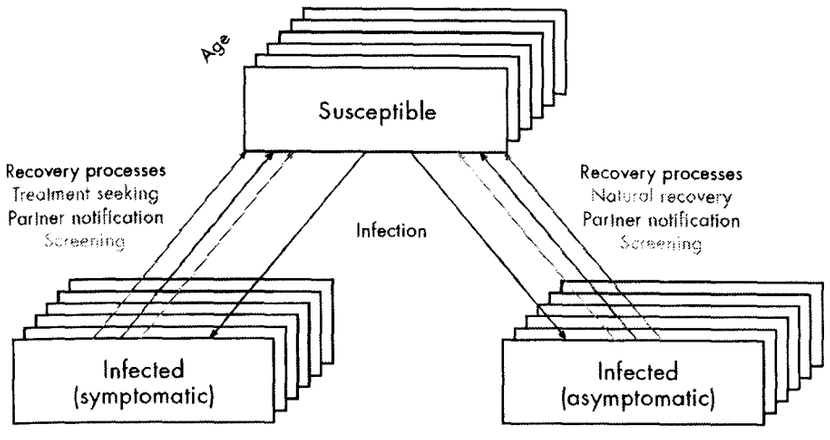

Figure 1 Illustration of chlamydia infection and recovery processes in the model.

health care seeking behaviour.[14] The National Survey of Sexual Attitudes and Lifestyles (Natsal) 2000 survey, the Chlamydia Screening Pilot, the Chlamydia Recall Study and other analyses of UK data were all used to inform parameter estimates.[4 14 17 20] The baseline parameter values for sexual behaviour, infection, and health care are given in table 1.

The model incorporates the effect of changing behaviour with age.[14] At the end of each year, individual preferences for number of partners and duration of partnership are adjusted (table 1). Partnerships become more stable and fewer new partnerships are formed, as individuals get older. The probability of a partnership forming between two individuals depends on their ages but not activity level.[14]

Individuals actively seeking treatment are assumed to recover faster (average duration of 1 month), compared to those who do not (6 months). Those with untreated infection may receive treatment via partner notification or screening (fig 1). The model was fitted to data on chlamydia prevalence in women attending GP clinics[4] and the proportion reporting ever having received chlamydia treatment (Natsal 2000),[17] to estimate the proportion of new infections which result in treatment seeking, the transmission probability, and the level of partner notification most consistent with the observed data. The proportion ever treated (owing to active treatment seeking or partner notification) at baseline is comparable to observed treatment rates in the United Kingdom.[14]

In the Chlamydia Recall Study, 85% of women reported that they had attended any healthcare setting within the last 12 months[20]; this is similar to the GP attending figures reported by Salisbury *et al*.[24] This was used to calculate a per day probability of attendance of:

$p_a = 1 - (1 - 0.85)^{(1/365)}$

The number of individuals attending per day was chosen from a Poisson distribution with mean p_a. For each screening strategy the number of individuals attending healthcare sites eligible for opportunistic screening per year was calculated.

Screening strategies

In England, the NCSP recommends once yearly screening for women and men under 25 years of age or more frequently if there is a change of sex partner.[7 25] The model, parameterised with the best fitting values, was used to explore the effect of a variety of different opportunistic screening strategies. Results are shown as the average of 40 stochastic realisations.

Three main strategies were defined and compared with a no-screening, baseline situation (box). Strategies 1–3 were implemented for different age groups (<20, <25, <30, <35, <40 years old). Variations on strategy 2 were used to investigate the effects of different programmatic algorithms—for example, differential rescreening intervals depending on previous test result, age, or sexual behaviour.

As screening is offered opportunistically, the planned screening interval will be shorter than the actual screening interval, as the woman (or man) has to attend an appropriate healthcare setting after they become eligible for a screen. Accepting or refusing a screen previously is assumed not to affect current or future behaviour. On each day an average of $N.p_a$ people attend, where N = population size and p_a = per day probability of attendance. Those eligible are offered a screen, and a proportion of those offered, accept. In all the base case scenarios there are no individuals or subpopulations more or less likely to attend or to accept screening, but in practice differences may exist, owing to the effects of patchy coverage of a screening programme or individual variation in the probability of attendance or acceptance.

Sensitivity analyses

To investigate the impact of differences in the probability of acceptance, partner notification efficacy, variability in coverage, or uptake of a screening programme and the use of different screening intervals on the efficacy of the programme, additional analyses were performed. The following modifications were made to strategy 3 (for those aged <25 years). This was chosen as it most closely approximates the NCSP recommendations.

Acceptance

The probability of accepting a screen when offered was varied (between 10–70%). An additional pessimistic simulation was performed assuming acceptances of 10% (women) and 1.4% (men) to capture the male:female ratio of screens currently observed in the NCSP.[26] The base case acceptance rates used (50%) were roughly midway between those observed in pilot screening programmes in the United Kingdom: the ClaSS study achieved an acceptance rate of 35%[22] and the Chlamydia Screening Pilot, 78%[19] overall (range 54%–100% depending on setting).

Partner notification efficacy

The efficacy of partner notification when screening is introduced was changed from 20% to 50% (applies to partners of those screened and those actively seeking treatment). Recent data suggest this level of partner completed therapy may be achievable.[20 27]

Unequal coverage

The model population was divided into two groups: 50% attend/are offered/always accept screening and 50% don't

Table 1 Baseline parameter values used in mathematical model

Parameter	Value	Source
Behavioural parameters		
Preferred number of concurrent partners	1 or 2	
Proportion wanting 2 partners (<35 years old)	0.05	Assumption based on Kretzschmar model[12]
Initial proportion of 16 year olds desiring short partnerships		Fitted to Natsal 2000[14 18]
Men	0.6	
Women	0.5	
Proportion who switch from desiring short to long partnerships per year		Fitted to Natsal 2000[14 18]
Men	0.04	
Women	0.08	
Mean duration of short partnerships (in days)	14	Assumption
Mean duration of long partnerships for 16 year olds (in days)	900	Fitted to Natsal 2000[14 18]
Increase in duration (in days) per year	200	Fitted to Natsal 2000[14 18]
Mean gap between partnerships (in days), (dispersion)*	14 (2)	Assumption
Number of sex acts per day		Assumption based on Kretzschmar model[12]
Short partnerships	1	
Long partnerships	0.25	
Infection parameters		
Transmission probability per sex act	0.0375	Fitted to Natsal 2000[17] and Adams *et al*[8]
Duration, no treatment seeking (in days)	180	Assumption
Duration, treatment seeking (in days)	30	Assumption
Proportion seeking treatment		Fitted to Natsal 2000[17] and Adams *et al*[8]
Men	0.0	
Women	0.045	
Mean refractory period following treatment (in days), (dispersion)*	7 (10)	Assumption based on CEG guidelines[21]
Healthcare parameters (baseline)		
Annual attendance rate at health care setting (proportion who report attending a healthcare setting in the last 12 months)	0.85	Chlamydia Recall Study[20]
Probability of accepting screen	0.5	Assumption based on screening studies[19 22]
Proportion of partners notified	0.2	Fitted to Natsal 2000[17] and Adams *et al*[8]
Treatment efficacy (in those partner notified or screened)	0.95	Treatment guidelines[23]
Mean delay (in days) before partner treatment (dispersion)*	7 (10)	Assumption based on Recall Study (unpublished)

Adapted from Turner *et al*.[14]
*Parameters drawn from a negative binomial distribution, mean, and dispersion.

attend/are not offered/never accept screening (baseline = all attend, all offered, all have 50% probability of accepting each time a screen is offered).

