MATHEMATICAL MODELS OF GONORRHOEA AND CHLAMYDIA: BIOLOGY, BEHAVIOUR AND INTERVENTIONS

Katherine Mary Elizabeth Turner

Imperial College London

PhD thesis submitted for examination
March 2004
Abstract
Gonorrhoea and chlamydia are curable, bacterial, sexually transmitted infections (STIs) of humans, with important long term consequences for health. Their epidemiology and biology are reviewed in chapter one.

The way the biology of the organisms and the behaviour of human hosts interact to influence the patterns of infection and the potential impact of interventions is the subject of the main body of the thesis. Mathematical models are presented, together with empirical data, to gain a better understanding of the epidemiology of gonorrhoea and chlamydia. New approaches are applied, using more complex measures of disease occurrence including reinfection (subsequent infection by the same organism) or coinfection (infection with both organisms simultaneously). Coinfection with gonorrhoea and chlamydia is investigated in chapter two.

The third chapter investigates the importance of heterogeneity in human behaviour (i.e. level of sexual activity, mixing patterns within and between populations) on the spread of disease in subpopulations, using a model incorporating race, gender and sexual activity level. This was parameterised and validated using data collected in South East London.

In chapter four, models of reinfection are used to investigate the interaction of population level parameters such as degree of assortative mixing and rates of reinfection. In chapter five, the characteristics of individuals coinfectected with both organisms are shown to provide additional information useful in determining how infection is distributed across a population.

The biology of the organism is demonstrated, in the fifth chapter, to play an important role in the prevalence and incidence of disease within the host population. The impact of the emergence of resistant or asymptomatic phenotypes under selective pressure by different treatment regimens is quantified using a two strain model, including asymptomatic and symptomatic infections. The final chapter considers the contribution of the research and discusses the implications of the results for STI intervention strategies.
Table of contents

Chapter 1  Introduction....................................................................................................9
Summary.......................................................................................................................9
Overview of gonorrhoea and chlamydia.................................................................10
Epidemiology of gonorrhoea and chlamydia............................................................15
Host factors................................................................................................................16
  Behaviour................................................................................................................16
  Sexual behaviour ..................................................................................................17
  Behaviour during infection ..................................................................................17
  Treatment seeking behaviour and condom use ..................................................17
  Mixing patterns and the sexual network ..............................................................18
Biology of host infection ..........................................................................................19
  Coinfection ..........................................................................................................19
  Reinfecition ............................................................................................................21
  Susceptibility and acquired immunity ................................................................22
Intervention strategies ..............................................................................................23
  Treatment .............................................................................................................23
  Screening and diagnostic tests ............................................................................27
  Partner notification (contact tracing) and partner delivered therapy................31
Bacterial factors .........................................................................................................32
  Multiple strains of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* ........33
  Transmissibility ..................................................................................................35
  Duration of infection ............................................................................................35
  Asymptomatic infection .......................................................................................36
  Drug resistance ..................................................................................................37
  Why do pathogens evolve?....................................................................................39
Mathematical models of sexually transmitted infections. ....................................40
Discussion..................................................................................................................41

Chapter 2  Coinfection with chlamydia and gonorrhoea........................................43
Summary.....................................................................................................................43
Introduction.................................................................................................................44
  Extent of coinfection with gonorrhoea and chlamydia.......................................47
Behavioural aspects of coinfection..........................................................................52
Biology of coinfection...............................................................................................53
Method ......................................................................................................................55
  Mathematical model ............................................................................................55
    Model details ....................................................................................................55
Results ......................................................................................................................64
  Impact of intervention strategies.......................................................................65
Discussion................................................................................................................69
Chapter 3  Sexual mixing patterns and the distribution of gonorrhoea in
different subpopulations............................................................................................................72
Summary........................................................................................................................................72
Background..................................................................................................................................73
Mixing patterns and disease spread..............................................................................................73
  Describing mixing patterns...........................................................................................................73
  Mixing patterns in people with STIs............................................................................................74
    Interrelationship between determinants of mixing patterns.......................................................74
  Activity level...............................................................................................................................74
  Age mixing...................................................................................................................................76
  Geography....................................................................................................................................76
  Ethnicity........................................................................................................................................77
  Implications of different mixing patterns for disease control and policy decisions..................77
Inequality in disease burden...........................................................................................................78
  Is ethnicity a valid epidemiological measure?............................................................................80
Objectives......................................................................................................................................81
Method...........................................................................................................................................82
  Sources of data on sexual behaviour...........................................................................................82
  Mixing patterns............................................................................................................................83
    Mixing by ethnicity......................................................................................................................83
    Mixing by activity and calculation of partner change rate.......................................................83
  Gonorrhoea diagnoses................................................................................................................90
  Estimation of other parameters..................................................................................................90
  Mathematical model..................................................................................................................90
    Model details.............................................................................................................................93
      Model constraints: Balancing the numbers of sexual partnerships in the model
      population...............................................................................................................................94
  Fitting the model..........................................................................................................................96
  Results........................................................................................................................................99
  Impact of intervention................................................................................................................100
Discussion.....................................................................................................................................108

Chapter 4  Epidemiology of reinfection with gonorrhoea..........................................................112
Summary........................................................................................................................................112
Introduction.....................................................................................................................................113
  Rates of reinfection with gonorrhoea and chlamydia.................................................................115
  Risk factors for reinfection..........................................................................................................116
  Reinfecion with gonorrhoea.........................................................................................................117
  Reinfecion with chlamydia.........................................................................................................118
  Comparison of gonorrhoea and chlamydia reinfection...............................................................119
  Estimation of parameters............................................................................................................120
Method............................................................................................................................................121
  Empirical data.............................................................................................................................121
  Mathematical model of reinfection.............................................................................................121
    Mathematical model 1 – simple reinfection............................................................................127
    Mathematical model 2 – including a refractory period..............................................................130
Results..........................................................................................................................................132
Discussion.....................................................................................................................................141
Limitations of method....................................................................................................................141
Chapter 5  Evolution of gonorrhoea and chlamydia ........................................... 145
Summary.......................................................................................................................... 145
Introduction...................................................................................................................... 146
Method ............................................................................................................................ 151
Mathematical models...................................................................................................... 154
  Model 1 - Two-strain model, including superinfection ........................................... 154
  Relation between $R_0$ and recovery rate and transmissibility.............................. 159
  Model 2 - Two strain model, including asymptomatic and symptomatic infections .......................................................................................................................... 159
Results ......................................................................................................................... 162
  Competition between strains during phases I and II............................................. 162
  Competition between strains during Phases III, IV and V.................................... 168
  Competition between strains during Phases III, IV and V.................................... 171
Discussion.................................................................................................................... 175

Chapter 6  Discussion ................................................................................................. 177
  Future directions....................................................................................................... 180
  Conclusions............................................................................................................... 181
Appendix ..................................................................................................................... 181
Antibiotics used in treatment of gonorrhoea and chlamydia.................................. 181

Bibliography............................................................................................................... 195

Acknowledgements.................................................................................................... 216
List of figures

Figure 1.1  Incidence of gonorrhoea and chlamydia in the UK and USA, 1990 – 2002 ................................................................................................................. 13

Figure 2.1  Increase in gonorrhoea and chlamydia reported to the HPA in the UK, 1994-2003 (HPA 2003b)................................................................. 45

Figure 2.2  The fraction of the combined reports of gonorrhoea and chlamydia in the UK represented by gonorrhoea.................................................. 51

Figure 2.3  Incident infections with chlamydia, gonorrhoea or both under different patterns of mixing (the infections are assumed to be independent but recovery from coinfection is faster than from a single infection).................................................... 66

Figure 2.4  Burden of disease by activity class under different mixing patterns (the number of cases contributed by each activity group is presented rather than the within group prevalence)................................................................. 67

Figure 2.5  Percentage change in prevalence of chlamydia seen under different control strategies and different patterns of mixing after 1 year..................... 68

Figure 3.1  Rates of gonorrhoea in South East London in different ethnic groups... 85

Figure 3.2  Rates of partner change calculated from reported data........................ 88

Figure 3.3  Model predictions compared with observed rates of gonorrhoea........ 102

Figure 3.4  Outcome of maximum likelihood analysis for unknown parameters.... 103

Figure 3.5  Model outputs which fit the observed data best are close to the limit of persistence .................................................................................... 104

Figure 3.6  Impact of different treatment strategies on the epidemiology of disease .... ........................................................................................................ 106

Figure 3.7  The relative impact of interventions on the incidence of disease in the population................................................................. 107
Figure 4.1  Mechanisms of reinfection ................................................................. 114
Figure 4.2  Proportion of gonorrhoea diagnosed in females................................. 123
Figure 4.3  Diagnoses of gonorrhoea at St Mary’s Hospital compared with KC60
diagnoses across London .................................................................................. 124
Figure 4.4  Flow diagram of reinfection model 1 ................................................ 125
Figure 4.5  Flow diagram of reinfection model 2 with refractory period .............. 126
Figure 4.6  Mean and median time to reinfection since first occurrence and most
recent occurrence for those who have previously been infected in each year of the
study .................................................................................................................. 135
Figure 4.7  Kaplan-Meier survival curve, showing the time to reinfection in St
Mary’s, London .................................................................................................. 136
Figure 4.8  Hazard function, showing the time to reinfection in St Mary’s, London... 137
Figure 4.9  Model 1 results, proportion of infections which are reinfections per year.. 139
Figure 4.10 Model 2 results with refractory period, proportion of infections which are
reinfections per year ......................................................................................... 140

Figure 5.1  Flow diagrams describing the categorisation of infections in two strain
models of gonorrhoea 153
Figure 5.2  Competition between strains .............................................................. 164
Figure 5.3  The equilibrium prevalence of individual infections and coinfection with
two strains ........................................................................................................ 167
Figure 5.4  Impact of treatment on resistant and susceptible strains during Phases III
and IV of an epidemic in the absence of superinfection (i.e. total cross immunity).... 170
Figure 5.5  The impact of treatment targeted at symptomatic or all infections on the
equilibrium prevalence of strains with different levels of resistance and propensities
to cause asymptomatic infections ................................................................... 172
List of tables

Table 1.1 Properties of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*…………11
Table 1.2 Different antibiotics and the susceptibility of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* demonstrated in selected studies…………………………………25
Table 1.3 Calculation of sensitivity and specificity…………………………………….28
Table 1.4 Criteria for screening for gonorrhoea and chlamydia ……………………30
Table 1.5 Costs and benefits of screening for gonorrhoea and chlamydia ………..30
Table 1.6 Symptoms and sites of infection with gonorrhoea and chlamydia …….34

Table 2.1 Summary of estimates of coinfection with gonorrhoea and chlamydia …..49
Table 2.2 Parameters required for the mathematical model of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* with estimates drawn from literature …………………57
Table 2.3 Parameter definitions used in the mathematical model of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* …………………………………………………59
Table 2.4 Activity class definitions …………………………………………………………60

Table 3.1 Mixing matrix. Probabilities of sexual partner choice, by sex and ethnicity ………………………………………………………………………………………86
Table 3.2 Reported rates of partner change and numbers of lifetime partners of 16-25 year olds in South East London……………………………………………………………87
Table 3.3 Average rates of partner change of four activity classes calculated from sexual behaviour survey …………………………………………………………………89
Table 3.4 Parameter definitions used in model ………………………………………….92
Table 3.5 Parameter combinations tested for maximum likelihood analysis…………98
Table 3.6 Differential homophily shown by both sexes and different ethnicities…105

Table 4.1 Table of parameters used in mathematical models 1 and 2 of reinfection……………………………………………………………………………………129
Table 4.2 Number of people reinfected and diagnosed at St Mary’s, London between 1995 and 2001 …………………………………………………………………………..133

Table 5.1 Table of parameters used in the mathematical models ……………………156
Table 5.2 Contact rates of hypothetical population in mathematical model………158
Table 5.3 Additional parameters for model 2, including asymptomatic infection….161

Table A.1 Treatment guidelines 1. Current recommendations for treatment of chlamydia and gonorrhoea from the UK national guidelines (CEG and Bignell 2002; CEG, Horner et al. 2002) …………………………………………………………188
Table A.2 Treatment guidelines USA. Current recommendations for treatment of chlamydia and gonorrhoea from CDC guidelines 1998 (MMWR 1989)……………190
Table A.3 Structure of antibiotics (http://www.medscape.com.) …………………..193
Chapter 1  Introduction

Summary

This chapter provides a brief introduction to the epidemiology of gonorrhoea and chlamydia in the developed world. The impact of control strategies and interventions are considered in the context of the biology and behaviour of the host and pathogen. Particular attention is drawn to the following areas which will be explored further in the thesis: coinfection with gonorrhoea and chlamydia (chapter 2), the sexual mixing patterns of host populations (chapter 3), reinfection with gonorrhoea (chapter 4) and the evolution of sexually transmitted bacteria (chapter 5). Treatment guidelines are outlined, as a reference for discussions of best treatment practice and the prevention of the evolution and spread of resistant strains. A mathematical framework for modelling sexually transmitted diseases is introduced and used in the body of the thesis to test predictions about the effect of interventions on the epidemiology of gonorrhoea and chlamydia.
Overview of gonorrhoea and chlamydia

Gonorrhoea and chlamydia are sexually transmitted infections, caused by the bacteria *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, respectively. This study will focus on resource-rich settings, such as in the UK and USA, where the prevalence of these infections among sexually active adults is low: less than 1% for gonorrhoea and up to 10% for chlamydia, (CDC 2003; HPA 2003b; Rottingen, Cameron *et al.* 2001). Both organisms are readily transmissible, but *C. trachomatis* more often causes asymptomatic infections, has a longer duration of infectiousness and is therefore able to infect a larger fraction of the population, including those with a lower rate of sexual partner change, than gonorrhoea (Brunham and Plummer 1990; Stoner, Whittington *et al.* 2000). The incidence of both infections is either stable or rising in the USA and UK, despite a variety of health care efforts. Case numbers for gonorrhoea and chlamydia, diagnosed in the UK and USA from 1990-2002 are illustrated in Figure 1.1 (MMWR 2002b; PHLS 2002, HPA 2003).

It is useful to study *N. gonorrhoeae* and *C. trachomatis* together because they share several features (summarised in Box 1.1). They are transmitted in the same way, through direct sexual contact and hence the risk behaviours associated with both infections is similar. Table 1.1 summarises the defining features of gonorrhoea and chlamydia infection.

Coinfection is correspondingly common, with approximately 20-40% of people infected with gonorrhoea also infected with chlamydia (Radcliffe, Ahmed-Jushuf *et al.* 1999) (Chapter 2, Table 2.1 summarises the estimates of the extent of coinfection). Routine cotreatment is recommended in the USA, but not in the UK, unless a patient is unlikely to return for test results or there is a high risk of coinfection (MMWR 1998; Radcliffe, Ahmed-Jushuf *et al.* 1999). Both chlamydia and gonorrhoea can be acquired repeatedly, and such repeat infections represent a significant proportion of the case load of sexually transmitted infections. Despite the similarities between chlamydia and gonorrhoea, there are important differences in the distribution of infection and the characteristics of those infected. These differences can provide information about the natural history of both pathogens.
## Table 1.1 Properties of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

<table>
<thead>
<tr>
<th></th>
<th><em>N. gonorrhoeae</em></th>
<th><em>C. trachomatis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of bacteria</strong></td>
<td>Gonococcal, aerobic, gram-negative bacteria</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complex developmental cycle</td>
</tr>
<tr>
<td><strong>Site of infection</strong></td>
<td>Grows on mucosal membranes</td>
<td>Obligate intracellular bacteria</td>
</tr>
<tr>
<td><strong>Ability to transform</strong></td>
<td>Piliated strains (P+) are able to transform by conjugation – enables gene transfer between strains – rapid evolution and spread of novel genes (e.g. drug resistance)</td>
<td>No transformation.</td>
</tr>
<tr>
<td><strong>Persistence within host</strong></td>
<td>None published</td>
<td>May have mechanisms for persistence (Dreses-Werringloer, Padubrin <em>et al.</em> 2000)</td>
</tr>
<tr>
<td><strong>Transmission probability</strong></td>
<td>Female-male transmission probability 20% after one exposure (vaginal-penile), 60-80% after 4 exposures (Hook and Handsfield 1999)</td>
<td>2/3 males with infected partner and 2/3 of females with an infected partner were also infected (Quinn, Gaydos <em>et al.</em> 1996).</td>
</tr>
<tr>
<td></td>
<td>Transmission probability high. Table 2.2</td>
<td>Transmission probability high. Table 2.2</td>
</tr>
<tr>
<td><strong>Incubation period</strong></td>
<td>Relatively short incubation time (Men; mean 8.3 days) (Sherrard 1996)</td>
<td>Incubation period not well characterised (Golden, Schillinger <em>et al.</em> 2000)</td>
</tr>
<tr>
<td></td>
<td>Onset of disease usually rapid, especially in males. Moderate symptoms</td>
<td>Onset usually gradual with mild symptoms</td>
</tr>
</tbody>
</table>
Gonorrhoea and chlamydia are a significant burden to health in the developed world. Infections with *Chlamydia trachomatis* or *Neisseria gonorrhoeae* may result in pelvic inflammatory disease (PID) and the associated sequelae of ectopic pregnancy and infertility in women and possibly infertility in men (Hook and Handsfield 1999). Together, they account for the majority of preventable infertility among women and possibly men. The economic burden is considerable, estimated to be $2013 million for chlamydia and $1051 million for gonorrhoea in the US in 1994 (*Institute of Medicine. The Hidden Epidemic: confronting sexually transmitted diseases* 1997). Despite the fact that both infections respond well to antibiotic treatment, patients may not seek or receive treatment for prolonged periods after infection, due to asymptomatic and unrecognised infections (Farley, Cohen *et al.* 2003). An increase in the proportion of gonorrhoea isolates with reduced susceptibility or resistance to antibiotics makes accurate diagnosis and effective treatment a priority (CDC 2000a; CDSC 2003; GRASP 2002).