Screening interval

The screening interval was varied between 3 months and 24 months for strategies 1 and 2 (baseline interval 12 months).

Limited acceptance

Individuals only accept a screen once. Evidence suggests that the probability of accepting a screen drops after the first screen.[28]

RESULTS

The prescreening equilibrium population prevalence (ages 16–44) was 3.5% (SD 0.4%) in men, 2.9% (SD 0.3%) in women and 3.2% (0.4% standard deviation) overall, averaged over 920 realisations. There was stochastic variation between realisations. Screening strategies 1–3 resulted in a significant decrease in the population prevalence. Table 2 shows the impact on population prevalence over time and the number of screens performed under each strategy (<25 years old) after 10 years. Strategy 1 reduced prevalence from 3.2% to 1.4% after 5 years and to a new stable level of 0.9% within 10 years. Including additional screening if recent partner change has occurred (strategy 2) increased the effectiveness

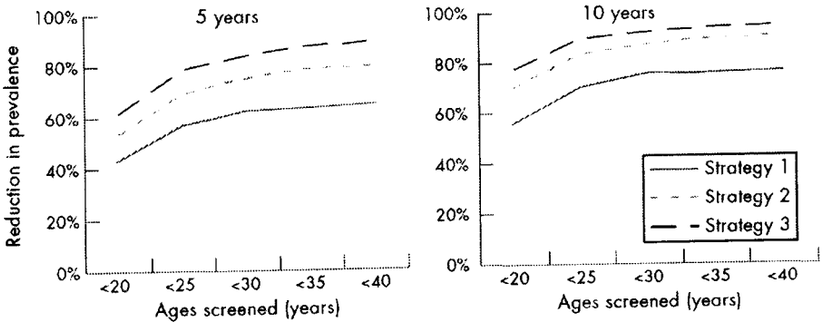

Figure 2 Reduction in population prevalence (men and women, all ages) 5 years and 10 years after screening implementation, for strategies 1, 2, and 3 with different age limits.

Screening strategies implemented

Strategy 1 Offer annual screen to women
Strategy 2 Offer annual screen to women and if changed their partner in the past 6 months
Strategy 3 Offer annual screen to women and men

Strategy 2b Offer annual screen to women <25 years old if initial test result is negative, women <25 years old twice a year if initial test result is positive, and women <25 years old if they have changed their partner in the last 6 months.
Strategy 2c Offer annual screen to women 16–20 years old, women 21–24 years old biennially, and women <25 years old if they have changed their partner in the past 6 months.
Strategy 2d Same as *strategy 2c* and stop the screening offer if a woman has no partner change in the last 6 months and two consecutive negative chlamydia tests. Screening restarts if she subsequently changes her partner.

of the screening programme and including men (strategy 3) resulted in further benefits. Approximately half of those eligible are screened each year under strategy 3 (<25 year olds). The more complex algorithms (strategies 2b–d) had similar effectiveness to strategy 2.

The effect of strategies 1, 2, and 3 (<25 year olds only) on chlamydia prevalence in different age groups is shown in figure 2. Before screening, prevalence was highest in the youngest age group and decreased with age (fig 3). Screening had the greatest impact in those targeted, although the prevalence also decreased in older women (fig 3) and in men (not shown). For all three strategies, screening those over 25 years of age resulted in small additional reductions in prevalence, but more screens were performed on negative individuals.

Including men (strategy 3) led to a faster and greater reduction in overall prevalence (to 0.7% after 5 years, fig 3), but twice as many tests were performed compared with strategy 1 and 10% more compared to strategy 2. Strategies screening only women also led to a significant reduction in male prevalence through partner notification and a reduction in risk of infection (indirect protection or herd immunity).

The effect of changing the logistical parameters of acceptance, partner notification, and unequal coverage was investigated under baseline strategy 3 (<25 year olds only) (table 2). Reducing the acceptance made screening less effective, but increasing acceptance above 50% had little additional benefit. Chlamydia prevalence after 5 years was 2.0%, 1.0%, 0.7%, and 0.5% for an acceptance of 10%, 30%, 50% and 70%, respectively. Changing the proportion of partners effectively notified from 20% to 50% when screening was introduced increased the impact of screening. However increasing PN to 50% with no screening also decreased the prevalence by about 7% after 10 years. Screening was less effective if only a fraction of the population was involved in the screening programme (table 2) and inequalities in health are generated. If the population is divided into those who attend/accept (or have access to screening) and those who do not, the overall prevalence is reduced, but the reduction is greater in those who are screened than in those who are not (fig 4).

The average number of screens per person indicates the screening frequency and is presented in figure 5 for strategies 1 and 2. In the model, women attend just under twice per year on average. The maximum screening frequency equals half the attending frequency (for acceptance at 50%), when a screen is offered at every attendance. Under strategy 1 (annual screening of women) the average number of screens

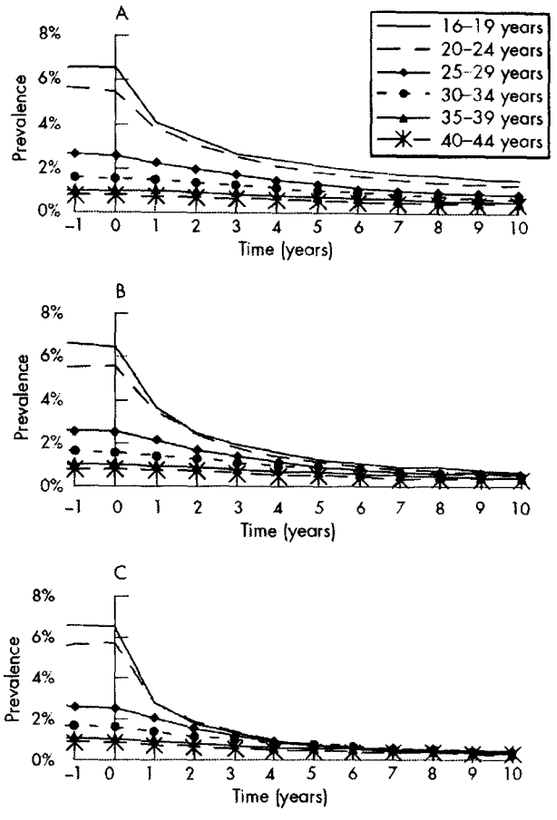

Figure 3 Age specific impact of screening strategies 1 (A), 2 (B), and 3 (C) (under 25 years) on chlamydia prevalence in women using the base case parameter set.

increased as the screening interval decreased. Under base case assumptions women aged 24 have had on average four screens since age 16—that is, annual opportunistic screening roughly equates to one screen every 2 years under base case assumptions of attendance and acceptance rates. When the screening interval was halved from 12–6 months, the average number of screens per woman per year increased from 0.5 to 0.7. With no screening interval (continuous eligibility), screening frequency saturated at 0.9 screens per woman per year. This was also the case for screening strategy 2 and changing the screening interval did not affect the average annual number of screens per person (fig 5), because young women changed partners more frequently in the model than they attended healthcare sites, hence were nearly always eligible for screening. Attendance is the rate limiting step.

DISCUSSION

The effects of different opportunistic screening strategies on the prevalence of chlamydia in the general population and in those targeted were investigated. Modifications were made to the individual based mathematical model of STI transmission developed by Ghani *et al.*[13] The extended model is a tool for public health decision makers to explore a range of planned interventions and "what if" scenarios. The model has been parameterised to reflect chlamydia transmission and epidemiology in the United Kingdom, but the conclusions drawn from it may be broadly applicable to other similar countries.

All strategies (1–3) resulted in a substantial reduction in prevalence, providing acceptance was at least 50%. The screening strategies investigated were based on opportunistic testing of individuals attending healthcare settings (box).

Table 2 Reduction in model population prevalence (males/females, all ages) under different screening strategies: 1, 5 and 10 years after introduction of screening

Strategy (<25 years old)	Reduction in population prevalence			Total screens in 10 years
	1 year	5 years	10 years	
Strategy 1 (women, annual)	23%	57%	70%	34 678
Strategy 2 (women, annual + partner change)	28%	69%	84%	63 669
Strategy 3 (women + men annual)	40%	79%	89%	69 444
Strategy 2b	28%	70%	83%	63 476
Strategy 2c	28%	69%	82%	63 501
Strategy 2d	21%	57%	71%	60 525
Sensitivity analyses (strategy 3 as baseline)				
10% acceptance women, 1.4% in men	9%	23%	29%	12 786
10% acceptance	12%	38%	50%	21 976
30% acceptance	29%	68%	82%	51 058
70% acceptance	46%	83%	91%	81 925
50% PN when screening starts	50%	86%	93%	69 347
Non-equitable coverage	29%	64%	77%	47 219
Screening accepted only once	38%	55%	58%	24 419

Strategies 1–3 have effective partner notification = 20%, acceptance = 50% and no variation in coverage (all attend, all offered screen, 50% accept).
PN, partner notification.

Screening based on recent partner change (strategy 2) allowed more frequent screening in the population and reduced overall and age specific prevalence more than annual screening alone (strategy 1). The more complex algorithms (strategies 2b–d) had a similar effect to strategy 2 because most women were eligible to be offered a screen each time they attended, so the strategies could not be distinguished. Including annual screening for men (strategy 3) caused a further reduction in prevalence compared with strategy 1, but the added benefit was small in relation to the increase in number of screening tests performed. If, however, acceptance is low screening may only have a small impact on prevalence as transmission continues. Attendance was assumed to be about twice per year and was the limiting factor to the impact of screening at different time intervals. For an opportunistic programme, the observed screening interval is longer than the recommended interval because attendance occurs infrequently. More data are required to define the average number of attendances per person at different settings offering chlamydia screening.

A mathematical model is an abstraction from reality, which aims to capture the important components to aid understanding and inform decisions. However, the predictions should not be regarded as truth, but rather as the likely outcome, if our description of reality is accurate. The strengths and weaknesses of the model are discussed further elsewhere.[14] We believe that the model represents an improvement over previous analyses of chlamydia screening effectiveness[29–34] although the model and results are broadly comparable to those of Kretzschmar *et al*.[12] We have used a transmission dynamic model,[14] which is able to capture the indirect benefits of population level programmes. It has been extensively parameterised to represent current sexual behaviour, treatment, partner notification practices, and chlamydia transmission dynamics in the United Kingdom. The proportion ever treated was used to validate the treatment seeking parameters, whereas previous models have not taken these data into account.[12] The model is individual based, thus enabling variability in infection risk and complex screening options, such as partner notification and flexible screening intervals based on individual clinical histories to be investigated.

The model predicted large reductions in prevalence under baseline scenarios. These are comparable to other model predictions—for example, Kretzschmar *et al* predicted a reduction from 4.2% to 1.4% prevalence after 10 years.[12] The effects of screening on prevalence may be large if the reproductive number (R_0) is low, as appears to be the case for chlamydia. The assumption was made for model fitting that chlamydia prevalence was at equilibrium but diagnoses have increased steadily since 2000.[35] This would also lead to overestimating the likely impact of screening since in reality the programme would have to first slow the rate of increase

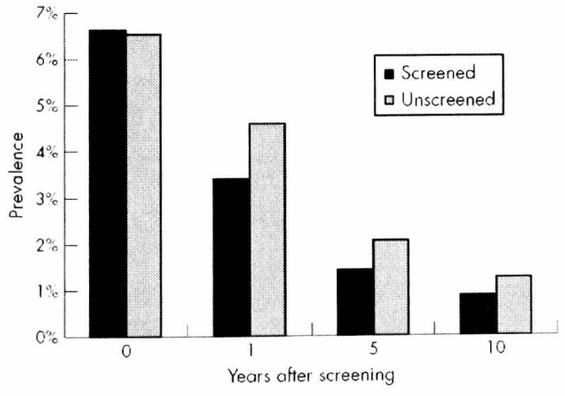

Figure 4 Prevalence of chlamydia (16–24 year old men and women) in the screened and unscreened populations over time (strategy 3, annual screen offer to men and women <25 year olds).

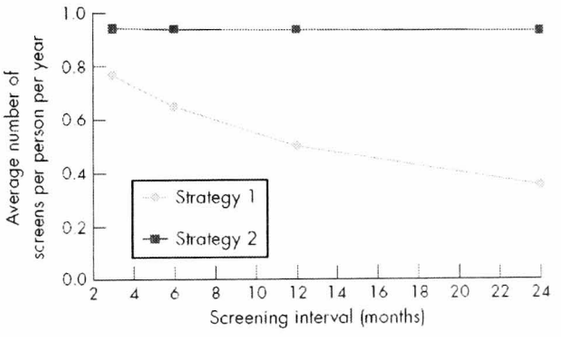

Figure 5 Average number of screens per woman by age under screening strategy 1 (screen women aged 16–24 annually) and strategy 2 (screen women aged 16–24 annually and if partner change in past 6 months), assuming different screening intervals.

before a reduction in prevalence would be seen. Finally, the average rate of partner change modelled is higher than recorded in young women.[14] This may, in part be because of under-reporting of sexual partners by females[28 29] or may be the result of the underlying model structure. The effect of this may be that the impact of screening based on partner change rates (strategies 2) are overestimated in this group, if the reported female rates are true. The positivity observed in NCSP is somewhat higher than we modelled (11% *v* 8% in 16–19 year olds and 9% *v* 6% in 20–24 year olds). Although this is positivity not prevalence, it seems likely that the prevalence now may be somewhat higher than we have modelled. The qualitative results would be unchanged, but the reduction may be slower to occur.