In Western Europe (including the UK) and in the USA (MMWR 2002b; PHLS 2002; Van der Heyden, Catchpole *et al.* 2000), there was a significant decline in incidence of gonorrhoea throughout the 1980s, attributed to a decrease in risky sexual activity including an increase in the use of condoms (Bankole, Darroch *et al.* 1999). During the same period there was an increase in the incidence of pharyngeal gonorrhoea and a decrease in the incidence of rectal gonorrhoea in men who have sex with men (MSM), indicating a shift in behaviour to safer (in terms of HIV risk) sexual practices (MMWR 1984). Since the mid 1990s incidence of both gonorrhoea and chlamydia have stabilised at high levels (USA) or risen (UK). In the UK, sustained increases have been seen since 1994. Between 1996 and 2002, gonorrhoea case reports have more than doubled and chlamydia case reports have increased even more, by 139% (HPA 2003b). In the UK, a national survey of the sexually active population (16-44 yrs old, NATSAL, 2000) found that overall 2.2% of men and 1.5% of women were infected with chlamydia (Fenton, Korovessis *et al.* 2001). Chlamydia screening and changes in reporting practice may partly explain the rise in diagnoses; however the increases have continued even when there have been no significant changes in public health provision from year to year (MMWR 1997b; PHLS 2002).
Figure 1.1  Incidence of gonorrhoea and chlamydia in the UK and USA, 1990 – 2002

(CDC 2003; HPA 2003b)

1.1a

1.1b

\(^1\)Chlamydia reportable in UK from 1995 onwards
National statistics are useful for investigating large scale temporal trends, but may mask wide variation in disease burden between different population subgroups. The difference in the prevalence of infection between groups may be many-fold. Risk factors associated with infection with either gonorrhoea or chlamydia include, urban residence, young age, low socio-economic status, sex work and intravenous drug use (IVDU). Low et al showed that a disproportionate burden of disease in the UK falls upon young, non-White ethnic groups (Low, Daker-White et al. 1997). In Seattle, USA, an annual incidence of gonorrhoea among inner city, low socio-economic level black African and Afro-Caribbean adolescent girls (aged 16-18) has been found to be as high as 1 in 4 (Hook and Handsfield 1999).

The epidemiology of gonorrhoea and chlamydia differs in men and women. Women experience a higher incidence and prevalence of chlamydia infection than their male counterparts, whereas men make up a greater proportion of gonorrhoea case reports. As symptoms are more likely in men this is probably not a true reflection of the sex ratios for incidence. Amongst MSM, gonorrhoea is more common than chlamydia. (CDC 2003; HPA 2003b)

Most STIs are concentrated in urban areas (CDC 2000b; PHLS 2002), although in some circumstances, specific features of rural areas such as poverty and poor access to care may also result in significant burden of disease (Thomas, Schoenbach et al. 1996). In both the UK and USA, the incidence of gonorrhoea and chlamydia are highest among

---

**Box 1.1 Summary of clinical features of *Neisseria gonorrhoeae* and *Chlamydia trachomatis***

- Sexually transmitted bacteria, causative agents of infectious disease of the genital tract
- Infection spread by contact of mucous membranes i.e. by sexual contact
- Variety of non-specific urogenital symptoms
- Long-term complications e.g. pelvic inflammatory disease (PID), leading to infertility, ectopic pregnancy
- Curable: effective antibiotics readily available
- Asymptomatic infections occur at a high rate in women
- High level of local variability in burden of disease
- Coinfection with both organisms is common, although prevalence estimates vary considerably
- Condom use protects against transmission, but probably has greater impact in men (Fitch, Stine et al. 2002)
- *N. gonorrhoeae* and *C. trachomatis* both probably enhance HIV transmission (Rotchford, Strum et al. 2000; Rottingen, Cameron et al. 2001)
young women aged 15-19 and men aged 20-24, in urban areas (CDC 2000b; Fenton, Korovessis et al. 2001). Within a geographic area, sexually transmitted infections are highly clustered in space, with overlapping core area distributions (Law, Serre et al. 2003).

The marked heterogeneity in incidence and prevalence of disease across a population is a key feature of STI epidemiology and challenges healthcare providers to reach those most at risk. Further heterogeneity is found locally in sexual behaviour and mixing patterns, which mediate risk of infection. Understanding how biological factors, such as natural history of infection in different individuals, interact with the behaviour of individuals and groups, to determine the distribution of disease in a population is the aim of this thesis.

**Epidemiology of gonorrhoea and chlamydia**

The epidemiology of any infectious disease is ultimately controlled by the basic reproductive number ($R_0$) of the organism, which is defined as the average number of secondary cases resulting from a typical index case in a fully susceptible population (Anderson and May 1991; Hethcote and Yorke 1984). For a sexually transmitted disease the $R_0$ is determined by transmission probability during sexual contact, the rate of sexual contact of the host and duration of infection. This can be expressed in the following equation, which provides the conceptual framework for the models used in this thesis:

$$R_0 = \beta.c.D$$  \hspace{1cm} \textbf{Equation 1.1}

For gonorrhoea and chlamydia one can consider three components: \textbf{host factors}, e.g. sexual partner change rate or susceptibility; \textbf{public health interventions}, e.g. treatment strategies or screening programmes and \textbf{bacterial factors}, e.g. transmissibility, duration of infection and severity of symptoms. These are considered in terms of biology, behaviour, and their effect on the basic reproductive number ($R_0$) and consequently the epidemiology of the organism.
Host factors

Both behaviour and biology have a role in determining the risk of a person becoming infected with gonorrhoea or chlamydia. Sexual behaviour determines the probability of coming into contact and engaging in sexual acts with an infected individual. Biological factors such as host susceptibility and previous exposure to infection, modulate the probability of transmission occurring within a particular partnership.

Behaviour

The best defined measure of risk of acquiring an STI for an individual is the rate of partner change. Those with a high rate of sexual partner change are at higher risk of acquiring an STI than those with few partners. The distribution of partner change rates within a population is highly heterogeneous, with most people having few partners per unit time and a small number having many (Johnson, Mercer et al. 2001).

In addition to an individual’s actions, the behaviour of their sexual partner is an important determinant of STI risk (Ghani and Garnett 2000). Mutually monogamous partnerships represent a transmission ‘dead end’ for an STI. Conversely, partnerships in which one or other person has other partners, either concurrently or serially, represent routes for STI spread. So a monogamous person in a partnership with someone who has other partners, is at elevated risk of STI compared with a mutually monogamous pair (Gorbach, Stoner et al. 2002; Morris and Kretzschmar 1997). The characteristics of the members and the timing of a partnership i.e. the pattern of mixing within a population, will determine the sexual network structure and accordingly, the epidemiology of STIs. An important component of mixing is the degree of assortativity (like-with-like mixing). There is a tendency for humans to choose sex partners similar to themselves in some way, e.g. age, ethnicity, geographic location and possibly rate of partner change (Aral 2000; Garnett and Anderson 1993a; Johnson 1994; Laumann, Gagnon et al. 1994). In recent years, STI research has focused increasingly on population level or network measures of risk rather than simply on individuals (Aral 1999; Ghani and Garnett 2000; Morris 1997).

Besides direct behavioural factors, many other characteristics of people and populations play a role in determining the distribution of gonorrhoea and chlamydia, for example, age, geographical location (urban vs. rural), socioeconomic status and ethnic group (Aral 2002a; Aral, Hughes et al. 1999; Johnson, Mercer et al. 2001; Low, Sterne et al. 2001; Radcliffe, Ahmad et al. 2001). All these interact in complex ways to determine
the pattern of sexual partnerships between infected and susceptible individuals, which ultimately determines the epidemiology of the disease.

**Sexual behaviour**

Opportunities for the transmission of gonorrhoea occur during sexual contact, so to understand the epidemiology of the bacteria accurate measurement of sexual behaviour of the human host is essential. Sexual behaviour is highly variable both between individuals or populations and over the course of an individual’s lifetime. An important risk factor for an individual is their rate of sexual partner change, which is a measure of their exposure to potential infection. Early mathematical modelling work (Hethcote and Yorke 1984) suggested that gonorrhoea could only persist if there was a “core group” of people with very high rates of partner change, which maintained infection within the population. This core group concept has remained a powerful influence in understanding sexually transmitted infections. A distinction can be drawn between those individuals who are at risk of acquiring disease from their partner and those who are likely to transmit infection further to additional partners (Ghani and Garnett 2000).

**Behaviour during infection**

Behaviour whilst infectious also affects the basic reproductive number \( R_0 \) of the infection. If all infected individuals ceased sexual activity until fully recovered, the transmission chain would be broken. However, even if a patient becomes symptomatic, there is a time lag between infection and symptom onset. Many patients never become symptomatic and only realise they are infected through partner notification or screening. Clinical guidelines recommend ceasing sexual activity for 7 days after receiving treatment, although evidence suggests that compliance with this is poor. Patients are more likely to notify regular partners and ensure that they obtain treatment than casual partners (Golden, Whittington *et al.* 1999; Golden, Whittington *et al.* 2001; van de Laar, Termorshuizen *et al.* 1997).

**Treatment seeking behaviour and condom use**

The likelihood of an individual seeking treatment and the speed of their doing so will be influenced by various factors including ability to recognise symptoms and degree of symptoms, perception of risk from partner(s), availability of treatment facilities and whether a partner or health provider informs them of potential infection.

A recent meta-analysis of studies of condom use indicated that transmission of gonorrhoea was reduced by using condoms, especially to men, but results for women
were equivocal (Fitch 2001; Fitch, Stine et al. 2002). Studies have shown consistent condom use to be protective against gonorrhoea, chlamydia, genital ulcer disease, bacterial vaginosis (BV) and pelvic inflammatory disease (PID) (Baeten, Nyange et al. 2001).

One of the difficulties in accounting for behaviour in predicting the future course of disease or understanding historical trends is the fluid nature of human behaviour over time. In a longitudinal study in London of female behaviour, significant changes were noted in consistent condom use, which increased from 3.6% in 1982 to 20.7% in 1992. There was also a decrease in the number of sex partners in the previous year reported and a decrease in incidence of gonorrhoea, chlamydia and trichomoniasis by approximately 60% (Evans, McCormack et al. 1995).

**Mixing patterns and the sexual network**

The sexual behaviour of an individual does not provide a full measure of their risk of acquiring infection. Recent work on sexual partner networks has illustrated that an individual’s position within the sexual partner network, especially the behaviour of their nearest neighbours, has a significant impact on disease risk (Ghani and Garnett 2000). The most obvious example is that of a monogamous woman whose husband visits female sex workers. Her partnership with a high activity individual places her at increased risk of infection, despite her own low risk behaviour (Rothenberg 2001).

Partner choice is a complex process combining current situation (single, married, co-habiting etc.), desired numbers of partners, availability of, and ability to obtain those partners, as well as social factors such as stigmatisation or approval of different sexual behaviours. From an epidemiological point of view it is necessary to go beyond considerations of individual risk, to group effects such as mixing patterns within populations, as these can also be shown to have a crucial role to play in determining the population level dynamics of disease (Aral, Holmes et al. 1996; Low, Sterne et al. 2001).

Mixing patterns within a population can have a dramatic influence on the incidence and prevalence of disease (Aral, Garnett et al. 2000). Mixing patterns between the highest activity group and the rest of the population will affect the overall prevalence of disease in the population. Garnett et al suggest that mixing between people of different activities is near random, (Garnett, Hughes et al. 1996), but other studies demonstrated a preference for assortative mixing, where high activity individuals report partnerships
with other people with higher numbers of partnerships, i.e. slightly assortative mixing (Renton, Whitaker et al. 1995).

There is a general tendency for respondents to underestimate the activity of their partners and for men to report more partners than women (Johnson 1994). Those with a high turnover of partners are less able to make accurate estimates of their numbers of sexual partners than those with few partners. In the National Survey of Sexual Attitudes and Lifestyles (NATSAL 1990 and 2000) (Fenton, Korovessis et al. 2001; Johnson, Mercer et al. 2001; Johnson 1994), those who report having more partners are more likely to report that their partners also have multiple partners, i.e. most people assume that their partner’s behaviour is similar to their own. To what extent this reflects actual mixing patterns or the perceptions of individuals are not entirely clear.

The discordance between reporting by males and females may be due to social factors which may encourage men to overestimate and women to underestimate their sexual activity (Johnson 1994). Another factor may be under-representation of female sex workers (FSW) in probability samples. FSW may have a very high number of sexual partners which may reduce the apparent discrepancy in reported behaviour. Most of the discrepancy occurs in the tail of the distribution, among those with higher numbers of sexual partners, which lends support to the hypothesis that FSW or a few very high activity women contribute disproportionally to the number of partnerships reported by females, who are not captured in random sample surveys (Morris 1993).

**Biology of host infection**

**Coinfection**

Patients with STIs such as chlamydia or gonorrhoea, are at higher risk of contracting other sexually transmitted infections, e.g. syphilis, herpes simplex virus (HSV) or human immunodeficiency virus (HIV). Transmission of additional pathogens may occur at the same time as initial infection from a coinfected partner or during subsequent contacts with the same or different partners. The biology of coinfection is very poorly described in most cases. For example, infection could result in increased risk for further infections, e.g. if the host is more susceptible through inflammation. There is good evidence to suggest that gonorrhoea is a cofactor for acquisition and transmission of HIV, via increased susceptibility and increased shedding of virus (Rottingen, Cameron et al. 2001). However for other organisms the interactions are less well described.
Coinfection of cases of gonorrhoea with chlamydia is particularly common. There have been significant improvements in the sensitivity of diagnostic tests for chlamydia using nucleic acid amplification in recent years, so earlier studies tend to underestimate the incidence and transmission of infection, especially in men. A recent study in a Glasgow GUM clinic suggests that up to 30% of heterosexual men and 50% of women infected with gonorrhoea are also infected with chlamydia (Hijazi, Thow et al. 2002). Other studies have shown considerable variation, dependent on the population tested, diagnostic test used and clinic location. These are summarised in Chapter 2, Table 2.1.

Most cephalosporins, spectinomycin and quinolones used for treating gonorrhoea are not active against chlamydia. In the UK, testing for chlamydia is recommended before cotreatment commences unless the patient is unlikely to return for test results or reinfection rates are high, in which case treatment should be administered. In practice however, most patients receive cotreatment for chlamydia when they are diagnosed with gonorrhoea (Personal communication, H. Ward). In the USA, cotreatment with doxycycline has been routine for 10 years and is believed to have reduced the prevalence of chlamydia (MMWR 1998). Coinfection with gonorrhoea may also cause reactivation of persistent chlamydia infection (Batteiger, Fraiz et al. 1989). Whether reactivated chlamydial infections are more transmissible than asymptomatic cases is not well understood, although no evidence was found that transmission of either infection was different if coinfection was present (Lin, Donegan et al. 1998).

Several studies have investigated the characteristics of patients with chlamydia and/or gonorrhoea and found that there is not a simple relationship. A higher fraction of those infected with gonorrhoea are also infected with chlamydia than the converse although there are important differences in the rate of coinfection by gender, age and sexual orientation. Simplistically, those infected with both pathogens have the highest mean rates of partner change, those with gonorrhoea the next highest and those with chlamydia the lowest but sexual activity is not a perfect predictor of infection due to the effects of chance and differences in treatment outcomes (Stoner, Whittington et al. 2000). Stoner et al. also found more complex relations between the infection networks in the study; with those in the gonococcal network more likely to report having used crack cocaine, sexual assault and incarceration than those in the chlamydial network i.e. the gonorrhoea network members occupy a more marginalised status in society. Men with gonorrhoea and chlamydia report higher rates of partner change than women, which may reflect the greater susceptibility of women to infections with either organism.
or reporting biases (Zimmerman, Potterat et al. 1990). Other infections such as HIV, bacterial vaginosis, syphilis are associated with gonorrhoea and chlamydia infection to some extent.

The presence of gonorrhoea infection is a marker of risk behaviour which increases the risk of HIV infection (Pinkerton 2001; Wardroper and Pattman 1995). Gonorrhoea infection as a proxy for HIV risk should be used cautiously, however, since the networks of these infections may be quite distinct and vary over time and place.