The proportion seeking treatment predicted by the model fitting[14] is very low. The data on the number of people who reported receiving treatment (Natsal 2000) may be an underestimate because of recall bias and changes in testing practice before 2000. However, KC60 data show that in 2000 there were only approximately 12 000 reports of chlamydia for men under 25 and 24 000 in women in England (www.hpa.org.uk). If partner notification was 50% (and each woman had on average one partner), the male reports could be explained entirely by partner notification. Low diagnosis rates, twice as high in women as in men, are consistent with the Natsal 2000 data on self reported history of chlamydia. These data imply that before screening active treatment seeking rates were very low, particularly in men. The proportion symptomatic used by Kretzschmar *et al* was 50% for men and 30% for women[12] (these values are similar to those used in other modelling studies[34 36]). However, such high rates of diagnosis combined with a prevalence of up to 10% in the under 25s would result in far greater numbers of reports of chlamydia diagnoses (either through routine surveillance or self reported history) than were observed. Thus we believe that our estimates of treatment seeking behaviour before screening are more realistic than have previously been assumed.

The maximum achievable coverage is determined by the provision of screening, and the rate of attendance and acceptance of those services. The behaviour of individuals may be mediated by demographic or socioeconomic factors and perception of risk.[19 37] Heterogeneity in acceptance and attendance reduced the overall effectiveness of the intervention (fig 4). Those who do not access screening benefit through herd immunity effects because of lower average population prevalence. However, those who access the intervention gain a greater benefit than those who do not, generating inequalities in health.

Increasing effective partner notification from 20% to 50% increased the effectiveness of screening. The Chlamydia Recall Study quantified the effectiveness of partner notification as 48% of known partnerships.[20] This is higher than the 20% estimated,[14] but the prospective nature of the study, recalling people for testing and extra follow up interviews and phone calls, may have increased the effective coverage of partner notification compared with routine practice. Recent data from the NCSP indicate an effective partner treatment rate of 49%, suggesting that a target of 50% completed partner treatment is achievable.[27]

In countries with well established opportunistic screening programmes (for example, Sweden, Canada), initial decreases in chlamydia diagnoses have been followed by an increase, sometimes to above prescreening levels.[9 17] Assuming that the change reflects a true increase in prevalence, there are several possible interpretations including (a) changes in sexual behaviour, increased number of partners or reduced condom use, (b) difficulties maintaining adherence—for example, people get screened once but do not believe themselves to be at risk in the future, (c) worsening provision of or access to sexual health services. It is also possible that early treatment may interfere with the development of acquired immunity[38] to chlamydia, as shown in a mouse model.[39] Further work to understand the observations is needed, but the impact of screening may be harder to realise than hoped.

The model results suggest that an opportunistic screening programme could reduce chlamydia prevalence, providing that the healthcare settings offer screening to the entire eligible population when they attend, partner notification is maintained or improved, attendance rates to these healthcare settings remain high, and a significant proportion of those offered screening accept the invitation.

Key messages

- Achieving a sustained reduction in chlamydia prevalence may be possible with continuous opportunistic screening but high acceptance, universal coverage, repeated testing, and effective partner notification are needed
- The model predictions are strengthened by the use of appropriate, high quality data to validate and fit the model
- The screening interval has little impact on the effectiveness of screening, because attendance and acceptance are the limiting factors

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CONTRIBUTORS

KMT wrote the first draft of the paper, designed and implemented changes to the computer program; EJA performed the simulations and analyses; WJE supervised and advised on the modelling and programming work; KMT, EJA, WJE, DSL contributed to the interpretation of results, contributed to the experimental design and implementation, critically reviewed drafts, and contributed to writing the paper; LE provided data from the Chlamydia recall study and critically reviewed drafts; KB provided statistical advice on data from the Chlamydia Recall study and critically reviewed drafts. All authors have seen and approved the final version and have no conflict of interest.

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Appendix 2. All studies that met the systematic review inclusion criteria, their extracted variables and computed prevalence (95% CI), based on the reported number tested and positive, from Chapter 3.

Notes on Setting/ selection criteria:

1. house to house interview
2. sexually active
3. postal survey
4. registered with GP
5. speculum exam, cervical smear/cytology test
6. asymptomatic patients
7. attending for contraception
8. pregnancy test
9. routine urine check
10. first/new visit, new problem
11. Intrauterine device (IUD) fitting/insertion
12. patients for TOP
13. all/consecutive patients
14. sexual health screen
15. rape victims
16. HIV test
17. gynaecology
18. HIV clinic

Note on patients who accepted testing:

a) overall 71% provided sample, of 65% who entered Natsal 2000 study
b) overall 45% acceptance
c) overall acceptance 98.5%
d) overall acceptance 76%
e) overall 98% acceptance (aged 20-35)
f) 16-24 year olds
g) unclear, but maybe overall acceptance of 8%
h) 97% overall acceptance
j) overall acceptance 68%-70%
k) approximately 98% acceptance
m) overall 55% acceptance

Note on Test:

PCR- polymerase chain reaction, LCR- ligase chain reaction, EIA- enzyme immunoassay, DFA- direct flourescence assay, DIF- direct immunoflourescence.

Note on Specimen:

US-urethral swab, CS- cervical swab, ES- endocervical swab, FCU/FVU- first catch/void urine.

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
Population-based		*Overall prevalence (all)*		1.9% (95%CI 1.5% – 2.3%)			*Overall prevalence (females only)*				1.8% (95%CI 1.3% – 2.6%)		
Fenton KA, *et al.* (2001)	Great Britain	5/99-2/01	Female	LCR	Urine	18-19	1,2	a	4	105	3.8%	1.0%	9.5%
						20-24			7	259	2.7%	1.1%	5.5%
						25-29			7	316	2.2%	0.9%	4.5%
						30-44			9	1045	0.9%	0.4%	1.6%
Stephenson J, *et al.* (2000)	London/Avon	Unknown	Female	LCR	Vulval swab/ Urine	18-25	3,4	31%	4	65	6.2%	1.7%	15.0%
Macleod J, *et al.* (1999)	Bristol	8/96-11/96	Female	LCR/EIA w/DFA confirmation	Urine	18-45	3,4	61%	3	63	4.8%	1.0%	13.3%
Fenton KA, *et al.* (2001)	Great Britain	5/99-2/01	Male	LCR	Urine	18-19	1,2	a	2	102	2.0%	0.2%	6.9%
						20-24			8	286	2.8%	1.2%	5.4%
						25-29			16	336	4.8%	2.7%	7.6%
						30-44			12	1080	1.1%	0.6%	1.9%
Stephenson J, *et al.* (2000)	London/Avon	Unknown	Male	LCR	Urine	18-35	3,4	36%	2	80	2.5%	0.3%	8.7%
Rogstad KE, *et al.* (2001)	Sheffield	9/98-8/99	Male	LCR	FVU	19-21	3, 1&3rd yr university students	29%	9	758	1.2%	0.5%	2.2%
Pierpoint T, *et al.* (2000)	London	11/95-12/97	Male	LCR w/DFA confirmation	FCU	18-24	3,4	b	2	130	1.5%	0.2%	5.4%
						25-29			0	108	0.0%	0.0%	3.4%
						30-35			7	178	3.9%	1.6%	7.9%
Macleod J, *et al.* (1999)	Bristol	8/96-11/97	Male	LCR/EIA w/DFA confirmation	Urine	18-45	3,4	52%	1	52	1.9%	0.0%	10.3%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
GP/ Community Clinic		*Overall prevalence (all)*		5.5% (95%CI 5.2% – 5.7%)			*Overall prevalence (females only)*				5.7% (95%CI 5.5% – 6.0%)		
Southgate L, *et al.* (1983)	London	Unknown	Female	Culture	ES	15-45	5	78%	19	248	7.7%	4.7%	11.7%
Smith J, *et al.* (1991)	Glasgow	89-90	Female	Culture w/DFA confirmation	CS	19-58	5,6	-	24	197	12.2%	8.0%	17.6%
Oakeshott P, *et al.* (1992)	London	4/90-10/91	Female	DIF	ES	17-45	5	-	36	409	8.8%	6.2%	12.0%
Longhurst H, *et al.* (1987)	London	1986/7	Female	DIF & Culture	ES	Unknown	5,7	-	18	169	10.7%	6.4%	16.3%
Oakeshott P (1995)	London	5/94-8/95	Female	EIA w/ DFA confirmation	ES	17-35	5	-	39	1255	3.1%	2.2%	4.2%
Hopwood J, *et al.* (1995)	Liverpool	Unknown	Female	EIA w/ DFA confirmation	ES	16	5	c	1	8	12.5%	0.3%	52.7%
						17			5	49	10.2%	3.4%	22.2%
						18			1	60	1.7%	0.0%	8.9%
						19			5	114	4.4%	1.4%	9.9%
						20			6	175	3.4%	1.3%	7.3%
						21			9	173	5.2%	2.4%	9.6%
						22			10	171	5.8%	2.8%	10.5%
						23			6	136	4.4%	1.6%	9.4%
						24			7	126	5.6%	2.3%	11.1%
						25			7	158	4.4%	1.8%	8.9%
						26-30			6	367	1.6%	0.6%	3.5%
Oakeshott P, *et al.* (1998)	London	5/94-10/95	Female	EIA/DFA	ES	<20	5	d	6	53	11.3%	4.3%	23.0%
						20-24			16	364	4.4%	2.5%	7.0%
						25-34			18	965	1.9%	1.1%	2.9%
Thompson C, *et al.* (1994)	Fife, Scotland	1992	Female	IFA	ES	15-29	5	-	5	145	3.4%	1.1%	7.9%
						30-40			0	142	0.0%	0.0%	2.6%
Scoular A, *et al.* (2001)	Glasgow	1999/2000	Female	LCR	US, Urine	15-44	5	-	920	18606	4.9%	4.6%	5.3%
Grun L, *et al.* (1997)	London	10/94-1/96	Female	LCR w/EIA/DFA confirmation	FCU & ES	18-20	GP invitation, well-woman check	80%	9	85	10.6%	5.0%	19.2%
						21-25			8	210	3.8%	1.7%	7.4%
						26-30			3	331	0.9%	0.2%	2.6%
						31-35			3	222	1.4%	0.3%	3.9%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
Pimenta JM, *et al.* (2003)	Portsmouth	2000/2001	Female	PCR	FCU	16-19	2	75% f	319	3093	10.3%	9.3%	11.4%
	Portsmouth					20-24		75% f	322	4453	7.2%	6.5%	8.0%
	Wirral					16-19		81% f	53	637	8.3%	6.3%	10.7%
	Wirral					20-24		81% f	85	942	9.0%	7.3%	11.0%
Tobin C, *et al.* (2001)	West Yorkshire	12/98-11/99	Female	PCR	FVU	13-24	2	45%	14	128	10.9%	6.1%	17.7%
Santer M, *et al.* (2000)	Edinburgh	1999	Female	PCR/LCR	Urine	<18	5,7,8	-	3	32	9.4%	2.0%	25.0%
						18	5,7,8		6	51	11.8%	4.4%	23.9%
						19-20	5,7,8		2	56	3.6%	0.4%	12.3%
						20-25	5		4	99	4.0%	1.1%	10.0%
						26-35	5		0	172	0.0%	0.0%	2.1%
Clay J, *et al.* (1996)	Nottingham	Unknown	Female	Unknown	CS	15-19	5	-	3	17	17.6%	3.8%	43.4%
	Nottingham					20-24			7	62	11.3%	4.7%	21.9%
	Nottingham					25-29			3	88	3.4%	0.7%	9.6%
	Nottingham					30-39			2	179	1.1%	0.1%	4.0%
	Nottingham					>40			0	99	0.0%	0.0%	3.7%
	South Lincolnshire (rural)					15-19			5	21	23.8%	8.2%	47.2%
	South Lincolnshire (rural)					20-24			5	64	7.8%	2.6%	17.3%
	South Lincolnshire (rural)					25-29			6	74	8.1%	3.0%	16.8%
	South Lincolnshire (rural)					30-39			7	156	4.5%	1.8%	9.0%
	South Lincolnshire (rural)					>40			2	282	0.7%	0.1%	2.5%
Kudesia G, *et al.* (1993)	Sheffield	1993	Male	Culture w/EIA & DIF confirmation	Urine	<30	9	-	15	99	15.2%	8.7%	23.8%
						30-40			2	59	3.4%	0.4%	11.7%
						>40			1	135	0.7%	0.0%	4.1%
Berry J, *et al.* (1995)	Bristol	Unknown	Male	EIA/DIF	Urine	18-34	Medical check for university	99%	2	77	2.6%	0.3%	9.1%
Ainsworth JG, *et al.* (1996)	London	1995	Male	Unknown	US	<40	-	-	4	27	14.8%	4.2%	33.7%
Ross J, *et al.* (1996)	Lothian, Scotland	1995	Both	EIA	Genital swab	Unknown	-	-	141	3943	3.6%	3.0%	4.2%
Dryden M, *et al.* (1994)	Winchester	1/91-3/93	Both	EIA w/ DFA confirmation	Urine	16-65	9	-	54	1025	5.3%	4.0%	6.8%
Rogstad KE, *et al.* (2000)	Sheffield/ Chesterfield	6/96-5/97	Both	EIA w/MIF confirmation	Unknown	Unknown	-	-	95	2237	4.2%	3.4%	5.2%
Stokes T, *et al.* (1997)	Leicestershire	1995	Unknown	EIA w/ DFA confirmation	Unknown	Unknown	-	-	79	1286	6.1%	4.9%	7.6%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
FPC		*Overall prevalence (all)*		6.8% (95%CI 6.5% – 7.2%)			*Overall prevalence (females only)*				6.9% (95%CI 6.5% – 7.3%)		
Fish A, *et al.* (1987)	London	1984-1986	Female	Culture	ES	17-46	10	-	11	327	3.4%	1.7%	5.9%
Macaulay M, *et al.* (1990)	Manchester	Unknown	Female	Culture w/EIA confirmation	ES	<25	-	-	24	185	13.0%	8.5%	18.7%
						>25			9	267	3.4%	1.6%	6.3%
James N, *et al.* (1997)	Nottingham	11/94-11/95	Female	EIA	ES	14-50	11	70%	9	220	4.1%	1.9%	7.6%
Murty J (1996)	Leeds	4/95-9/95	Female	EIA	Unknown	<16	11	-	0	1	0.0%	0.0%	97.5%
						16-19			2	8	25.0%	3.2%	65.1%
						20-24			1	36	2.8%	0.1%	14.5%
						25-29			2	49	4.1%	0.5%	14.0%
						30-34			2	39	5.1%	0.6%	17.3%
						>35			0	45	0.0%	0.0%	7.9%
Simms I, *et al.* (2000)	Liverpool	1996	Female	EIA	ES	16-19	11,12	g	38	375	10.1%	7.3%	13.6%
						20-24			54	687	7.9%	6.0%	10.1%
						25-29			25	553	4.5%	2.9%	6.6%
						>29			6	550	1.1%	0.4%	2.4%
Sprague D, *et al.* (1990)	South Shields	11/85-11/86	Female	EIA	CS	<20	7	-	10	67	14.9%	7.4%	25.7%
						20-29			13	253	5.1%	2.8%	8.6%
						30-39			1	168	0.6%	0.0%	3.3%
						40-49			3	54	5.6%	1.2%	15.4%
Willmott F, *et al.* (2000)	Southampton	6/98-5/99	Female	EIA	ES	Unknown	Clinical/ opportunistic screening	-	47	590	8.0%	5.9%	10.5%
Rogstad KE, *et al.* (2000)	Sheffield/ Chesterfield	6/96-5/97	Female	EIA w/MIF confirmation	Unknown	Unknown	-	-	31	537	5.8%	4.0%	8.1%
Harvey J, *et al.* (2000)	Mereyside	Unknown	Female	LCR	Urine	<20	13.00	99%	77	905	8.5%	6.8%	10.5%
Macmillan S, *et al.* (2000b)	Aberdeen	3/97-12/98	Female	LCR	FVU	<19	13	h	19	190	10.0%	6.1%	15.2%
						20-24			4	153	2.6%	0.7%	6.6%
						25-29			1	72	1.4%	0.0%	7.5%
						30-34			1	47	2.1%	0.1%	11.3%
						>35			1	45	2.2%	0.1%	11.8%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
Macmillan S, *et al.* (2000a)	Aberdeen	1/98-5/98	Female	LCR	Vulval swab/Urine	<25	13	68%	12	103	11.7%	6.2%	19.5%
Scoular A, *et al.* (2001)	Glasgow	1999/2000	Female	LCR	US, Urine	15-44	-	-	180	3723	4.8%	4.2%	5.6%
Pimenta JM, *et al.* (2003)	Portsmouth	2000/2001	Female	PCR	FCU	16-19	2	54% f	168	1626	10.3%	8.9%	11.9%
	Portsmouth					20-24		54% f	132	1431	9.2%	7.8%	10.8%
	Wirral					16-19		68% f	42	405	10.4%	7.6%	13.8%
	Wirral					20-24		68% f	59	594	9.9%	7.6%	12.6%
Kilcoin A (2001)	Essex	Unknown	Female	Unknown	Unknown	13-14	2	-	4	24	16.7%	4.7%	37.4%
						15			7	70	10.0%	4.1%	19.5%
						16-19			72	714	10.1%	8.0%	12.5%
						20-25			43	604	7.1%	5.2%	9.5%
Sin J, *et al.* (1996)	Manchester	Unknown	Female	Unknown	ES	16-39	-	-	29	666	4.4%	2.9%	6.2%
Tobin J, *et al.* (1999)	Portsmouth	2/96-6/96	Female	Unknown	Unknown	Unknown	11,12	-	36	740	4.9%	3.4%	6.7%
Harvey J, *et al.* (2000)	Mereyside	Unknown	Male	LCR	Urine	<20	13	99%	3	53	5.7%	1.2%	15.7%
Stokes T, *et al.* (1997)	Leicestershire	1995	Unknown	EIA w/ DFA confirmation	Unknown	Unknown	-	-	38	649	5.9%	4.2%	7.9%