**Reinfection**

Repeated attendance at a clinic with gonorrhoea or chlamydia is common and may occur via transmission of infection from an existing or new partner or treatment failure, due to drug resistance or persistent infection. Due to the significant proportion of asymptomatic and untreated infections, reinfection from existing partners is likely. The risk of reinfection is also modified by behavioural factors which can increase (continuing high risk behaviour or sex with a high risk partner) or reduce (by adopting safer sexual practices or abstaining) risk following infection. There may be gender-specific differences in behaviour following infection with an STI. A French investigation found that women showed a statistically significant change in their behaviour following STI infection to adopt preventative behaviours, but men did not (Warszawski and Meyer 2002).

A study of reinfection in adolescents showed that almost half of partners uninfected at baseline were infected by 7 months follow up and 60% of men and 73% of women infected initially were estimated to be reinfected within 7 months (Orr, Johnston et al. 2001). Approximately 18% of individuals, who had repeat infections, contributed 30% of total cases of gonorrhoea, between 1976-9 in a study in Sheffield (Kinghorn, Pryce et al. 1982). More recently in the USA, 24% of index cases were reinfected with either chlamydia or gonorrhoea within 18 months (Thomas, Weiner et al. 2000). In a recent study over nearly 5 years, the median time to reinfection was 1.0 year which suggests that behavioural risk persists for a considerable time after initial infection and these patients may represent a target for screening even several years after initial infection (Mehta, Erbelding et al. 2003).

Incidence of reinfection may provide information about sexual mixing patterns, phase of the epidemic and behaviour occurring in the population most at risk. Individuals who have previously been treated but then become infected again are prime targets for health
Katherine Turner
Chapter 1 - Introduction

education messages. A recent attempt to quantify the effective reproductive number for those with repeat infections showed that is higher than 1, but is less than 1 in ‘non-repeaters’. The difference was because of a higher average rate of partner change in those individuals with repeated infections. Hence those with repeat infections maintain the disease, constituting a population where interventions could be effectively targeted (Jolly and Wylie 2002).

**Susceptibility and acquired immunity**

An individual may be repeatedly infected with gonorrhoea or chlamydia (Fortenberry, Brizendine *et al.* 1999; Mehta, Erbelding *et al.* 2003; Orr, Johnston *et al.* 2001; Whittington, Kent *et al.* 2001). There is debate over whether strain-specific immunity to gonorrhoea can be acquired. The microbiological evidence for immunity is equivocal. One longitudinal study found no evidence of strain specific immunity, in fact, reinfection with the same strain was slightly more common than would be expected by chance, but this is confounded by the potential for repeated exposure to the same strain from an untreated partner (Fox, Thomas *et al.* 1999). The poor immune response to infection is likely due to the high variability of surface antigens expressed during infection. One study showed that those that did resist infection had a greater immune response than those who did not (Schmidt, Schneider *et al.* 2001). There is some evidence that serious sequelae are less likely with repeat infections of the same strain, compared with different strains of gonorrhoea (Buchanan, Eschenbach *et al.* 1980). Acquired resistance to chlamydia has been demonstrated (Loomis and Starnbach 2002). Chapter 4 on reinfection reviews the evidence for of acquired immunity to gonorrhoea and chlamydia.

Another line of evidence for some level of acquired immunity to gonorrhoea and chlamydia is based on estimates of the basic reproductive number using mathematical modelling approaches, which gave low estimates of the reproductive number (Brunham, Nagelkerke *et al.* 1994). The authors conclude that some form of acquired immunity occurs with both chlamydia and gonorrhoea (Brunham, Nagelkerke *et al.* 1994), although this assumes that the underlying model captured sufficient complexity to accurately assess the reproductive number. Age-stratified disease reports show declining incidence with age, even when accounting for sexual activity, which suggests either that older women are less susceptible, or have acquired some degree of protection from previous infections (Stamm 1999). Previous infection does not provide complete protection against future infection, however and reinfection is very common especially
amongst young people, and is associated with increasing risk of the serious long-term sequelae.

There is considerable between-host variability in susceptibility to infection with gonorrhoea or chlamydia. During a single act of penile-vaginal intercourse, women are twice as likely to become infected with gonorrhoea as men (a transmission probability of 0.5 - 0.7 compared with 0.2 - 0.3) (Wiesner and Thompson 1980). The transmission probability of chlamydia per act is not well defined. One recent study using PCR tests found that roughly two thirds of the partners of people infected with chlamydia were also infected and there was no gender difference (Quinn, Gaydos et al. 1996). Young women are likely at greater risk of becoming infected with gonorrhoea and chlamydia than older women, because of differences in the lining of the womb (Cohen, Britigan et al. 1987). Use of the oral contraceptive pill is associated with an increased risk of gonorrhoea (Louv, Austin et al. 1989) and chlamydia (Baeten, Nyange et al. 2001) apparently due to changes in vaginal flora. Previous infection with gonorrhoea or chlamydia is a risk factor for PID and associated sequelae, although the mechanism for this is not clearly established.

**Intervention strategies**

**Treatment**

Highly effective therapy is available for gonorrhoea and chlamydia. Control efforts in a developed setting centre on speeding up treatment rates, through education to better recognise symptoms, screening to identify asymptomatic cases and partner notification or contact tracing to identify individuals who have been exposed to infection. Syndromic management, where treatment is prescribed on the basis of signs and symptoms without waiting for test results is more appropriate for a developing world setting e.g. Peru, where facilities for testing are not easily accessible (Adams, Garcia et al. 2003).

Current treatment guidelines for UK and USA are summarised in the Appendix in Table A.1 and Table A.2. The main difference concerns cotreatment of gonorrhoea infections for chlamydia, which is recommended in the USA, but not UK. Although it is not clear how different clinical practice is in reality on the basis of these recommendations. Until the mid twentieth century there was no effective treatment for gonorrhoea, when highly effective therapies became available: sulfonamides (1936) and penicillin (1943). Since the introduction of penicillin, several classes of antibiotics have been used successfully
Neisseria gonorrhoeae has evolved resistance to most of these classes of drugs (Table 1.2), resulting in changes to treatment guidelines in 1989, when penicillin was no longer recommended as first line therapy (MMWR 1989; Radcliffe, Ahmed-Jushuf et al. 1999). Guidelines were changed again in 2003 in the UK and ciprofloxacin is no longer recommended as first line therapy as the proportion of resistant isolates has risen above the 5% level (CDSC 2003). Single-dose oral therapy is the preferred mode of treatment for STIs, since compliance is better than with multiple dose regimes.
Table 1.2  Different antibiotics and the susceptibility of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* demonstrated in selected studies

Unless Chlamydia trachomatis resistance is stated, the bacteria referred to Neisseria gonorrhoeae

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MICs (µg/mL)</th>
<th>Comments</th>
<th>(Sparling 1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin (Pc)</td>
<td></td>
<td>1940s penicillin was effective therapy for gonorrhoea</td>
<td>(Sparling 1999)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Now penicillin resistance is a problem globally</td>
<td>WHO report.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="http://www.who.int/HIV_AIDS/figures/global_report.html">http://www.who.int/HIV_AIDS/figures/global_report.html</a></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Independent chromosomal mutations in <em>penA, mtr</em> and <em>penB</em>. Low level</td>
<td>(Sparling 1999)</td>
</tr>
<tr>
<td></td>
<td>2-4</td>
<td>1985 increased chromosomally mediated resistance, mechanism not known.</td>
<td>(Faruki 1985)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>First documented in 1976. Also resistant to ampicillin, cephaloridine</td>
<td>(Phillips 1976)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and spectinomycin. Plasmid-mediated (PPNG) resistance 5.3 or 7.2 kb</td>
<td>(Ashford 1976)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>plasmid (Pc&lt;sup&gt;4&lt;/sup&gt;). May have ‘jumped’ from <em>H. ducreyi</em></td>
<td>(Brunton and Bennett 1981)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPNG prevalence remains high in The Netherlands, 1995 and surveillance</td>
<td>(Anderson,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>data suggest that sensitivity to other antimicrobials is decreasing amongst</td>
<td>Albritton <em>et al</em>. 1984)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPNG strains</td>
<td>(van de Laar,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>van Duynhoven <em>et al</em>. 1997)</td>
</tr>
<tr>
<td>Tetracycline (Tc)</td>
<td>2 - 4</td>
<td>Low level resistance from chromosomal mutations in <em>mtr, penB</em> and <em>tet</em></td>
<td>(Sparling 1999)</td>
</tr>
<tr>
<td></td>
<td>16 to 64</td>
<td>High level resistance. 38 kb (25.2 MDa) conjugative plasmid-derived</td>
<td>(Morse, Johnson <em>et al</em>. 1986)</td>
</tr>
<tr>
<td></td>
<td>≥64</td>
<td>from 36 kb (24.5 MDa) conjugal plasmid plus <em>tetM</em> determinant. <em>TetM</em></td>
<td>(Sparling 1999)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>encodes a protein that protects ribosomes from Tc. Conjugation can still</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>occur efficiently, thus providing a pathway for the transfer of the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>plasmid into other gonococci</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High level tetracycline resistant <em>N. gonorrhoeae</em> (TRNG) first reported in</td>
<td>(Ison, Bindayna <em>et al</em>. 1988; Reimann,</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>MICs (µg/mL)</td>
<td>Comments</td>
<td>References</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Antibiotic</td>
<td></td>
<td></td>
<td>(Sparling 1999)</td>
</tr>
</tbody>
</table>
| Spectinomycin    |             | 1985, now spreading worldwide  
| (Spc)            |             | High level resistance can occur via chromosomal mutation of spc locus, which alters ribosomal target for spc.                                                                                                 | (Sparling 1999)                                                                                                                                 |
|                  |             | Spc resistance seen in Korea in 1987                                                                                                                                                                         | (Boslego, Tramont et al. 1987)                                                                                                                                 |
| Streptomycin     |             | High level resistance common. Str locus near to spc, also linked to resistance genes for tetracycline (tet), rifampin (rif) and others. Not used for gonorrhoea treatment. | (Sparling 1999)                                                                                                                                 |
| (Str)            |             | Resistance increasing in certain areas, especially to ciprofloxacin.                                                                                                                                     | WHO http://www.who.int/HIV_AIDS/figures/global_report.html                                                                                   |
| Fluoroquinolones |             | Resistance to fluoroquinolones endemic in many Asian countries and Western Pacific region.                                                                                                                                 | WHO http://www.who.int/HIV_AIDS/figures/global_report.html                                                                                   |
| Ciprofloxacin    |             | Increased incidence reported in Scotland, 1991-99  
Increased incidence in Newcastle-upon-Tyne, UK 1995-7  
Resistance reported in Hawaii, 1999                                                                                                   | (Forsyth, Moyes et al. 2000)                                                                                                                |
| (Fq)             |             |                                                                                                                                                                                                          | (Tayal, Sankar et al. 1999)                                                                                                                |
|                  | >4          | Chlamydia: clinically significant multidrug resistance to doxycycline, azithromycin and ofloxacin reported in 2000                                                                                          | (Somani, Bhullar et al. 2000)                                                                                                                |
| Azithromycin     |             | Decreased susceptibility reported in Missouri, 1999                                                                                                                                                        | (MMWR 2000)                                                                                                                              |
| Multidrug        | >4          |                                                                                                                                                                                                          | (MMWR 2000)                                                                                                                              |
Providing appropriate, accessible care is an issue in STI management. A recent survey in UK showed that a significant proportion of patients attending genitourinary (GU) clinics have already attended their general practice (GP) and that attending a GP delays getting appropriate treatment by 2 days on average compared with those who attend the GU clinic straightaway (Cassell, Brook et al. 2003). The study does not take account of those who are seen, treated and not referred on from a GP, but there remain a significant proportion of patients who could potentially be treated earlier. In the UK the policy is to shift a larger proportion of STI care into the primary care setting, therefore it is important to ensure that treatment, counselling and partner tracing provision is adequate and that those who never attend a GP for STI care are not “lost” due to difficulties accessing a GP (Cassell, Brook et al. 2003). In the USA STI care is split between public STI clinics and private physicians. In a recent study of STI care, Golden et al found that private providers did inform patients to notify partners, but that few knew whether partners did in fact, seek treatment or not (Golden, 2001).

**Screening and diagnostic tests**

In the late twentieth century rapid advances in genetic techniques enabled new diagnostic tests to be developed with increased sensitivity and acceptability of testing for both gonorrhoea and chlamydia, e.g. urine PCR tests or other gene detection tests, which makes screening a viable option (Tapsall, Limnios et al. 1998). These improvements have made screening more cost-effective and accurate diagnosis and treatment easier.

Changes in screening practice or sensitivity of diagnostic tests may alter the apparent incidence (increased screening may increase diagnoses), whilst the real incidence remains unchanged. Incidence measures the number of new cases of an infection over a given period of time (usually a year). Reported diagnoses in clinics underestimate the numbers of cases of disease within a population, since some people with disease will not attend a clinic and not all infections are reported. Prevalence measures the number of people infected in a population at a given time point.

The calculation of specificity, sensitivity and positive predictive value (PPV) of a hypothetical diagnostic test are defined below in Table 1.3. (Adapted from Modern Epidemiology (Weiss 1998))
Table 1.3 Calculation of sensitivity and specificity

(Adapted from Modern Epidemiology (Weiss 1998))

<table>
<thead>
<tr>
<th>General criterion</th>
<th>reference</th>
<th>Test criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Negative</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Sensitivity (Sens) = $a/(a+b)$
Proportion of those with the condition who test positive

Specificity (Spec) = $d/(c+d)$
Proportion of those without the condition who test negative

Positive predictive value (PPV) = $a/(a+c)$
Proportion of those who test positive that have the disease, assuming $(a+b)/n$ is representative of the true prevalence (Prev) in the population.

Estimate of PPV, using Bayes theorem:

$$PPV = \frac{\text{Sens} \times \text{Prev}}{\left(\text{Sens} \times \text{Prev}\right) + \left(1-\text{Spec}\right) \times (1-\text{Prev})}$$

If screening is done in a low prevalence setting, a non-trivial number of false positive tests are expected. For example, Zenilman used Bayes’ theorem to estimate the positive predictive value; at a prevalence of 0.5%, nearly 20% of positive tests would be false, even if the test has a 99% sensitivity and 95% specificity (Zenilman, Miller et al. 2003).

The possibility of false positives therefore needs to be made clear to those undergoing screening.

Screening programmes require satisfactory, cheap diagnostic tests to be available which produce results rapidly. The disease being tested for must have a long latent period or asymptomatic infection and early detection should improve health outcomes. A full list of the criteria for adopting a screening program and applicability to chlamydia and gonorrhoea are illustrated in Table 1.4, based on Wilson and Jungner 1968, WHO criteria. The costs and benefits of screening programmes are summarised in Table 1.5.

Chlamydia fits the criteria for screening somewhat better than gonorrhoea although it may be worth testing patients for gonorrhoea who test positive for chlamydia, especially if they fall into higher risk groups (Harindra, Tobin et al. 2002). Alternatively, targeted
screening of particular risk groups may be appropriate. Various studies of chlamydia screening programs have demonstrated their cost-effectiveness (Yeh 2003). A pilot study in Portsmouth UK detected an overall prevalence of chlamydia of 9.6%, with significantly higher levels in women attending for termination of pregnancy or antenatal care, and women and men with GU symptoms or attending GU clinics (Gleave 2002; Pimenta, Catchpole et al. 2003; Underhill, Hewitt et al. 2003). In the Pacific Northwest USA, a screening program was implemented in women attending family planning clinics (1988) and in STD clinics (1993) to test for *Chlamydia trachomatis*. The prevalence of chlamydia was reduced from 10-12% in late 1980s to 4-5% in 1995 (MMWR 1997b).