Youth clinic		*Overall prevalence (all)*	12.2% (95%CI 10.8% – 13.7%)			*Overall prevalence (females only)*			12.2% (95%CI 10.8% – 13.7%)			
James NJ, *et al.* (1999)	Nottingham	5/95-5/97	Female	EIA/DFA	ES	13-19	5,7	-	32	332	9.6%	6.7%	13.3%
							7		20	187	10.7%	6.7%	16.0%
							7,risk behaviour		14	156	9.0%	5.0%	14.6%
							7,12		22	143	15.4%	9.9%	22.4%
Pimenta JM, *et al.* (2003)	Portsmouth	2000/2001	Female	PCR	FCU	16-19	2		24	139	17.3%	11.4%	24.6%
	Portsmouth					20-24		62% f	1	11	9.1%	0.2%	41.3%
	Wirral					16-19		82 % f	100	721	13.9%	11.4%	16.6%
	Wirral					20-24		82 % f	31	307	10.1%	7.0%	14.0%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
TOP		*Overall prevalence (all)*		7.7% (95%CI 7.1% – 8.2%)			*Overall prevalence (females only)*				7.7% (95%CI 7.1% – 8.2%)		
Duthie S, *et al.* (1987)	Liverpool	5/84-12/84	Female	Culture	CS	Unknown	12	-	19	167	11.4%	7.0%	17.2%
Blackwell AL, *et al.* (1999)	Swansea	1/92-10/93	Female	EIA	CS	13-49	12,13	-	132	1951	6.8%	5.7%	8.0%
Blackwell A, *et al.* (1993)	Swansea	10/90-3/91	Female	EIA	CS	Unknown	12,13	100%	36	400	9.0%	6.4%	12.2%
Southgate L, *et al.* (1989)	London	9/86-9/87	Female	EIA	ES	16-45	12,13	86%	12	103	11.7%	6.2%	19.5%
Macmillan S, *et al.* (2000b)	Aberdeen	3/97-12/98	Female	EIA/DFA	ES	<19	13	100%	21	178	11.8%	7.5%	17.5%
						20-24			14	206	6.8%	3.8%	11.1%
						25-29			2	138	1.4%	0.2%	5.1%
						30-34			2	110	1.8%	0.2%	6.4%
						>35			2	82	2.4%	0.3%	8.5%
Pimenta JM, *et al.* (2003)	Portsmouth	2000/2001	Female	PCR	FCU	16-19	2	55% f	22	160	13.8%	8.8%	20.1%
	Portsmouth					20-24		55% f	28	198	14.1%	9.6%	19.8%
	Wirral					16-19		38% f	6	26	23.1%	9.0%	43.6%
	Wirral					20-24		38% f	2	34	5.9%	0.7%	19.7%
Hopwood J, *et al.* (2001)	Mereyside	2/00-3/00	Female	LCR	ES	15-19	12,13	-	10	89	11.2%	5.5%	19.7%
						20-24			16	119	13.4%	7.9%	20.9%
						25-29			4	65	6.2%	1.7%	15.0%
						30-34			0	67	0.0%	0.0%	5.4%
						35-39			1	29	3.4%	0.1%	17.8%
						40-44			0	9	0.0%	0.0%	33.6%
Unpub.	North West England	Unknown	Female	LCR	Unknown	Unknown	-	-	71	1070	6.6%	5.2%	8.3%
Uthayakumar S, *et al.* (2000)	Stevenage	2/00-3/00	Female	LCR	ES	<20	13, TOP counselling	-	6	17	35.3%	14.2%	61.7%
						>20			6	100	6.0%	2.2%	12.6%
Hopwood J, *et al.* (1998)	Mereyside	5/96-8/96	Female	LCR/EIA/IFA	Urine/ ES	<16	12	-	2	14	14.3%	1.8%	42.8%
						16-20			23	188	12.2%	7.9%	17.8%
						21-25			18	238	7.6%	4.5%	11.7%
						26-30			1	144	0.7%	0.0%	3.8%
						>30			0	3	0.0%	0.0%	70.8%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
Chima-Okereke C, *et al.* (2002)	Swansea	1999	Female	Unknown	Unknown	<25	10	-	67	627	10.7%	8.4%	13.4%
		2000				<25			48	504	9.5%	7.1%	12.4%
		2001				<25			75	618	12.1%	9.7%	15.0%
		1999				>25			20	537	3.7%	2.3%	5.7%
		2000				>25			13	433	3.0%	1.6%	5.1%
		2001				>25			15	450	3.3%	1.9%	5.4%
Smith N, *et al.* (1994)	London	1991	Female	Unknown	ES	15-41	12,14	72%	6	63	9.5%	3.6%	19.6%
Antenatal		*Overall prevalence (all)*		7.2% (95%CI 5.9% – 8.8%)		*Overall prevalence (females only)*					7.7% (95%CI 6.2% – 9.4%)		
Wood P, *et al.* (1984)	Liverpool	Unknown	Female	Culture	CS	Unknown	10	-	18	252	7.1%	4.3%	11.1%
Roberts RN, *et al.* (1991)	Belfast	3/89-7/89	Female	DFA	ES	Unknown	10	-	3	104	2.9%	0.6%	8.2%
Macmillan S, *et al.* (2000b)	Aberdeen	3/97-12/98	Female	LCR	FVU	<19	13	h	3	15	20.0%	4.3%	48.1%
						20-24			1	37	2.7%	0.1%	14.2%
						25-29			5	70	7.1%	2.4%	15.9%
						30-34			0	54	0.0%	0.0%	6.6%
						>35			0	28	0.0%	0.0%	12.3%
Pimenta JM, *et al.* (2003)	Portsmouth	2000/2001	Female	PCR	FCU	16-19	2	82% f	11	71	15.5%	8.0%	26.0%
	Portsmouth					20-24		82% f	5	94	5.3%	1.7%	12.0%
	Wirral					16-19		90% f	18	150	12.0%	7.3%	18.3%
	Wirral					20-24		90% f	25	284	8.8%	5.8%	12.7%
Stokes T, *et al.* (1997)	Leicestershire	1995	Unknown	EIA w/ DFA confirmation	Unknown	Unknown	-	-	2	97	2.1%	0.3%	7.3%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
GUM		*Overall prevalence (all)*		12.45% (95%CI 12.1% - 12.8%)			*Overall prevalence (females only)*				12.2% (95%CI 11.8% – 12.5%)		
Arya OP, *et al.* (1981)	Liverpool	1/76-10/78	Female	Culture	ES/CS, US	Unknown	-	-	158	474	33.3%	29.1%	37.8%
Oriel J, *et al.* (1978)	London	2/75-6/75	Female	Culture	CS	Unknown	13	-	58	284	20.4%	15.9%	25.6%
Richmond S, *et al.* (1980)	Bristol	2/79-5/79	Female	Culture	ES	Unknown	10	-	86	446	19.3%	15.7%	23.3%
Shanmugaratnam K, *et al.* (1989)	Newcastle	1985-1988	Female	Culture	ES	Unknown	13	96%	1614	12490	12.9%	12.3%	13.5%
Woolfitt JM, *et al.* (1977)	Manchester	9/73-9/74	Female	Culture	CS, US	Unknown	13	-	53	200	26.5%	20.5%	33.2%
Ross JD, *et al.* (1991)	Edinburgh	87-89	Female	Culture	Endocervical swab	Unknown	13,15	-	2	43	4.7%	0.6%	15.8%
McKenna JG, *et al.* (1990)	Edinburgh	1986-1989	Female	Culture,EIA, IF	Unknown	Unknown	13	-	979	8974	10.9%	10.3%	11.6%
Foulkes SJ, *et al.* (1985)	Bradford	12/83-1/84	Female	Culture/DIF	ES	Unknown	-	-	28	126	22.2%	15.3%	30.5%