If screening programmes are successful at reducing the prevalence, careful planning and resource allocation is required to determine if or when screening could be relaxed, since incidence could rise rapidly in new cohorts of adolescents entering the sexually active population if screening is stopped. Other methods of maintaining a decline in incidence are needed, for example testing during six monthly blood pressure checks to get oral contraceptive pill prescriptions or school-based education programmes. One advantage of screening programmes is that they provide useful data on prevalence of infection in the screened population.
### Table 1.4  Criteria for screening for gonorrhoea and chlamydia

<table>
<thead>
<tr>
<th></th>
<th>Chlamydia</th>
<th>Gonorrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comment</strong></td>
<td>Important health problem, &gt;5% prevalence found in pilot studies</td>
<td>&lt;1% overall prevalence</td>
</tr>
<tr>
<td><strong>Disease status</strong></td>
<td>Well recognized pre-clinical stage, asymptomatic infection common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long period between first signs and overt disease</td>
<td>Yes, main morbidity due to PID, infertility can occur many years after initial infection</td>
</tr>
<tr>
<td><strong>Diagnostic test</strong></td>
<td>Valid (sensitive and specific)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Simple and cheap</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Safe and acceptable</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Reliable</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Diagnosis and treatment</strong></td>
<td>Facilities are adequate, effective, acceptable and safe treatment is available</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Cost effective, sustainable</td>
<td>Yes, No</td>
</tr>
</tbody>
</table>

### Table 1.5  Costs and benefits of screening for gonorrhoea and chlamydia

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allows early identification and treatment of infection</td>
<td>Takes time and resources to organise</td>
</tr>
<tr>
<td>Provides basis for national surveillance schemes – identify changes in incidence and prevalence</td>
<td>People at most risk are often least likely to attend screening clinics (e.g. young people, low socio-economic status, black African/Caribbean (gonorrhoea))</td>
</tr>
<tr>
<td>Identifies asymptomatic infections early, prevents further spread</td>
<td>May not identify them early enough to have a significant impact</td>
</tr>
<tr>
<td>Provides forum for health education</td>
<td>Psychological ‘cost’ of false positives, especially when screening in low prevalence populations.</td>
</tr>
</tbody>
</table>
Partner notification (contact tracing) and partner delivered therapy

An important part of the control of STIs is through contact tracing or partner notification either by the patient or clinic staff. Approximately two thirds of untreated partners of gonorrhoea or chlamydia patients are infected (Lin, Donegan et al. 1998). Therefore, partners of those infected represent a high risk population. Treating partners as quickly as possible benefits the individual who may not have known they were infected, their partner since reinfection is prevented and the population in general. In this way, part of the transmission chain is broken, decreasing the size of that particular network component.

Partner notification by clinic staff is time consuming and resource intensive (NIH report) so recent efforts have been undertaken to redesign partner notification systems in the USA (Golden 2003; Schillinger, Kissinger et al. 2003). Golden et al describe a randomised controlled trial of patient delivered therapy (PDT), where partners are not only notified by the index patient that they may be infected, but also receive a treatment pack for immediate, presumptive therapy (Golden 2003; Golden, Whittington et al. 2001). Schillinger and colleagues undertook a multicentre-randomised controlled trial of partner delivered azithromycin therapy to prevent reinfection with Chlamydia trachomatis in a variety of settings (Schillinger, Kissinger et al. 2003). Whilst they found no statistically significant improvement in the incidence of reinfection with chlamydia, Golden and colleagues found that overall, reinfection with chlamydia and gonorrhoea was reduced significantly, with the greatest reduction in reinfection with gonorrhoea. This study also provides tentative evidence for persistent chlamydial infection, since several patients (6%) who reported no sexual activity between interviews were found to be infected with chlamydia. Most patients appear willing to contact partners and chlamydia patients were more successful in contacting all untreated partners than were gonorrhoea patients (Golden 2003; Golden, Whittington et al. 2001).
**Bacterial factors**

The properties of sexually transmitted bacteria which determine the basic reproductive number and epidemiology of the diseases they cause are primarily biological, i.e. transmissibility, duration of infectiousness, pathology and symptoms. Bacteria cannot be said to have behaviour in the same way as human sexual behaviour, but as will be shown, they are able to evolve rapidly and develop new ways of surviving in a changing, competitive environment.

**Pathogen biology**

The bacterial characteristics which affect the basic reproductive number ($R_0$) and consequently the rate of growth of an epidemic and endemic prevalence are transmissibility and duration of infection. Genetic mechanisms, population dynamics and behaviour (of the host and of the bacteria) interact to determine the course of disease in the individual and in the population as a whole. Clinical presentation of the disease may affect duration of infection or transmission through differences in seeking treatment or host behaviour. Drug resistant infections may result in extended duration of infectiousness due to treatment failure or suboptimal treatment.

**Clinical properties of bacteria**

There is considerable heterogeneity in the clinical presentation of both gonorrhoea and chlamydia, ranging from no clinical signs (asymptomatic) to severe symptoms (Table 1.6) (Hook and Handsfield 1999; Stamm 1999). Asymptomatic infections are more common for chlamydia than for gonorrhoea: up to 50% of men with chlamydia and up to 75% - 80% of women may be asymptomatic (Radcliffe, Ahmed-Jushuf et al. 1999). Clinical symptoms of the disease will influence the selective pressures acting on the organism. For example, intensive case finding, contact tracing and pharmacotherapy will select for drug resistance strains, whereas syndromic management of cases will select for less symptomatic infections.

The influence of treatment strategies on the evolutionary pressures on the organism is investigated further in Chapter 5. The differences in symptom severity are partly due to differences in host immune response and partly due to differences in bacterial strains. Other phenotypic differences such as the ability to survive in different microhabitats will also play a role in the distribution of disease within a population.
Multiple strains of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

A variety of strains of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* can be distinguished. *N. gonorrhoeae* has been typed in various ways according to available technology. Serotyping, auxotyping and drug susceptibility testing methods were the earliest ways of discriminating different strains, with genetic tests coming into use more recently. Chlamydia variants are discriminated on the basis of serovar type and genotype, and these may be related to disease symptoms in women (Geisler, Suchland et al. 2003) or epidemiological characteristics of patients (Geisler, Whittington et al. 2002). *N. gonorrhoeae* strains have been associated with particular specialisations or phenotypic effects e.g. AHU auxotype is associated with asymptomatic infection (Handsfield, Knapp et al. 1980; Whittington and Holmes 2000).

Infection with multiple strains of *Neisseria gonorrhoeae* can also occur. *Neisseria gonorrhoea* is constitutively able to recombine and this may represent an important route for the transmission of novel genetic material (Hook and Handsfield 1999; Spratt, Bowler et al. 1992). For an obligate human parasite like gonorrhoea recombination with multiple genotypes requires coinfection. It is not known how frequently individuals become infected with multiple strains, but recent typing studies have demonstrated the existence of coinfection in a few samples (Martin and Ison 2003). The effect of existing infection on the risk of acquiring additional strains is not known.
### Table 1.6 Symptoms and sites of infection with gonorrhoea and chlamydia

<table>
<thead>
<tr>
<th>Gonorrhoea (Hook and Handsfield 1999)</th>
<th>Chlamydia (Schachter 1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative bacteria</strong></td>
<td></td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td><em>Chlamydia trachomatis</em></td>
</tr>
<tr>
<td><strong>Site of infection</strong></td>
<td></td>
</tr>
<tr>
<td>Urethra</td>
<td>Cervix</td>
</tr>
<tr>
<td>Endocervix</td>
<td>Endocervicitis</td>
</tr>
<tr>
<td>Rectum</td>
<td>Cervicitis</td>
</tr>
<tr>
<td>Pharynx</td>
<td>Pharyngitis</td>
</tr>
<tr>
<td></td>
<td>Bartholinitis</td>
</tr>
<tr>
<td></td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td><strong>Asymptomatic infection</strong></td>
<td></td>
</tr>
<tr>
<td>Infection is asymptomatic in 10% of men and up to 50% of women (CEG and Bignell 2002)</td>
<td>Infection is asymptomatic in up to 50% of men and up to 80% of women (CEG, Horner et al. 2002)</td>
</tr>
<tr>
<td><strong>Syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>Urethritis</td>
<td>Nongonococcal urethritis</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>Endocervicitis,</td>
</tr>
<tr>
<td>Proctitis</td>
<td>Cervicitis</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Cervical metaplasia</td>
</tr>
<tr>
<td>Bartholinitis</td>
<td>Bartholinitis</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Inclusion conjunctivitis</td>
</tr>
<tr>
<td><strong>Local complications</strong></td>
<td></td>
</tr>
<tr>
<td>Salpingitis</td>
<td>Salpingitis</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>Epididymitis</td>
</tr>
<tr>
<td>Bartholin abscess</td>
<td>Bartholinitis</td>
</tr>
<tr>
<td>Lymphangitis</td>
<td></td>
</tr>
<tr>
<td>Penile oedema</td>
<td></td>
</tr>
<tr>
<td>Periurethral abscess/Prostatitis</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic disease</strong></td>
<td></td>
</tr>
<tr>
<td>Disseminated gonococcal infection (DGI)</td>
<td></td>
</tr>
<tr>
<td><strong>Sequela</strong></td>
<td></td>
</tr>
<tr>
<td>Pelvic inflammatory disease (PID), infertility and ectopic pregnancy</td>
<td>PID, infertility and ectopic pregnancy</td>
</tr>
<tr>
<td></td>
<td>Reactive arthritis (previously known as Reiter’s disease)</td>
</tr>
</tbody>
</table>
Transmissibility

*Neisseria gonorrhoeae* and *Chlamydia trachomatis* are highly transmissible pathogens, which appear to be somewhat more easily passed from males to females than vice versa. Obtaining good contemporary estimates of the per sex act probability of transmission is difficult for ethical reasons, due to availability of effective treatment and the obligation to treat diagnosed infections. In addition, it is not known how infectivity varies with duration of infection, infecting strain, duration of sex acts, frequency of sex acts per day, symptomatic or asymptomatic infection, susceptibility of partner, infection status of partner, immunocompetence of partner, or use of condoms (Garnett, Mertz *et al.* 1999).

For gonorrhoea, estimates of transmission probability in the region of 0.5-0.8 per partnership from men to women and slightly less from women to men seem to be reasonable (Table 2.2, Hook and Handsfield 1999). The transmission probability for chlamydia per partnership is comparable to that for gonorrhoea, but perhaps slightly lower (Lin, Donegan *et al.* 1998; Lycke, Lowhagen *et al.* 1980a). There is some evidence that host susceptibility may affect transmission, so that a higher fraction of people never become infected than would be predicted by simple models of transmission probability (Schmidt, Schneider *et al.* 2001) (Garnett and Rottingen 2001).

**Duration of infection**

Duration of infection is not well characterised for either gonorrhoea or chlamydia (Golden 2003). Early studies of gonorrhoea suggest a duration of about 6 months, followed by spontaneous cure, in the absence of treatment (Hook and Handsfield 1999). Time to recovery is likely to be highly variable for both infections. Infections with both pathogens may spontaneously clear, or persist for many months, although chlamydia appears to be more persistent than gonorrhoea, especially in women. Chlamydial infections appear to take longer to clear in women compared to men and in younger women compared to older women (Golden 2003). Assuming treatment is available and is effective, the time from infection to seeking treatment for gonorrhoea is in the order of 7-10 days for men (Garnett, Mertz *et al.* 1999; Hook and Handsfield 1999). The subjective view of the patient also plays an important role in the length of time to seek treatment, which is related to complex factors such as perceived risk, exposure, recognition of symptoms and partner referral.
Asymptomatic infection

For both men and women, infections with gonorrhoea or chlamydia are often asymptomatic, which may delay or prevent treatment being sought. The WHO estimates that for gonorrhoea up to 80% of cases in women and 10% in men are asymptomatic (WHO 2001). The UK guidelines estimate that up to 50% of women and 10% of men with prevalent gonorrhoea infection are asymptomatic (CEG and Bignell 2002). It seems likely that asymptomatic or unnoticed infection will last for longer than symptomatic infection due to the delay or failure in obtaining treatment. It is not known whether asymptomatic infections are in fact less transmissible than symptomatic cases. However, asymptomatic infection may increase the relative probability of transmission, since patients with symptomatic disease may cease or reduce sexual activity or increase their use of condoms. There is some evidence to suggest however that a high proportion of symptomatic men with gonorrhoea continue sexual activity after diagnosis with an STI (Garnett, Mertz et al. 1999). This link between virulence (symptom severity) and transmission is not well established for gonorrhoea, although is biologically feasible.

If asymptomatic infections are less transmissible than symptomatic cases, then strains with increased likelihood of fewer symptoms will only evolve if there is an evolutionary benefit to doing so, e.g. longer duration of infection in the host (Bull 1994; Lipsitch and Moxon 1997). Recent studies suggest that for chlamydia, asymptomatic infection in men may have been underestimated, in part due to lack of sensitivity of diagnostic tests previously used in men (LaMontagne, Fine et al. 2003). Estimates are also sensitive to whether one considers incident or prevalent infections. If asymptomatic infections tend to last longer than symptomatic infections, then they will tend to accumulate in the population. For modelling purposes one wishes to know what proportion of new infections will become symptomatic and remain asymptomatic, which is not the same as the proportion of infections at a given time in a population that are asymptomatic.

Asymptomatic infections contribute disproportionately to the transmission of gonorrhoea and can result in serious sequelae of PID and infertility, in addition to transmission resulting in disease in partners. Sherrard and Barlow found that asymptomatic gonorrhoeal infections tend to be less susceptible to treatment and also that patients coinfected with Chlamydia trachomatis were more likely to be asymptomatic, which agreed with other findings (David, Wade et al. 1997; Sherrard and Barlow 1996).
Particular strains of gonorrhoea may be associated with asymptomatic or very mild infection e.g. the AHU auxotype (Brunham, Plummer et al. 1985; Crawford, Knapp et al. 1977). In Washington State, the prevalence of the AHU auxotype has declined steadily from 52% in 1971-74 to 0% in 1994–96. This was believed to be due to increased screening efforts, resulting in treatment of more asymptomatic infections. More recently, however between 1986-97 the CU auxotype, which is also associated with asymptomatic infection, has increased in prevalence in this region, despite an overall decline in gonorrhoea incidence of 80% (Whittington and Holmes 2000). The reasons for the changes in subtype distribution of gonorrhoea are not well understood. The CU auxotype may be more likely than other auxotypes to be misdiagnosed as non-gonococcal urethritis (NGU), which may account for part of its increase. Other possible explanations include decreased screening, decreased competition between strains or stochastic genetic drift, leading to random introduction and disappearance of subtypes if incidence falls beneath a threshold for sustained transmission (Whittington and Holmes 2000). Certain auxotypes of gonorrhoea are associated with an asymptomatic phenotype (Crawford, Knapp et al. 1977; Whittington and Holmes 2000) and other auxotypes are associated with rectal gonorrhoea (Handsfield, Knapp et al. 1980; Morse, Lysko et al. 1982), but how these relate to other characteristics such as duration of infection or transmissibility are not well understood.

**Drug resistance**

One of the biggest threats to long-term treatment and control of gonorrhoea is the ever expanding array of drug resistant strains of bacteria (Table 1.2). Since the first reports of high-level resistance to penicillin in 1976 (Phillips 1976), many Neisseria gonorrhoeae strains have now been isolated, which show reduced susceptibility to antimicrobial agents. In general Chlamydia trachomatis does not exhibit reduced sensitivity to antibiotics, but recent studies have demonstrated clinically significant resistance (Somani, Bhullar et al. 2000). Nevertheless, at present resistance in chlamydia is less of a problem than in gonorrhoea. If chlamydial cases are found and treated more often, as screening programmes continue to expand and there is routine co-treatment, there will be increasing selective pressure for the development of drug resistance. There is evidence to suggest that treatment with antibiotics can lead to persistent of chlamydial infection, which may test culture negative, but be positive by PCR (Dreses-Werringloer, Padubrin et al. 2000). However the clinical significance of persistent infection is not known.
Current guidelines recommend that 95% of those treated should be cured, so prevalence of resistance above 5% results in changes of treatment practice. US gonorrhea treatment guidelines were changed in 1989 in response to increasing penicillin resistance. Recent reports in UK show levels of ciprofloxacin resistance have increased from 2.1% in 2000 to 3.1% in 2001 and again to 9.8% in 2002, with a higher level of resistance outside London compared with London (GRASP 2002; GRASP 2003; Ison, Martin et al. 2001). Older patients were more likely to be infected with resistant isolates (GRASP 2002). In some parts of the country, including Yorkshire and Humberside, prevalence of ciprofloxacin resistance has reached close to 20% (CDSC 2003). In response to the rapid rises to above 5% across most of the country the guidelines have been recently updated in the UK and ciprofloxacin is no longer recommended as first line therapy (Fenton, Rogers et al. 2000; GRASP 2003). Similarly in California, USA, the prevalence of ciprofloxacin resistant strains has increased from 1% in 2000 to 5% in 2001 (CDC 2002a). These rapid rises in ciprofloxacin resistance have led to recommending other agents (e.g. ceftriaxone, penicillin, where local prevalence of resistance is low, or spectinomycin) as first line therapy. Although it was appreciated early on in the history of antimicrobials that resistance could emerge quickly, there was little response to these concerns in terms of patterns of prescribing antimicrobials and their consumption which has continued to rise (Austin, Kristinsson et al. 1999).

*Neisseria gonorrhoeae* demonstrates a variety of mechanisms of resistance or decreased susceptibility to antibiotics. An understanding of the mechanisms of resistance and the mechanism of action of antibiotics is crucial in explaining the observed trends in the distribution of resistant strains of gonorrhoea (Appendix). Use of antibiotics exerts a selective pressure on the emergence of resistance at different scales, ranging from background levels of antibiotic use to specific pressure exerted by treatment of gonorrhoea, as illustrated in Table 1.2 (Austin, Kristinsson et al. 1999; Fox, del Rio et al. 2001; Fox and Knapp 1999; Fox, Knapp et al. 1997).

Various studies have assessed the changes in resistant strains of gonorrhoea in the developed world, including Europe (Forsyth, Moyes et al. 2000; Ison and Martin 1999; Kyriakis, Tzelepi et al. 1999; McCutchan, Adler et al. 1982; Nissinen, Jarvinen et al. 1997; van de Laar, van Duynhoven et al. 1997), USA(MMWR 1985; Schwarcz, Zenilman et al. 1990; Whittington and Knapp 1988), Australia (Tapsall, Limnios et al. 1998) and Japan (Tanaka, Matsumoto et al. 1995). The changes seen in the patterns of drug resistance among *N. gonorrhoeae* isolates have resulted in treatment failure and
necessitated changes in treatment recommendations e.g. penicillin was no longer recommended after 1989 (MMWR 1989). Even in areas where sexually transmitted diseases continue to decrease, e.g. Scandinavia, the proportion of resistant strains appears to be rising (Nissinen, Jarvinen et al. 1997; Van der Heyden, Catchpole et al. 2000). Recent years have seen a global increase in the total number and relative proportion of cases of gonorrhoea strains with reduced susceptibility or resistance to antibiotics (WHO 2001). Increased resistance results in economic and health costs, due to:

- Increasing use of newer, more expensive drugs (effective and cheap treatments, such as penicillin and tetracycline are no longer recommended for first line therapy in the UK (CEG and Bignell 2002; CEG, Horner et al. 2002) or USA (MMWR 1998)).
- Treatment failure, resulting in a need for repeated treatment and an increase in transmission to susceptible partners.
- Costs associated with long-term effects of chronic infection, such as PID and subsequent infertility and ectopic pregnancy.

**Why do pathogens evolve?**

There are two reasons why bacterial pathogens are forced to evolve: firstly, due to competition with related organisms for hosts or resources within a host, and secondly, due to competition with the host. Competition with other bacteria may occur across a host population or within a host. Competition between the pathogen and host may occur through direct interaction with the host immune system which acts to kill the invading organism or indirectly via changes in the host behaviour in terms of sexual activity: rate of sexual partner change, type and frequency of sex acts or treatment with antibiotics. The competitive environment for the bacteria is therefore constantly changing, each new host is immunologically distinct and the immune response and host response (e.g. behavioural change, treatment seeking) changes during the course of an infection. The fitness of a strain relative to other strains present in a host population will vary as strains become extinct or new strains evolve or migrate in.
Mathematical models of sexually transmitted infections

Mathematical models of the transmission dynamics of sexually transmitted infections may be formulated in a variety of ways. They have in common the three components of $R_0$ (Equation 1.1) i.e. a description of the pattern of sexual contacts in the population (c), transmission of infection during a sexual contact and a probability of recovery based on the expected duration of infection (Anderson and May, 1991). The two main types of modelling approaches used for STIs are compartmental models and individual-based models. Both types may be stochastic (include random effects, each realisation is different) or deterministic (all outcomes are predetermined, so each time the model is run under a particular set of conditions the outcome is the same). Compartmental models make the assumption that the population can be divided into a finite number of discrete groups (e.g. men, women, high or low activity), who behave in the same way. These models are most often deterministic. Individual based models explicitly model each individual in the population and their sexual contacts.

The particular choice of model depends on the question under consideration. Deterministic, compartmental models are the simplest to formulate and analyse. Hethcote and Yorke first used deterministic compartmental models for analysing gonorrhoea in the US (Hethcote and Yorke, 1984). They are useful for examining large scale effects and for initial insights into problems where parameters are poorly estimated as sensitivity analysis can be performed quickly.

Individual based network models are more computationally intensive and require more advanced statistical analysis and interpretation. Recent advances in computing technology have stimulated the further development of such models. Several authors have used individual based models to investigate STIs, (Krestzchmar et al 1996, Ghani et al 1996). The advantages of individual based models are that one can track the infection history and sexual behaviour of individuals over time and observed stochastic events such as local extinctions. A difficulty with individual based network simulation models is determining when the sexual network simulated is representative of the true sexual network under study, in part due to difficulties in measuring sexual networks of humans (Ghani et al 1998).

This thesis will use a series of deterministic compartmental models to investigate a range of questions on coinfection, mixing patterns, reinfection and the evolution of the organism.
Discussion

Together, human biology and sexual behaviour, pathogen biology and public health interventions, interact to determine the epidemiology of sexually transmitted disease. Understanding the dynamics of this system requires an appreciation of each component and its effect on the rest of the system. Gonorrhoea and chlamydia share many characteristics; risk factors, clinical presentation, long term sequelae, asymptomatic infections, and they are both treatable and preventable. However there are important differences in the distribution of infection and in the networks which support infection. Many crucial parameters which describe the epidemiology of sexually transmitted infections are poorly estimated, e.g. the duration of untreated infections is very variable (Golden, Schillinger et al. 2000). Estimating the impact of interventions within a dynamic framework is important for planning policy. Mathematical modelling approaches provide a means of simulating and predicting the behaviour of a complex, dynamic situation.

This thesis presents a series of mathematical models, together with new empirical data which will demonstrate how an integrated approach can be used in a variety of situations, to better understand and explain host behaviour, pathogen biology and public health interventions, to inform public health efforts.

The distribution of gonorrhoea and chlamydia are modelled in Chapter 2 to investigate the patterns of coinfection and determine whether it is more likely in particular risk groups. The relative effectiveness of screening and cotreatment are assessed in a deterministic framework.

Chapter 3 investigates the impact of host behaviour on the distribution of disease within a population. Data from a behavioural study and cross sectional study of incidence of gonorrhoea in South East London are used to parameterise and validate a model of gonorrhoea. The effect of partner choice in determining the network structure i.e. mixing patterns is investigated. Host behaviour is considered with respect to partner choice and rates of partner change for a population in South East London, in which mixing patterns play a crucial role in gonorrhoea epidemiology.

Chapter 4 looks at reinfection and the biological features of STIs which make them able to infect the same individual many times. The model is used to compare with rates of reinfection and try to tease out biological characteristics of reinfection. A simple deterministic model of reinfection with gonorrhoea is compared with a more complex
model to quantify the difference in expected reinfection rates between the two scenarios. The ability of the models to predict reinfection with gonorrhoea is compared with empirical data from London GU clinic.

Chapter 5 examines at the effect of different evolutionary strategies of gonorrhoea and chlamydia to investigate what effect interventions have on the evolutionary advantage of one strain or infection over another. Particular attention is paid to the evolution of drug resistance and bacterial mechanisms of gonorrhoea which allow it to develop drug resistance very quickly and spread rapidly within a population.

In Chapter 6 the findings of the thesis are reviewed and the work placed in a wider context. Common themes and features from different chapters which are relevant to each other are highlighted.
Chapter 2  Coinfection with chlamydia and gonorrhoea

Summary

In this chapter, the epidemiology of infection with gonorrhoea, chlamydia and coinfection is examined. The risk factors for these infections are similar and coinfection is common. The chapter will examine the extent of coinfection and the epidemiological characteristics of patients with chlamydia, gonorrhoea or both, and how these are influenced by the biology of the pathogens and the sexual behaviour of the host.

A review of the current literature regarding coinfection with gonorrhoea and chlamydia is presented. Estimates are made of additional parameters values for use in a mathematical model of single infection and coinfection. The relevant similarities and differences between the two pathogens and their treatment and control are highlighted. A mathematical model of two sexually transmitted pathogens is then developed. The model is used to examine the impact of different treatment and control options, such as routine cotreatment or chlamydia screening on prevalence and incidence.
Introduction

Gonorrhoea and chlamydia share many epidemiological and clinical characteristics (Box 1.1, Table 1.1 and Table 1.6): they are both caused by sexually transmitted bacteria, are often asymptomatic and include in their sequelae, pelvic inflammatory disease (PID), ectopic pregnancy and infertility. There are also important differences between them: chlamydia is much more prevalent than gonorrhoea. Of reported diagnoses in women in the UK in 2002, chlamydia was diagnosed almost 6 times more often than gonorrhoea, and in heterosexual men more than twice as often (HPA 2003a). Gonorrhoea and chlamydia share the same mode of transmission and coinfection with both pathogens is common. Most estimates of coinfection are based on the proportion of patients with gonorrhoea who also have chlamydia, as this proportion is expected to be higher.

In the UK, recent years have seen a marked increase in the number of diagnoses of gonorrhoea and chlamydia. Possible explanations for this change are an increase in sexual activity, an increase in testing and awareness or a reduction in the quality of healthcare provision. The national surveys of sexual attitudes and lifestyles undertaken in 1990 and 2000, offer a good opportunity to relate changes in sexual behaviour with changes in disease incidence (Johnson, Mercer et al. 2001). There is also some evidence that STI clinic services are not coping with this increased demand, resulting in a vicious cycle of longer time to recovery and therefore more opportunities for transmission of infection and long term sequelae of disease (Adler 2003; White, Cassell et al. 2003).

Figure 2.1 shows the increase in diagnoses of gonorrhoea and chlamydia reported in the UK (on different axes) between 1995 and 2002. It is not clear how much of the increases can be explained by increased testing and diagnosis, especially of chlamydia. Data on the number of tests performed might provide some indication of whether the increased diagnoses are a result of increased testing or true increases in incidence. It is also important to estimate the proportion of false positives detected. Both infections appear to have increased at the same rate, which suggests a possible common cause, e.g. a general trend of increasing sexual activity (Johnson, Mercer et al. 2001), or some other common factor e.g. declining STI health services (Adler 2003) could explain the temporal trends. Although this is a very simple approach, using information about both infections can provide additional information about the changing epidemiology.
Figure 2.1  

Increase in gonorrhoea and chlamydia diagnoses reported to the HPA in the UK, 1994-2003 (HPA 2003b).

![Diagram showing the increase in gonorrhoea and chlamydia diagnoses from 1994 to 2003.](image-url)
Understanding the epidemiology of coinfection with gonorrhoea and chlamydia is of clinical relevance because cotreatment of both infections is often implemented when a patient is diagnosed with gonorrhoea. Most antibiotics which are effective against one organism will not clear the other. In the USA, routine cotreatment of gonorrhoea patients for chlamydia is recommended, but in the UK presumptive cotreatment is only given if a patient is unlikely to return for a follow-up appointment (Appendix, Treatment Guidelines, Table A.1 and Table A.2). In the current context of a continuing failure to control both gonorrhoea and chlamydia, as evidenced by a sustained increase in gonorrhoea and chlamydia incidence in the UK, new approaches to the management and prevention of these infections are required. Interventions for chlamydia and gonorrhoea can be combined by health care providers as the risk groups for each infection are overlapping. In addition, screening programmes for chlamydia could potentially be used for identifying those who would benefit from additional screening for gonorrhoea (Fenton, Korovessis et al. 2001).

There is debate over the usefulness and appropriateness of routine cotreatment. The advantage of presumptive cotreatment of patients who present with gonorrhoea is that there is a high index of suspicion that they are also infected with chlamydia, so treatment is likely to benefit the patient. The antibiotic drugs used to treat chlamydia are effective and very safe so there is a large potential benefit to the infected individual, balanced by a very small potential cost of therapy to an uninfected person. Epidemiologically there is an indirect benefit to society of preventing further transmission of chlamydia by treating the patient as soon as possible. In addition there are potential economic benefits as the cost of treating uncomplicated chlamydia is low, but long term complications such as infertility and PID are potentially very expensive. However, some would argue that routine cotreatment means unnecessary therapy for a significant number of people and that most of those infected get treated anyway (Das, Allan et al. 2002).
Extent of coinfection with gonorrhoea and chlamydia

The proportion of patients coinfected with these bacteria varies by age, gender and sexual orientation. Young age and female gender are associated with an increased risk of coinfection (Creighton, Tenant-Flowers et al. 2003; Hijazi, Thow et al. 2002). Men who have sex with men (MSM) with gonorrhoea have been shown in most studies to be less likely to be coinfected with chlamydia than heterosexuals (Dragovic, Greaves et al. 2002; Hijazi, Thow et al. 2002; HPA 2003a). In the UK in 2002, the GRASP survey found that 35% of females, 24% heterosexual males and 7% MSM infected with gonorrhoea were also infected with chlamydia (HPA 2003a). A similar level of coinfection have been reported in the USA, where two surveys of GU clinic attendees found that approximately 40% of women and 20% of men with gonorrhoea also had chlamydia and this proportion was highest in young age groups (Dicker, Mosure et al. 2003; Lyss, Kamb et al. 2003).

Various other studies have calculated the proportion of selected groups of patients with gonorrhoea or chlamydia who are also infected with the other pathogen. Table 2.1 summarises these estimates of coinfection. The estimates vary considerably but show that coinfection in young females is more common than in men, reflecting the higher prevalence of chlamydia in women and longer duration of infection compared with men. For example 40-50% of young women with gonorrhoea are typically also infected with chlamydia (Dicker, Mosure et al. 2003).

Coinfection is not reported directly in the national STI surveillance system (KC60), so other means for estimating temporal trends are required, to use in conjunction with studies, which directly measure the proportion of patients infected with gonorrhoea who are coinfected with chlamydia or vice versa. Reported diagnoses in clinics underestimate the numbers of cases of disease and infection within a population. Some people with disease will not attend a clinic because they are unaware of their infection (asymptomatic), they get treated elsewhere, or the infection is not reported. Changes in the relative level of reporting of gonorrhoea or chlamydia may influence the apparent rate of concurrent infection over time. For example, increases in screening or in the sensitivity of diagnostic tests may alter the apparent incidence of infection, whilst the real incidence remains unchanged. Trends in coinfection could shed light on the extent of reporting changes on the change in observed incident cases or true changes in disease occurrence.
The setting and test used in different studies may affect the comparability of the results. In particular, non-PCR methods tend to underestimate the number of men infected with chlamydia. Reports prior to the mid 1990s are likely to underestimate coinfection in men. From the late 1990s the sensitivity of available tests increased, especially in men. This has led to increased diagnoses of chlamydia and more coinfections with gonorrhoea and chlamydia observed in men which, has in turn, led to a greater awareness of the need to test and treat men for chlamydia too. Men who have sex with women (MSW) are more likely to be coinfected with chlamydia than MSM (Creighton, Tenant-Flowers et al. 2003; HPA 2003a). This is due to their contact with a higher prevalence population i.e. women. One USA study found a higher proportion men MSM coinfected than MSW, although this was not significant. The authors suggest that this could have been due to a reduction in immunity to chlamydia due to lower exposure to past infection (Ciemins, Flood et al. 2000).

This can be further examined by plotting the number of cases of gonorrhoea divided by the number of cases of gonorrhoea and chlamydia combined, for females, heterosexual men and MSM, which is shown in Figure 2.2. In general the ratio of gonorrhoea and chlamydia infections has remained roughly stable over the last 5 years, the exception being in MSM, where diagnoses of chlamydia infections have increased faster than gonorrhoea infections, i.e. the proportion of infections due to gonorrhoea has declined. This could be explained by a slower increase in the incidence of gonorrhoea infections or due to increases in testing and increased test sensitivity of chlamydia tests, particularly changes in the ability to detect pharyngeal and rectal infection.
<table>
<thead>
<tr>
<th>% infected with GC, who have CT</th>
<th>Comments (Study setting, diagnostic test)</th>
<th>Reference (most recent first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>35</td>
<td>UK national surveillance of GC isolates 2001-2 Variable chlamydia tests (majority sensitive) (HPA 2003a)</td>
</tr>
<tr>
<td>M</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>F (136/353)</td>
<td>38.5</td>
<td>GUM clinic, London UK 1998 LCR test: M first pass urine; F endocervical swab 13% F with CT had GC (136/1022) 18.8% MSW with CT had GC (124/660) 20.0% MSM with CT had GC (5/25) Young age and female gender associated with CT coinfection: &gt;50% of 15-19 women coinfection. Ethnicity had no effect (control age and gender) (Creighton, Tenant-Flowers et al. 2003)</td>
</tr>
<tr>
<td>MSW (124/512)</td>
<td>24.2</td>
<td></td>
</tr>
<tr>
<td>MSM (5/73)</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>F (FPC)</td>
<td>34.7</td>
<td>GUM clinic, London, UK, 1999 ELISA. 257 cases, from 238 patients, Don’t routinely screen M (Newell, Herbert et al. 2003)</td>
</tr>
<tr>
<td>M</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>F (STD)</td>
<td>43.1</td>
<td>15-24 F, USA, 2000 Nucleic acid probe (Dicker, Mosure et al. 2003)</td>
</tr>
<tr>
<td>F (Prenatal)</td>
<td>38.4</td>
<td></td>
</tr>
<tr>
<td>BSW (124/512)</td>
<td>49.2</td>
<td></td>
</tr>
<tr>
<td>F (64/151)</td>
<td>42</td>
<td>5 public STD clinics, USA 1993-95. PCR test 3885 tested (%): CT (M=16, F=9), GC (M=19, F=15), Both (M=4, F=4) Age &lt;25 associated with coinfection (&gt;50% F) (Lyss, Kamb et al. 2003)</td>
</tr>
<tr>
<td>MSW (91/411)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>All, not MSM</td>
<td>10.7</td>
<td>London GUM clinic 1998 ELISA test endocervical/urethral for W, urine for M May underestimate incidence in men (Dragovic, Greaves et al. 2002)</td>
</tr>
<tr>
<td>F</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>41.4</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>MSW</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>F (29/64)</td>
<td>48</td>
<td>Glasgow, STD clinic. 2000 LCR test (M- urine, F – endocervical swab) Young age and female sex independent predictors of co-infection (logistic regression) (Hijazi, Thow et al. 2002)</td>
</tr>
<tr>
<td>M (57/287)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>MSM (15/134)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>MSW (42/153)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>26</td>
<td>GU clinic Coventry, UK. 1989-2000 CT ELISA, confirmed with immunoassay 8% CT cases had GC. 1250 GC, 4127 CT, 332 Both (Das, Allan et al. 2002)</td>
</tr>
</tbody>
</table>
### Chapter 2 - Coinfection with gonorrhoea and chlamydia