Horner P, *et al.* (1995)	London	Unknown	Female	DFA	CS, US, Urine	17-49	5,10	-	39	139	28.1%	20.8%	36.3%
Hay P, *et al.* (1994)	London	11/90-5/91	Female	DFA/EIA	US, ES, Urine	Unknown	10	-	41	150	27.3%	20.4%	35.2%
Opaneye A, *et al.* (1994)	Sunderland, Tyne and Wear, UK	1/91-12/91	Female	EIA	US, CS	Unknown	-	-	121	1461	8.3%	6.9%	9.8%
Woolley PD, *et al.* (1997)	Manchester	Unknown	Female	EIA	ES	Unknown	10	-	97	1353	7.2%	5.9%	8.7%
Crowley T, *et al.* (1997)	Bristol	2/94-10/94	Female	EIA/DFA	CS, US	15-19	5	-	26	156	16.7%	11.2%	23.5%
						20-24			36	319	11.3%	8.0%	15.3%
						25-29			12	245	4.9%	2.6%	8.4%
						30-34			12	174	6.9%	3.6%	11.7%
						35-39			2	64	3.1%	0.4%	10.8%
						40-44			1	37	2.7%	0.1%	14.2%
Butt A, *et al.* (2001)	Glasgow	Unknown	Female	EIA/PCR	ES	Unknown	10,14	-	10	153	6.5%	3.2%	11.7%
Scoular A, *et al.* (2001)	Glasgow	1999/2000	Female	LCR	US, Urine	15-44	-	-	159	1850	8.6%	7.4%	10.0%
Pimenta JM, *et al.* (2003)	Portsmouth	2000/2001	Female	PCR	FCU	16-19	2	97% f	81	500	16.2%	13.1%	19.7%
	Portsmouth					20-24		97% f	82	715	11.5%	9.2%	14.0%
	Wirral					16-19		92% f	50	240	20.8%	15.9%	26.5%
	Wirral					20-24		92% f	50	329	15.2%	11.5%	19.5%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
Young H, *et al.* (1998)	Edinburgh	Unknown	Female	PCR	Urine	Unknown	10	-	21	232	9.1%	5.7%	13.5%
Dimian C, *et al.* (1992)	London	6/90-8/90	Female	Unknown	CS	16-45	14	-	34	363	9.4%	6.6%	12.8%
Mohanty KC (1990)	Bradford	1987/1988	Female	Unknown	ES	Unknown	6,10	-	20	123	16.3%	10.2%	24.0%
							6,10,16	42%	42	115	36.5%	27.7%	46.0%
Radja N, *et al.* (2001)	Swansea	1/97-12/97	Female	Unknown	Unknown	11-16	10	-	6	22	27.3%	10.7%	50.2%
	London								2	30	6.7%	0.8%	22.1%
70	Cambridge	4/92-1/94	Female	Unknown	Unknown	Unknown	5,no colposcopy patients	-	33	653	5.1%	3.5%	7.0%
Hunter JM, *et al.* (1981)	Edinburgh	10/79-1/80	Male	Culture	US	Unknown	10	-	77	480	16.0%	12.9%	19.6%
Zelin JM, *et al.* (1995)	London	1991	Male	Culture	US	17-77	13, heterosexual	-	34	356	9.6%	6.7%	13.1%
Harry T, *et al.* (1994)	Sunderland	1/92-12/92	Male	EIA	US	17-46	10,13	-	90	1318	6.8%	5.5%	8.3%
Matthews R, *et al.* (1989)	Birmingham	Unknown	Male	EIA	FCU	Unknown	13	-	68	422	16.1%	12.7%	20.0%
Crowley T, *et al.* (1992)	Bristol	1991	Male	EIA w/ DIF confirmation	Urine, US	Unknown	10	-	99	402	24.6%	20.5%	29.1%
Evans BA, *et al.* (1999)	London	9/93-9/94	Male	EIA/DIF	Unknown	>13	10,black patients	89%	33	180	18.3%	13.0%	24.8%
Paul I, *et al.* (1990)	Bristol	1990?	Male	EIA/DIF	FCU	Unknown	10	-	103	615	16.7%	13.9%	19.9%
Butt A, *et al.* (2001)	Glasgow	Unknown	Male	EIA/PCR	US	Unknown	14	-	23	148	15.5%	10.1%	22.4%
Caul E, *et al.* (1997)	Bristol	Unknown	Male	LCR	Urine	Unknown	-	-	41	123	33.3%	25.1%	42.4%
Dixon L, *et al.* (2002)	Edinburgh	1999	Male	LCR	Urine	Unknown	10, heterosexual	-	350	2402	14.6%	13.2%	16.0%
Higgins SP, *et al.* (1998)	Manchester	Unknown	Male	PCR	Urine/US	Unknown	10	-	58	390	14.9%	11.5%	18.8%
Young H, *et al.* (1998)	Edinburgh	Unknown	Male	PCR	Urine	Unknown	10	-	27	215	12.6%	8.4%	17.7%
Mohanty KC (1990)	Bradford	1987/1988	Male	Unknown	US	Unknown	6,10	-	8	227	3.5%	1.5%	6.8%
							6,10,16	44%	14	263	5.3%	2.9%	8.8%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
Other/mixed													
Woolfitt JM, *et al.* (1977)	Manchester	9/73-9/75	Female	Culture	CS, US	Unknown	Hospital staff	-	2	200	1.0%	0.1%	3.6%
Lacey HB (1990)	Manchester	1989	Female	Culture	ES	13-77	14,15,sexual assault centre	-	7	90	7.8%	3.2%	15.4%
Smith J, *et al.* (1991)	Glasgow	89-90	Female	Culture w/DFA confirmation	CS	19-58	10,abnormal smear for colposcopy	-	6	101	5.9%	2.2%	12.5%
Madge S, *et al.* (1996)	London	8/93-4/95	Female	EIA	ES	Unknown	18	59%	5	143	3.5%	1.1%	8.0%
Ridgway GL, *et al.* (1983)	London	Unknown	Female	Culture	CS	Unknown	12,17	-	7	89	7.9%	3.2%	15.5%
Fish A, *et al.* (1989)	London	2/85-2/86	Female	Culture	ES	<16	5,13,17	j	0	2	0.0%	0.0%	84.2%
						16-20			15	103	14.6%	8.4%	22.9%
						21-25			14	203	6.9%	3.8%	11.3%
						26-30			6	203	3.0%	1.1%	6.3%
						31-35			4	197	2.0%	0.6%	5.1%
						36-40			4	200	2.0%	0.5%	5.0%
						>46			0	230	0.0%	0.0%	1.6%
						41-45			2	129	1.6%	0.2%	5.5%
Edet E (1993)	Chatham, Kent	1988-1990	Female	EIA	ES	26-29	17	-	20	439	4.6%	2.8%	6.9%
						<25			64	668	9.6%	7.5%	12.1%
						>30			18	504	3.6%	2.1%	5.6%
Scoular A, *et al.* (2001)	Glasgow	1999/2000	Female	LCR	US, Urine	15-44	GP, GUM & FPC	-	951	15289	6.2%	5.8%	6.6%
Macmillan S, *et al.* (2000b)	Aberdeen	3/97-12/98	Female	LCR	ES	<19	13,Infertility, colposcopy, miscarriage	k	3	39	7.7%	1.6%	20.9%
						20-24			4	99	4.0%	1.1%	10.0%
						25-29			11	183	6.0%	3.0%	10.5%
						30-34			1	161	0.6%	0.0%	3.4%
						>35			2	128	1.6%	0.2%	5.5%
Barlow RE, *et al.* (2001)	Sheffield/Bristol	Unknown	Female	PCR/Southern blot	Endometrium, fallopian tube & ovary	33-57	Hysterectomy/ laparoscopic sterilisation	-	4	20	20.0%	5.7%	43.7%