<table>
<thead>
<tr>
<th>Gender</th>
<th>% infected with GC, who have CT</th>
<th>Comments (Study setting, diagnostic test)</th>
<th>Reference (most recent first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>15.2</td>
<td>San Francisco STD clinic 1997 Urine LCR test. Young age associated with CT</td>
<td>(Ciemens, Flood et al. 2000)</td>
</tr>
<tr>
<td>MSW</td>
<td>8.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (24/69) M (10/134)</td>
<td>36.4 8</td>
<td>GUM, Newcastle upon Tyne, UK, 1999 Lab culture for CT, EIA test, PCR confirmation 65% GC cases - attendance of sex partners. CT screening/co-treating in 98% of cases of GC</td>
<td>(Watson 2000)</td>
</tr>
<tr>
<td>All</td>
<td>38</td>
<td>GUM, Coventry, UK, 1991-94. EIA test</td>
<td>(David, Wade et al. 1997)</td>
</tr>
<tr>
<td>M</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (6/34) M (4/113)</td>
<td>17.6 3.5</td>
<td>Sydney, Australia</td>
<td>(Tapsall and Kinchington 1996)</td>
</tr>
<tr>
<td>F (pregnant)</td>
<td>46</td>
<td>Texas, USA. Pregnant women. CT culture</td>
<td>(Christmas, Wendel et al. 1989)</td>
</tr>
<tr>
<td>M</td>
<td>15</td>
<td>USA</td>
<td>(Stamm, Guinan et al. 1984)</td>
</tr>
<tr>
<td>F</td>
<td>48.3</td>
<td>474 women. CT significantly associated with GC, oral contraceptives, cervical ectopy, cervicitis and sex within a week.</td>
<td>(Arya, Mallinson et al. 1981)</td>
</tr>
<tr>
<td>F</td>
<td>44</td>
<td>STD clinic, UK. 638 women Cervical swab</td>
<td>(Burns, Darougar et al. 1975)</td>
</tr>
<tr>
<td>M (15/44)</td>
<td>34</td>
<td></td>
<td>(Oriel, Reeve et al. 1975)</td>
</tr>
<tr>
<td></td>
<td>26-48</td>
<td></td>
<td>(Washington, Browner et al. 1987)</td>
</tr>
</tbody>
</table>

Notes: CT = *Chlamydia trachomatis*; NG = *Neisseria gonorrhoeae*; F = female; M = male; MSM = men who have sex with men; MSW = men who have sex with women; GUM = genitourinary medicine; STD = sexually transmitted disease; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction; LCR = ligase chain reaction

ELISA or EIA tests may underestimate prevalence in men by up to 20%
Figure 2.2 The fraction of the combined reports of gonorrhoea and chlamydia in the UK represented by gonorrhoea
Behavioural aspects of coinfection

Differences exist between patients with chlamydia, gonorrhoea or both. As described in chapter 1, gonorrhoea is highly clustered geographically and socially, whereas chlamydia is more widely dispersed within the general population, although still concentrated in particular risk groups. The sexual networks in which STIs are transmitted vary, e.g. MSM, sex workers and their clients and heterosexual adolescents. These networks provide different types of sexual contact (penile-vaginal or penile-anal sex) and involve different people (men or women). Such differences may favour one pathogen over another, due to differences in the transmissibility or duration of infectiousness in the members of the network.

Men infected with gonorrhoea report higher rates of partner change than women with gonorrhoea and similarly for chlamydia (Zimmerman, Potterat et al. 1990). This may reflect the greater susceptibility of women to infections with either organism and longer duration of infection i.e. a difference in the natural history of infection between men and women. However, men report higher rates of partner change than women in general, so it may simply be reporting bias (Johnson 1994). Concurrency of sex partners may also play an important role in determining the likelihood of infection and coinfection with STI (Kraut-Becher and Aral 2003). It appears that differences exist between carriers of different strains of pathogen, for example, strains of gonorrhoea are better adapted to survival in the rectum and are therefore found more commonly among MSM (Whittington and Holmes 2000). This suggests that host characteristics do indeed affect the distribution of bacteria species or strains within a population, both spatially and temporally.

The observed differences in individuals with gonorrhoea infection compared with chlamydia infection, have led to the suggestion that these represent different sexual networks (Jolly and Wylie 2002; Kretzschmar, van Duynhoven et al. 1996; Stoner, Whittington et al. 2000; Van Duynhoven, van de Laar et al. 1997). In a recent, detailed study of the epidemiology of gonococcal and chlamydial infection in sexual networks (Stoner, Whittington et al. 2000), patients infected with chlamydia had a lower average number of partners, and were less likely to report crack-cocaine use or to have served a prison sentence than gonorrhoea patients. In addition, chlamydia patients are on average wealthier and better educated than those infected with gonorrhoea.
This can be explained in terms of the basic reproductive number. For two infections (gonorrhoea and chlamydia) with a similar transmission probability, higher frequency transmitters can maintain an infection (gonorrhoea) with a fairly short duration because there are sufficient opportunities for transmission of the bacteria to new hosts. In contrast, a longer duration of infectiousness allows a pathogen (chlamydia) to persist in a population of lower frequency transmitters as well. The higher prevalence and incidence of chlamydia compared with gonorrhoea suggests that the reproductive number of chlamydia is higher than for gonorrhoea. Extending this line of reasoning, one would expect those infected with both pathogens to have the highest risk behaviour, those with gonorrhoea the next highest and those with chlamydia the lowest level of risk. People identified as coinfected are therefore potential targets for interventions.

Other markers of increased STI risk, such as history of infection may indicate individuals in the core group who are likely to be important in the onward transmission and maintenance of endemic infection. The absence of such risk markers may indicate that a person represents the end of a chain of transmission or is non-core. Such proxy markers of risk behaviour are useful for identifying people who would benefit most from interventions. Rogers et al demonstrate this principle in finding that individuals with a current infection who self-reported a history of STI (marker of risk) were found to be more likely to have had multiple partners than those with no self-reported history (Rogers, Miller et al. 2002). In the same study however, behavioural characteristics did not describe those with current asymptomatic infection very well (Rogers, Miller et al. 2002).

A two-pathogen model with good parameter estimation of the natural history of infection, together with a good representation of sexual behaviour and mixing patterns should be able to produce realistic simulations of disease incidence and prevalence. Even if the parameters are estimated imperfectly, the relative effects can be analysed and compared with observed incidence of single infections with gonorrhoea or chlamydia or with coinfection. This could also be used to inform estimates of unknown parameters such as mixing by activity level and parameters related to the natural history of coinfection.

**Biology of coinfection**

The natural history of coinfection with gonorrhoea and chlamydia is not well described. Questions which remain unanswered include: what happens to the transmission
probability and rate of recovery from each infection? Is transmission of each infection independent or are both transmitted simultaneously more frequently than would be expected? What happens during treatment, are both infections cleared or only one? If the new infection results in overt symptoms then the duration of the existing infection may be reduced, due to the individual seeking care for an unrelated infection. Conversely, existing infection may increase susceptibility to acquiring further infections, due to inflammation in the genitourinary tract.

Little is known about the interaction between gonorrhoea and chlamydia during coinfection. It is now accepted that gonorrhoea increases the transmission probability of HIV, which suggests that the presence of another pathogen can affect the replication or adhesion and hence the transmission of other pathogens (Rottingen, Cameron et al. 2001). A study by Lin et al (Lin, Donegan et al. 1998), designed to investigate transmission of chlamydia and gonorrhoea, found that there was no difference in the transmission of gonorrhoea or chlamydia infection from coinfected versus singly infected individuals to naïve partners. Approximately two thirds of partners were infected with either chlamydia or gonorrhoea and more than half of the partners of coinfected patients were also coinfected. It is unknown how recovery is affected by coinfection. For example the rate of recovery in those coinfected who are treated for both infections is unknown, as is the fraction that remain infected with either Neisseria gonorrhoeae or Chlamydia trachomatis.

The fraction of cases which do not develop symptoms has a strong influence on the epidemiology of the disease. For example, people with asymptomatic infections may be less likely than those with symptomatic infections to alter their sexual behaviour and less likely to seek care even if notified. For both gonorrhoea and chlamydia, asymptomatic infections comprise an important reservoir of infection, although gonorrhoea is more likely to cause symptoms than chlamydia. A potential means of treating some asymptomatic or unrecognised infections is to presumptively treat gonorrhoea cases for chlamydia as coinfection in gonorrhoea patients is common. The impact of asymptomatic disease adds to the need for effective screening programs for chlamydia in men and women. Where screening programs for chlamydia have been trialled, they have shown considerable success in reducing prevalence, e.g. in various US states (LaMontagne, Fine et al. 2003; MMWR 1997a). The proportion of contacts of infected cases that are asymptomatic may be very high, in the order of 80%. The same study found that only 10% of index cases were asymptomatic (David, Wade et al.
Chapter 2 - Coinfection with gonorrhoea and chlamydia

1997). It is not known whether the transmissibility of asymptomatic infections is the same as that for symptomatic infections. Potentially there could be an increase in the relative transmissibility of asymptomatic infections due to lack of awareness of infections and therefore, no change in sexual behaviour (e.g. condom use or abstention).

Coinfection may have an impact on the probability of a patient becoming symptomatic or having a symptomatic partner and therefore of seeking care. There is some evidence that infection with gonorrhoea may reactivate latent chlamydia infection (Batteiger, Fraiz et al. 1989). This may have benefits if chlamydia is diagnosed and treated due to attending a clinic for gonorrhoea when it would have otherwise gone unrecognised. Reactivation of chlamydia may have other implications for the patient, for example if it increases the risk of PID due to an enhanced inflammatory response, but these effects are not well characterised. It is not known whether coinfection results in an increased risk of PID compared with single infection with either bacterial species.

Method

Mathematical model

A deterministic model of gonorrhoea and chlamydia which allows for coinfection with the two bacteria was developed, based on previous work (Anderson and May 1991; Garnett, Mertz et al. 1999; Hethcote and Yorke 1984). The model was developed to allow the introduction of various treatment or intervention strategies aimed at gonorrhoea, chlamydia or both during the course of the simulation. These could be targeted at specific groups or the whole population. The interventions act to reduce the duration of infection in those infected to simulate an increased rate of diagnosis and treatment. The influence of patterns of sexual partner choice and sexual mixing on the impact of treatment was also assessed.

Model details

The model represents an exclusively heterosexual population stratified according to gender, sexual activity based on rate of partner change and infection status: infected with gonorrhoea; chlamydia; or both, and whether infection is symptomatic or asymptomatic. The model population was a constant size with a constant supply of new susceptibles, balanced by a constant rate of loss representing death or cessation of sexual activity. All sexual contacts are assumed to be chosen from within the model population.
Chapter 2 - Coinfection with gonorrhoea and chlamydia

The literature was consulted to obtain parameter estimates of the natural history of the infections for the model. The available, observed values from empirical studies are presented in Table 2.2. The parameter values used in the model are presented in Table 2.3. Those which directly affect the basic reproductive number are the rate of sexual contact (c), the transmission probability per partnership (β) and the duration of infection (D) (Chapter 1, Equation 1.1). The contact rates of each of four activity classes are given in Table 2.4. These values reflect observed trends; most people have few partners and a few have many, but the model does not directly aim to simulate observed values.

Many of the parameters required for an accurate model of either gonorrhoea or chlamydia are poorly defined or unknown e.g. the transmissibility and duration of asymptomatic infections. Including both infections in the same model requires additional parameters to account for potential interactions during coinfection which may affect the transmission or duration of infection of the pathogens. The advantage of modelling both infections is it may be possible to extract additional information about both diseases.

Parameters which are not well defined for a model of coinfection include the and transmission from or to a site with another pathogen present. Another unknown is how recovery is affected by coinfection. This is represented by a parameter, \( \omega \), which determines the proportion of those recovering from coinfection who remain infected with either infection, or who recover from both infections at the same time (e.g. due to cotreatment). The extreme case is when all recovery is from coinfection to the susceptible class (\( \omega_{CT} = \omega_{GC} = 0 \)). Superscripts denote the proportion recovering from chlamydia (CT) or gonorrhoea (GC)); or all recovery is from one infection at a time (\( \omega_{CT} + \omega_{GC} = 1 \)). In the examples presented in the results, it assumed that 40% of recovery from coinfection is from a single strain (equally split between the two strains), and 60% is recovery to the susceptible class directly, e.g. due to treatment. The rate of recovery depends on the proportion of infected people that seek treatment, although this is likely to be different for asymptomatic and symptomatic infections.
Table 2.2 Parameters required for the mathematical model of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* with estimates drawn from literature

<table>
<thead>
<tr>
<th></th>
<th><em>Chlamydia trachomatis</em></th>
<th><em>Neisseria gonorrhoeae</em></th>
<th>Reference &amp; type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transmission probability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65%</td>
<td>F - CT from M (CT only)</td>
<td>73%</td>
<td>F - GC from M (GC only)</td>
</tr>
<tr>
<td>79%</td>
<td>F - CT from M (CT + GC)</td>
<td>71%</td>
<td>F - GC from M (CT + GC)</td>
</tr>
<tr>
<td>57%</td>
<td>F - CT+GC, M (CT+GC)</td>
<td>57%</td>
<td>F - CT+GC, M (CT+GC)</td>
</tr>
<tr>
<td>Study designed to evaluate male to female transmission of CT and NG No difference in treatment observed between coinfected and singly infected people</td>
<td></td>
<td></td>
<td>(Lin, Donegan <em>et al.</em> 1998)</td>
</tr>
<tr>
<td>68%</td>
<td>M (42% culture positive)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70%</td>
<td>F (57% culture positive)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR test of sex partners of those infected with chlamydia. Couples enrolled at STD clinic in Baltimore, USA. Infection associated with history of STD</td>
<td></td>
<td></td>
<td>(Quinn, Gaydos <em>et al.</em> 1996)</td>
</tr>
<tr>
<td>22%</td>
<td>M - per sexual contact with infected females</td>
<td></td>
<td>(Holmes, Johnson <em>et al.</em> 1970)</td>
</tr>
<tr>
<td>Culture method was used, so may have underestimated chlamydia transmission especially in men. Male partners more often infected with GC than CT. Of the female partners of men with GC only, 38% were found to have CT, compared with 14% of the male partners of women with GC only.</td>
<td></td>
<td></td>
<td>(Lycke, Lowhagen <em>et al.</em> 1980b)</td>
</tr>
<tr>
<td><strong>Chlamydia trachomatis</strong></td>
<td><strong>Neisseria gonorrhoeae</strong></td>
<td><strong>Reference &amp; type of study</strong></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Estimate</strong></td>
<td><strong>Comment</strong></td>
<td><strong>Estimate</strong></td>
<td><strong>Comment</strong></td>
</tr>
<tr>
<td>Recovery rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;61</td>
<td>F No treatment (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;21</td>
<td>M no treatment (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of data on duration of infection of chlamydia. Evidence quite poor for duration of untreated infection</td>
<td></td>
<td>6 mo</td>
<td>Untreated duration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8 mo</td>
<td>Treated duration</td>
</tr>
<tr>
<td>Proportion asymptomatic and symptomatic</td>
<td>33%</td>
<td>GC in GU clinic, UK GC+CT</td>
<td>(David, Wade et al. 1997)</td>
</tr>
<tr>
<td>50%</td>
<td>M</td>
<td>Most cases identified through contact tracing and screening, USA. 40% geographic overlap.</td>
<td>(Zimmerman, Potterat et al. 1990)</td>
</tr>
<tr>
<td>80%</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>43%</td>
<td>M</td>
<td>STD clinic study in Baltimore, USA</td>
<td>(Quinn, Gaydos et al. 1996)</td>
</tr>
<tr>
<td>79%</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11%</td>
<td>M become symptomatic</td>
<td>45%</td>
<td>M become symptomatic</td>
</tr>
<tr>
<td>6%</td>
<td>F become symptomatic</td>
<td>14%</td>
<td>F become symptomatic</td>
</tr>
<tr>
<td>Model of rural Ugandan setting. Sensitive to assumptions on relative duration of symptomatic/asymptomatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms are higher in men and more likely for GC than CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated the proportion of infection that will become symptomatic, approx 1.5 times higher than point prevalence of symptomatic cases in cross sectional survey in rural Uganda</td>
<td>(M, NG 33±9%; M CT 7±3.6%; F NG 9±4% ; F CT 4±2.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63%</td>
<td>4.9% prevalence (474/9662 tests done in male STD clinic attendees in NY USA by DNA test (urethral swab)</td>
<td>(Urban, Coury-Doniger et al. 1997)</td>
<td></td>
</tr>
<tr>
<td>26%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2.3 Parameter definitions used in the mathematical model of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Default value</th>
<th>Range of values used in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>Entry rate to maintain a constant population size, the entry and exit rates are assumed to be equal.</td>
<td>0.02 per year</td>
<td>n/a</td>
</tr>
<tr>
<td>$\beta^{NG}<em>{k}$, $\beta^{CT}</em>{k}$</td>
<td>Transmission probability of NG or CT to sex $k$ per contact, where $x=a$ denotes asymptomatic infection and $x=s$ symptomatic infection</td>
<td>0.5 per contact</td>
<td>$0 &lt; \beta &lt; 1$</td>
</tr>
<tr>
<td>$\beta^{DX}<em>{k}$, $\beta^{DX}</em>{k}$</td>
<td>Transmission probability of both infections to sex $k$ per contact, where $x=a$ denotes asymptomatic infection and $x=s$ symptomatic infection</td>
<td>0.5 per contact</td>
<td>$0 &lt; \beta &lt; 1$</td>
</tr>
<tr>
<td>$\gamma^{NG}$, $\gamma^{CT}$</td>
<td>Proportion of contacts with superinfected individuals, which result in transmission of NG or CT only. (If $\gamma^{A} + \gamma^{B} = 0$, then all contacts result in transmission of coinfection, if $\gamma^{A} + \gamma^{B} = 1$, then all contacts with coinfected individuals result in the transmission of a single strain).</td>
<td>$\gamma^{A} = \gamma^{B} = 0.4$ Therefore proportion of contacts which result direct transmission of coinfection is: $1 - (\gamma^{A} + \gamma^{B}) = 0.2$.</td>
<td>$0 \leq \gamma \leq 1$ $\gamma^{A} + \gamma^{B} \leq 1$</td>
</tr>
<tr>
<td>$\omega^{A}$, $\omega^{B}$</td>
<td>Proportion of those recovering from coinfection that remain infected with NG or CT. The extreme cases are when either all recovery is from mixed infection to the susceptible class ($\omega^{A} = \omega^{B} = 0$); or all recovery is from single infections ($\omega^{A} + \omega^{B} = 1$).</td>
<td>$\omega^{A} = \omega^{B} = 0.2$, $0 \leq \omega \leq 0.5$ $\omega^{A} + \omega^{B} \leq 1$</td>
<td></td>
</tr>
<tr>
<td>$\rho_{klm}$</td>
<td>Mixing matrix, element $klm$ is probability that individual of sex $k$ in activity class $l$ will form a partnership with a member of activity class $m$, sex $k'$ (opposite)</td>
<td>See below</td>
<td>n/a</td>
</tr>
<tr>
<td>$c_{kl}$</td>
<td>Contact rate of individual of sex $k$, activity class $l$ (see below)</td>
<td>See below</td>
<td>n/a</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Pattern of mixing (0=fully assortative, 1= random)</td>
<td>1 (random)</td>
<td>$0 \leq \varepsilon \geq 1$</td>
</tr>
<tr>
<td>$\theta^{NG}$, $\theta^{CT}$</td>
<td>Percentage of infections with NG or CT which are symptomatic.</td>
<td>$\theta^{NG} = 0.8$ $\theta^{CT} = 0.4$</td>
<td>n/a</td>
</tr>
</tbody>
</table>
### Chapter 2 - Coinfection with gonorrhoea and chlamydia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Default value</th>
<th>Range of values used in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_{NGa_k, CTa_k}$</td>
<td>Recovery rate from asymptomatic infection with NG or CT per year (recovery rate = 1/duration)</td>
<td>$\sigma = 2$ per year, i.e. average duration of 6 months without treatment, decreasing to 10 per year, i.e. 1.2 months duration with treatment.</td>
<td>With treatment, recovery depends on efficacy of treatment and the average time taken to seek treatment. Assumed to be the same for NG and CT.</td>
</tr>
<tr>
<td>$\sigma_{NGs_k, CTs_k}$</td>
<td>Recovery rate from symptomatic infection with NG or CT per year (recovery rate = 1/duration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{Ds_k, Da_k}$</td>
<td>Recovery rate from dual infection</td>
<td>Assumed to be faster than from single infections</td>
<td>As above</td>
</tr>
</tbody>
</table>

### Table 2.4 Activity class definitions

<table>
<thead>
<tr>
<th>Activity class</th>
<th>Rate of partner change (per year)</th>
<th>Proportion of population in class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>4.4</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>0.2</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
<td>0.65</td>
</tr>
</tbody>
</table>
Katherine Turner

Chapter 2 - Coinfection with gonorrhoea and chlamydia

The mathematical equations describing the model are given below, along with further definitions of the parameters. Subscripts refer to the sex and activity class. In the case of sex, \( k=0 \) for men, \( k=1 \) for women while \( k' \) refers to the opposite sex to \( k \) and for activity \( l \) defines the class (from 1 to 4), according to average rate of partner change per year, \( c_{kl} \). The superscripts \( CT, NG \) associated with parameters identify the infecting organism and \( D \) a dual infection. Addition of \( a \) or \( s \) denotes asymptomatic and symptomatic infections, respectively.

The subscripts stratify the state variables, which are as follows:

- \( X_{kl} \) - population of susceptibles of sex \( k \) and activity class \( l \)
- \( NGA_{kl} \) - population of hosts infected with asymptomatic NG, of sex \( k \), activity class \( l \)
- \( NGS_{kl} \) - population of hosts infected with symptomatic NG of sex \( k \), activity class \( l \)
- \( CTA_{kl} \) - population of hosts infected with asymptomatic CT of sex \( k \), activity class \( l \)
- \( CTS_{kl} \) - population of hosts infected with symptomatic CT of sex \( k \), activity class \( l \)
- \( Da_{kl} \) - population of hosts infected with asymptomatic NG and CT of sex \( k \), activity class \( l \)
- \( DS_{kl} \) - population of hosts infected with symptomatic NG and CT of sex \( k \), activity class \( l \)
- \( N_{kl} \) - total population, sex \( k \), activity class \( l \)

In order to simplify the equations the force of infection is defined for symptomatic and asymptomatic infections of each strain independently (NG and CT) and for coinfection (D). The force of infection is the product of the transmissibility of the pathogen to each sex (\( \beta \)), the contact rate (partner change rate) (\( c \)) of the host population and the proportion of the total population infected with the strain, contacts with whom are determined by the elements (\( \rho_{klm} \)) of the mixing matrix (\( P_{klm} \)). The force of infection here is the incidence per susceptible contributed by the type of infectious individuals.
Chapter 2 - Coinfection with gonorrhoea and chlamydia

Thus for an individual of sex \( k \), activity class \( l \), the forces of infection for strains NGa, NGs, CTa or CTs, or coinfection Da or Ds are:

\[
\lambda_{kl}^{NGs} = c_{kl} \beta_{k}^{NGs} \sum_{m=1}^{4} \left( \frac{\rho_{klm}^{NGs} k}{N_{k} k} \right) \\
\lambda_{kl}^{NGa} = c_{kl} \beta_{k}^{NGa} \sum_{m=1}^{4} \left( \frac{\rho_{klm}^{NGa} k}{N_{k} k} \right) \\
\lambda_{kl}^{CTs} = c_{kl} \beta_{k}^{CTs} \sum_{m=1}^{4} \left( \frac{\rho_{klm}^{CTs} k}{N_{k} k} \right) \\
\lambda_{kl}^{CTa} = c_{kl} \beta_{k}^{CTa} \sum_{m=1}^{4} \left( \frac{\rho_{klm}^{CTa} k}{N_{k} k} \right) \\
\lambda_{kl}^{Ds} = c_{kl} \beta_{k}^{Ds} \sum_{m=1}^{4} \left( \frac{\rho_{klm}^{Ds} k}{N_{k} k} \right) \\
\lambda_{kl}^{Da} = c_{kl} \beta_{k}^{Da} \sum_{m=1}^{4} \left( \frac{\rho_{klm}^{Da} k}{N_{k} k} \right)
\]
The equations describing the model are as follows:

\[
\begin{align*}
\frac{dX_{kl}}{dt} &= \mu X_{kl} - \mu X_{kl} - X_{kl} \left( \lambda_{NG}^{NGa} + \lambda_{NG}^{NGs} + \lambda_{CT}^{CTa} + \lambda_{CT}^{CTs} + \lambda_{Da}^{Da} + \lambda_{Ds}^{Ds} \right) + \sigma_k^{NG} NGa_{kl} \\
&+ \sigma_k^{NG} NGs_{kl} + \sigma_k^{CT} CTa_{kl} + \sigma_k^{CT} CTs_{kl} + \left( 1 - \left( \omega^A + \omega^B \right) \right) \left( \sigma_k^{Da} Da_{kl} + \sigma_k^{Ds} Ds_{kl} \right) \\
\frac{dNGa_{kl}}{dt} &= (1 - \theta^NG) X_{kl} \left( \lambda_{NG}^{NGa} + \lambda_{NG}^{NGs} + \gamma^{NG} \left( \lambda_{Da}^{Da} + \lambda_{Ds}^{Ds} \right) \right) - NGa_{kl} \left( \lambda_{CT}^{CTa} + \lambda_{CT}^{CTs} + \left( 1 - \gamma^NG \right) \left( \lambda_{Da}^{Da} + \lambda_{Ds}^{Ds} \right) \right) \\
&+ \sigma_k^{Da} \omega^{D-NG} Da_{kl} + \left( 1 - \xi^{NG} \right) \sigma_k^{Da} \omega^{D-NG} Ds_{kl} - \left( \sigma_k^{NG} + \mu \right) NGa_{kl} \\
\frac{dNGs_{kl}}{dt} &= \theta^NG X_{kl} \left( \lambda_{NG}^{NGa} + \lambda_{NG}^{NGs} + \gamma^{NG} \left( \lambda_{Da}^{Da} + \lambda_{Ds}^{Ds} \right) \right) - NGs_{kl} \left( \lambda_{CT}^{CTa} + \lambda_{CT}^{CTs} + \left( 1 - \gamma^NG \right) \left( \lambda_{Da}^{Da} + \lambda_{Ds}^{Ds} \right) \right) \\
&+ \sigma_k^{Da} \omega^{D-NG} Da_{kl} + \left( 1 - \xi^{CT} \right) \sigma_k^{Da} \omega^{D-CT} Ds_{kl} - \left( \sigma_k^{NG} + \mu \right) NGs_{kl} \\
\frac{dCTa_{kl}}{dt} &= (1 - \theta^CT) X_{kl} \left( \lambda_{CT}^{CTa} + \lambda_{CT}^{CTs} + \gamma^{CT} \left( \lambda_{Da}^{Da} + \lambda_{Ds}^{Ds} \right) \right) - CTa_{kl} \left( \lambda_{NG}^{NGa} + \lambda_{NG}^{NGs} + \left( 1 - \gamma^CT \right) \left( \lambda_{Da}^{Da} + \lambda_{Ds}^{Ds} \right) \right) \\
&+ \sigma_k^{Da} \omega^{D-CT} Da_{kl} + \left( 1 - \xi^{CT} \right) \sigma_k^{Da} \omega^{D-CT} Ds_{kl} - \left( \sigma_k^{CT} + \mu \right) CTa_{kl} \\
\frac{dCTs_{kl}}{dt} &= \theta^CT X_{kl} \left( \lambda_{CT}^{CTa} + \lambda_{CT}^{CTs} + \gamma^{CT} \left( \lambda_{Da}^{Da} + \lambda_{Da}^{Da} \right) \right) - CTs_{kl} \left( \lambda_{NG}^{NGa} + \lambda_{NG}^{NGs} + \left( 1 - \gamma^CT \right) \left( \lambda_{Da}^{Da} + \lambda_{Da}^{Da} \right) \right) \\
&+ \sigma_k^{Da} \omega^{D-CT} Da_{kl} - \left( \sigma_k^{CT} + \mu \right) CTs_{kl} \\
\frac{dDa_{kl}}{dt} &= (1 - \theta^D) X_{kl} \left( \left( 1 - \gamma^NG - \gamma^CT \right) \left( \lambda_{Da}^{Da} + \lambda_{Da}^{Da} \right) \right) - \left( \sigma_k^{Da} + \mu \right) Da_{kl} \\
&+ \left( 1 - \gamma^D^{NGa} \right) \left( \lambda_{NG}^{NGa} + \lambda_{NG}^{NGs} + \left( 1 - \gamma^NG \right) \left( \lambda_{Da}^{Da} + \lambda_{Da}^{Da} \right) \right) \\
&+ \left( 1 - \gamma^D^{CTa} \right) \left( \lambda_{CT}^{CTa} + \lambda_{CT}^{CTs} + \left( 1 - \gamma^CT \right) \left( \lambda_{Da}^{Da} + \lambda_{Da}^{Da} \right) \right) \\
\frac{dDs_{kl}}{dt} &= \theta^D X_{kl} \left( \left( 1 - \gamma^NG - \gamma^CT \right) \left( \lambda_{Da}^{Da} + \lambda_{Da}^{Da} \right) \right) - \left( \sigma_k^{Da} + \mu \right) Ds_{kl} \\
&+ \left( \gamma^D^{NGa} \right) \left( \lambda_{NG}^{NGa} + \lambda_{NG}^{NGs} + \left( 1 - \gamma^NG \right) \left( \lambda_{Da}^{Da} + \lambda_{Da}^{Da} \right) \right) \\
&+ \left( \gamma^D^{CTa} \right) \left( \lambda_{CT}^{CTa} + \lambda_{CT}^{CTs} + \left( 1 - \gamma^CT \right) \left( \lambda_{Da}^{Da} + \lambda_{Da}^{Da} \right) \right)
\end{align*}
\]
Chapter 2 - Coinfection with gonorrhoea and chlamydia

$P_{lm}$ is a mixing matrix, whose elements $\rho_{klm}$ are the probability that an individual of sex $k$ in activity class $l$ will form a partnership with a member of activity class $m$ of the opposite sex. The value of $\rho_{klm}$ depends on the pattern of mixing and could vary from fully assortative, where partnerships only form within the same activity group to random, where partnerships form randomly between different activity classes.

$$\rho_{klm} = (1 - \varepsilon)\delta_{lm} + \varepsilon c_{lm} \frac{N_{lm}}{\sum_{a=1}^{N_c} N_{ku}}$$

$\delta_{lm} = 1$ when $l = m$ and $\delta_{lm} = 0$ when $l \neq m$.

It is necessary that the number of partnerships formed by sex $k$ match those of the other sex. For the sake of simplicity in these models both sexes are divided into classes of identical size and activity levels. The models were solved numerically using a standard fourth order Runge-Kutta method. Parameters used in the model are defined in Table 2.3.

**Results**

It was assumed that the only differences between gonorrhoea and chlamydia are in the duration of infection and the proportion of cases which become asymptomatic. The model was run under a variety of mixing patterns, which were varied from fully assortative (within activity class mixing only) to random (mixing proportional to the number of partnerships contributed by a class).

In the absence of additional interventions, the prevalence and incidence of chlamydia, gonorrhoea and coinfection varied with mixing pattern. One fifth (20%) of dual infections are transmitted together, although this was chosen arbitrarily in the absence of data. The change in incidence is shown in Figure 2.3. The highest incidence is observed when mixing is fully assortative (left hand column) and infection is very rapidly passed around the highest activity group, but the overall prevalence is low. As the mixing becomes more random the effective population size increases which is mirrored by a corresponding increase in the number of infections, but the infection also becomes more diffuse. A turning point is observed and at higher levels of mixing between groups, the incidence begins to drop again. The effect of mixing pattern on the observed incidence follows a curve with some optimal level of mixing for incidence. This optimum value depends also on the biological parameters of the organism and the relative size of each activity group and may fall anywhere on the continuum of mixing.
Chapter 2 - Coinfection with gonorrhoea and chlamydia

pattern (from assortative to random). The behaviour when mixing is fully assortative is a special case. One effect is that there may be two levels of mixing which produce the same combined incidence overall, however the pattern of coinfection will be different in each case. Coinfection is more frequent when mixing is relatively assortative and both infections are concentrated in a high activity part of the population. When mixing is close to assortative (like with like) 34% of those with gonorrhoea also have chlamydia, compared to proportionate (random) mixing, when 13% of those with gonorrhoea have chlamydia. Women with gonorrhoea are more likely to be coinfected than men, since women are more likely to be infected with chlamydia. The relative prevalence of the two infections is similar to that observed in the UK when mixing is slightly assortative.