Author	Location	Date of testing	Gender	Test used	Specimen	Age group	Setting/ Selection note	% Tested	No. positive	Total tested	Prevalence	Lower 95% CI	Upper 95% CI
Chima-Okereke C, *et al.* (2002)	Swansea	1999	Female	Unknown	Unknown	<25	10, colposcopy	-	21	242	8.7%	5.5%	13.0%
		2000				<25			15	221	6.8%	3.8%	10.9%
		2001				<25			13	200	6.5%	3.5%	10.9%
		1999				>25			8	449	1.8%	0.8%	3.5%
		2000				>25			11	447	2.5%	1.2%	4.4%
		2001				>25			7	386	1.8%	0.7%	3.7%
Opaneye A (1997)	Coventry	1/92-3/91	Female	Unknown	Unknown	<30	2,10,FPC/ GUM	-	86	211	40.8%	34.1%	47.7%
						>30			19	77	24.7%	15.6%	35.8%
Scoular A, *et al.* (2001)	Glasgow	1999/2000	Male	LCR	US, Urine	15-44	GP, GUM & FPC	-	337	3476	9.7%	8.7%	10.7%
Pierpoint T, *et al.* (2000)	London	11/95-12/97	Male	LCR w/DFA confirmation	FCU	25-29	10,Various clinics	m	4	181	2.2%	0.6%	5.6%
						30-35			6	231	2.6%	1.0%	5.6%
						18-24			0	174	0.0%	0.0%	2.1%
Madge S, *et al.* (1996)	London	8/93-4/94	Male	EIA	US	Unknown	18	69%	1	217	0.5%	0.0%	2.5%
McKay L, *et al.* (2003)	Edinburgh	4/01-4/02	Male	Unknown	Urine	16-19	New military recruits	100%	49	529	9.3%	6.9%	12.1%
						20-24			27	246	11.0%	7.4%	15.6%
						>25			2	23	8.7%	1.1%	28.0%
Rogstad KE, *et al.* (2000)	Sheffield/ Chesterfield	6/96-5/97	Both	EIA w/MIF confirmation	Unknown	Unknown	Hospital staff	-	38	1115	3.4%	2.4%	4.6%
Dedicoat M, *et al.* (2000)	Birmingham	10/96-8/97	Both	Unknown	Unknown	Unknown	18	24%	7	200	3.5%	1.4%	7.1%
		9/97-6/98						56%	15	426	3.5%	2.0%	5.7%
Stokes T, *et al.* (1997)	Leicestershire	1995	Unknown	EIA w/ DFA confirmation	Unknown	Unknown	Eye Clinic	-	22	203	10.8%	6.9%	15.9%
							Various clinics		5	103	4.9%	1.6%	11.0%
							17		27	816	3.3%	2.2%	4.8%

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