Different activity groups experience varying burden of infection (Figure 2.4). As the mixing pattern becomes more assortative, sexually transmitted infections become concentrated in the highest activity group and may saturate the group, preventing increases in prevalence.

Impact of intervention strategies

The intervention strategies for the control of gonorrhoea and chlamydia examined in this chapter are:

Screening for chlamydia in women, men or both (5% coverage, 10 times per year)

Routine cotreatment of chlamydia in gonorrhoea patients

Under different mixing patterns, both screening and routine cotreatment of women and/or men reduce the prevalence of chlamydia (Figure 2.5). However, incident infections may actually increase due to replenishment and subsequent reinfection of susceptibles, especially when mixing is highly assortative due to the increased turnover of infections within the highest activity group. The impact of cotreatment on the prevalence of chlamydial infection declines over time, as coinfection decreases. As mixing becomes more random, screening is more effective, since it removes a certain proportion of the infected population at each time point, and reinfection is less rapid than when mixing is highly assortative.
Figure 2.3  Incident infections with chlamydia, gonorrhoea or both under different patterns of mixing (the infections are assumed to be independent but recovery from coinfection is faster than from a single infection)
Figure 2.4 Burden of disease by activity class under different mixing patterns (the number of cases contributed by each activity group is presented rather than the within group prevalence)

Activity class

Mixing close to random (\(\varepsilon = 0.8\))

Mixing somewhat assortative (\(\varepsilon = 0.4\))

Mixing mainly assortative (\(\varepsilon = 0.2\))

Mixing somewhat proportionate (\(\varepsilon = 0.6\))

GC
CT
Both

Incidence per 100,000

Annual incidence of infections per 100,000 population

Chapter 2 - Coinfection with gonorrhoea and chlamydia
Katherine Turner
Figure 2.5 Percentage change in prevalence of chlamydia seen under different control strategies and different patterns of mixing after 1 year

Cotreatment – coinfected women recover from both infections rather than one on treatment.

Screening – a percentage of those infected are identified at random and treated n times each year. (For whole population screening, 5% of those infected recover 10 times per year. When both males and females are screened the coverage is halved such that the total fraction of those infected who are screened and treated is kept constant)
Discussion

The model was used to investigate the patterns of infection with gonorrhoea, chlamydia and coinfection in a population stratified by gender and sexual activity. The mixing pattern between activity classes has a strong effect on the proportion of cases which are coinfections. When mixing is highly assortative, more people are infected with both bacteria than when mixing is more random. This is associated with increasing restriction of the infection to the highest activity group when mixing is highly assortative. Few dynamic models have attempted to parameterise the dynamic models for two infections. Interventions are shown to have different effects under different mixing patterns. In particular cotreatment is an effective strategy when coinfection is common and therefore a relatively high fraction of those people with chlamydia have gonorrhoea. In the USA, it was hoped that routine cotreatment could be monitored and relaxed when chlamydia prevalence declined due to screening programmes. However, Lyss et al, found a continuing high burden of chlamydia infection in patients diagnosed with gonorrhoea (Lyss, Kamb et al. 2003). This could be explained if chlamydia screening was systematically missing those at highest risk for STIs and particularly gonorrhoea, for example the poor, prison populations, sex workers or injection drug users. In this case one would expect that as screening continues to reduce the prevalence of chlamydia in the general population, the infection becomes more concentrated in high risk individuals who do not access screening and therefore the proportion coinfected remains high. This would imply that a combined approach is necessary: routine cotreatment of gonorrhoea patients who are likely to be at high risk even in the presence of good screening programmes, and screening of women and men to try to reduce the prevalence of the reservoir of asymptomatic infections.

The stability of the relative incidence between chlamydia and gonorrhoea in women supports the notion that differences in the natural history of the organisms largely dictate the observed epidemiology and that differences in the level of sexual activity determine the overall extent of both diseases, with chlamydia being able to penetrate a larger (and therefore lower activity) part of the sexual network. Differences in host characteristics can therefore be explained by the ability of chlamydia to colonise a larger proportion of hosts, including those with lower partner change rates, due to a longer duration of infection and higher proportion of asymptomatic infection.
The impact of an intervention in this model is sensitive to the mixing pattern assumed and also to the transmission dynamics of coinfection, but the relationship is not straightforward. Coinfections are concentrated in the highest activity individuals. Therefore, cotreatment may prevent proportionately more infections in this group than in the population as a whole. However, without screening or partner notification, treatment is restricted to infections that are symptomatic, consequently treatment is limited in its impact. Furthermore there is very rapid reinfection in the highest activity group which means that treatment in this group is more rapidly undermined than treatment of those with a lower risk. The assumptions made regarding the pattern of recovery from coinfection are important in the results presented.

**Future work**

Further sensitivity analyses are required using contact rates derived from national survey data to try to assess the relative quality of the parameter estimates for gonorrhoea and chlamydia. Different parameter combinations can produce the same prevalence or incidence within a model. Therefore further investigating and validation of methods for measuring the fit of theoretical mathematical models and testing hypotheses with an internal control could potentially be very useful. However, due to the uncertainty of the parameter estimates a more extensive sensitivity analysis should be undertaken to test a broader range of scenarios. Better data on the natural history of coinfection with gonorrhoea and chlamydia is needed.

Modelling of sexually transmitted diseases reported in the literature has been largely focused on single infections, most commonly gonorrhoea or HIV (Anderson, Gupta et al. 1991; Garnett and Anderson 1993a; Hethcote and Yorke 1984; Morris, Zavisca et al. 1995). This chapter shows how integrating data from both gonorrhoea and chlamydia into a single model framework is possible. Such a model may provide a useful tool for investigating the impact of different potential control strategies such as routine cotreatment that rely on the relative prevalence of each infection for their success. The parameters required for model such as the duration of coinfection and potential interactions between infections highlight areas where knowledge of the natural history of both gonorrhoea and chlamydia is lacking. The pattern of mixing between activity classes has a strong influence on the distribution of disease. For a particular population being simulated, the pattern of mixing which accurately represents their behaviour of should produce comparable prevalence and incidence estimates for gonorrhoea,
Chapter 2 - Coinfection with gonorrhoea and chlamydia

Parameter estimates for both infections can be tested within this framework.

By modelling both infections together it may be possible to extract additional information about both diseases. For example, if realistic prevalence and incidence of infection can be obtained for both diseases, then one may have greater confidence that the model is representative. This approach is not straightforward because introducing the complexity of a second disease means the introduction of additional parameters, in particular to represent any interactions during coinfection which may affect the transmission or duration of infection of either pathogen.

To what extent does the presence of both gonorrhoea and chlamydia predict that an individual of either gender is a transmitter? How much more likely are they to transmit at least one infection to a contact than someone with either infection singly? Identification of coinfectected individuals may represent a useful measure of current and future risk and an opportunity for prevention efforts. Such individuals are likely to have contacts who are infected with either or both infections and the case-finding rate is potentially higher than with single infections, increasing the cost effectiveness of contact tracing based interventions. Quantifying such epidemiological parameters should be the subject of future work.

Finally, the most valuable continuation of this work would be to use NATSAL 1990 and 2000 data to parameterise the model of gonorrhoea and chlamydia and model the behaviour change during that time period. The model generated prevalence and incidence could then be fitted to the time series data (1990-2000), allowing a closer analysis of the biological parameters, and determine the scenarios of behaviour which could explain the observed changes in STI epidemiology in the UK.
Chapter 3  Sexual mixing patterns and the distribution of gonorrhoea in different subpopulations

Summary

This chapter explores the impact of sexual mixing patterns and sexual behaviour on the distribution of sexually transmitted infections in a community with high levels of infection. Empirical data from two cross-sectional studies of gonorrhoea in a South East London population inform model structure and relate theoretical model findings to practical intervention strategies. The ethical and practical difficulties of using ethnicity as a measure of sexual behaviour are discussed in detail.

A simple deterministic, mathematical model of gonorrhoea transmission dynamics is used. This simulates a population stratified by gender, sexual activity (rate of partner change) and ethnic group (White, Black African and Black Caribbean). This model then provides the framework for investigating the impact of interventions. The literature on patterns of sexual mixing is reviewed, with particular emphasis on large studies of sexual behaviour and the results of other modelling approaches.

Reported behaviours and mixing patterns are sufficient to generate major differences in the incidence of gonorrhoea experienced by each subpopulation in model simulations, with the Black Caribbean population bearing the greatest burden of disease. A variety of parameters are varied systematically to find, using maximum likelihood methods, the best fit to the observed data.

The consistency between the model results and empirical data shows that large differences in gonorrhoea incidence between ethnic groups can be explained by modest differences in sexual behaviour and mixing patterns. Heterogeneity in sexual behaviour and partner choice interact through the dynamic feedback inherent in infectious disease epidemiology and cause large differences in disease incidence. Standard statistical methods exploring potential confounding variables such as socioeconomic status do not capture these dynamic effects.
Background

Mixing patterns and disease spread

To model the spread of an STI within a population, the pattern of choice of sexual partners must be understood. The way in which sexual partnerships form and dissolve is a determinant of an individual’s risk of disease, the pattern of mixing between groups and their consequent risk profile and describes the sexual network as a whole. One of the unanswered questions in sexually transmitted disease epidemiology is how best to characterise and describe the patterns of mixing within a population and how this relates to risk of infection for individuals, partnerships and the population.

Various characteristics of individuals are markers of differential risk of STIs, including age, ethnicity, sexual activity level, location of residence, drug use and sex work (CDC 2000b; Fenton, Korovessis et al. 2001; Hillis, Nakashima et al. 1994; HPA 2003a). These are therefore also the characteristics of epidemiological interest in determining the effect of mixing patterns on the epidemiology of STIs. Mixing within high risk groups provides a mechanism for the endemic maintenance of low prevalence infections such as gonorrhoea (Garnett and Anderson 1993a). Mixing between low and high risk groups has a strong influence on the overall distribution and prevalence of disease within a population and also on the potential impact of intervention strategies (Hethcote and Yorke 1984).

Describing mixing patterns

A key measure of mixing within populations is how likely individuals are to choose partners similar to, or different from themselves, according to a variety of measurable characteristics such as age, socioeconomic status, sexual activity, ethnicity or geographic location. This probability is defined by whether a sexual partnership is more or less likely than expected by random chance (in which mixing is simply proportionate to the number of partnerships contributed = group size * rate of partner change). Thus partnerships which form preferentially within a group are assortative (alternatively “like with like”, concordant or show “differential homophily”), whereas partnerships which form preferentially between different groups are disassortative (alternatively discordant). Random (proportionate) mixing occurs if the probability of partnership formation is the same as the proportion of partnerships contributed by that group (Anderson and May 1991).
In general most people choose their sex partners in an assortative manner i.e. young people mix with other young people, people choose partners who live near them and so forth (Johnson, Mercer et al. 2001; Johnson 1994; Laumann, Gagnon et al. 1994). However, evidence suggests that individuals with STI are more likely to form partnerships with people who differ from themselves, for example in age or social class, than those without STIs. It should also be noted that mixing patterns are not necessarily independent of group, so that a young female with a particular sexual partner change rate will not necessarily choose a partner in the same way as an older man with the same rate of partner change. This makes the formulation of mixing matrices for more stratified representations of populations increasingly difficult.

**Mixing patterns in people with STIs**

Directly measuring the pattern of mixing in a population is difficult, but efforts have been made to estimate parameters and validate models. Ideally information would be available from all partners in a network, but clearly this is difficult to achieve and the results from one setting cannot necessarily be applied in other settings. The results described below do indeed show different patterns in different settings. This emphasises the need for appropriate local knowledge when developing models in the process of formulating policy and making planning decisions. Ascertaining the difference between those with and those without STIs helps to understand the mechanisms for the spread of infection in a particular place.

**Interrelationship between determinants of mixing patterns**

Factors determining mixing patterns via partner choice are likely highly interrelated, making it difficult to analyse the influence of specific factors. Furthermore, the dynamics of infectious diseases are highly non-linear so even small differences in behaviour or choice of partner can be magnified into large differences in disease incidence, especially in small populations. A common theme of studies of individuals with STI and their patterns of partner choice or sexual mixing is the importance of discordant partnerships. In the USA, individuals with STI were likely to be involved in discordant partnerships (by a variety of criteria such as age, socioeconomic status, education etc) than those without STI (Aral, Garnett et al. 2000).

**Activity level**

The pattern of mixing between individuals with different rates of partner change can have a dramatic influence on the distribution of disease within a population and on the
Katherine Turner

Chapter 3 - Sexual mixing patterns and gonorrhoea overall prevalence of infection. Accurately determining the pattern of mixing between individuals of different activity levels is difficult to do on a large scale although methods such as snowball sampling could in theory be effective in obtaining network data on behaviour (Boily, Poulin et al. 2000; Ghani, Donnelly et al. 1998). Simply asking an index case about their partners’ behaviour is not satisfactory since an individual’s perception is a poor indicator of their partner’s behaviour and is not independent of disease status or index behaviour. Those with more partners are more likely to report that their partners have multiple partners (Aral, Garnett et al. 2000; Garnett, Hughes et al. 1996; Stoner, Whittington et al. 2003).

A variety of patterns of mixing by activity level have been observed in practice. Laumann and Youm investigated the pattern of mixing by activity levels and ethnicity in the USA, and suggested that African Americans, who had higher incidence of STIs, were more likely to form “core-periphery” (high-low activity) type partnerships than whites, who had lower incidence of STIs (Laumann and Youm 1999). Using partner notification, Ramstedt et al constructed mixing matrices for young heterosexual women, based on socioeconomic status and activity. They concluded that mixing was not random, the assumption of which would cause an overestimation of the spread of disease (Ramstedt, Giesecke et al. 1991). A study of MSM in Iceland found disassortative mixing by activity level, which would lead to larger epidemics, but slower initial growth of an epidemic (Haraldsdottir, Gupta et al. 1992).

Mathematical models can be used to estimate the likely pattern of mixing between different activity groups. Public health clinic attendees were interviewed in Seattle and their reported behaviour used to estimate the pattern of mixing by activity, which was found to be weakly assortative (Garnett, Hughes et al. 1996). In another study of gonorrhoea transmission in Newark, New Jersey, an almost random pattern of mixing by activity was initially inferred using a mathematical model (Garnett, Mertz et al. 1999). Several studies have looked at the impact of mixing patterns on the course of the HIV epidemic (Anderson, Gupta et al. 1990; Boily, Lowndes et al. 2002; Garnett and Anderson 1993b; Garnett and Anderson 1994b; Gupta, Anderson et al. 1989; Kault 1995; Sattenspiel, Koopman et al. 1990; Stigum, Falck et al. 1994). It has been demonstrated that assortative mixing by activity may lead to a more rapid initial growth but an ultimately restricted epidemic. However for HIV, which causes disease-induced mortality, the supply and demand of partnerships is unbalanced due to differential mortality by age, gender and activity. This needs to be accommodated in models
Chapter 3 - Sexual mixing patterns and gonorrhoea (Garnett and Anderson 1994b). A model which maintains consistency of partnership formation, to try to overcome this problem of partnership imbalance, shows that under certain conditions, bigger epidemics may be associated with increasingly assortative mixing (Kault 1995). This is not a consideration for uncomplicated gonorrhoea and chlamydia, since these do not cause excess mortality. A modelling study using the NATSAL 1990 data estimated the mixing matrix by activity level and provided some support for assortative mixing amongst the highest activity individuals (Renton, Whitaker et al. 1995).

Age mixing

One pattern of mixing by age which is well described occurs when younger women form partnerships with older men. In Africa men are on average 5-10 years older than their female partners and this pattern of mixing has been shown to influence the pattern of HIV infection, leading to more rapid rises in HIV incidence in young women (Garnett and Anderson 1994b; Gregson, Nyamukapa et al. 2002). Data from NATSAL 1990 suggests that a similar pattern occurs in the UK, but that the average age difference is 1.5 years (Nigel Gay, personal communication 2004). A similar influence on disease amongst young MSM was seen due to their forming partnerships with older MSM in San Francisco (Service and Blower 1996).

Geography

Following early work in Colorado Springs, which found that 51% of cases of gonorrhoea disease incidence occurred in 4 census tracts, Potterat called gonorrhoea a “social disease” and coined the term “socio-geographic” space to describe the geographic clustering of gonorrhoea (Potterat, Rothenberg et al. 1985). Similar studies in the UK found that 66.5% of gonorrhoea and 41% of chlamydia cases occurred in 8 adjacent wards in the city of Birmingham (Shahmanesh, Gayed et al. 2000). Geocoding or mapping infection has been a fertile topic of research recently, often using sophisticated mapping technology to show striking geographic and temporal trends in STI incidence (Krieger, Waterman et al. 2003; Law, Serre et al. 2003). The association between location and infection appears to be stable over time and provides a means of identifying “hotspots” which could be a target for interventions (Law, Serre et al. 2003). Most people tend to choose local partners. One estimate based on a survey in Baltimore, USA suggested that partners lived <100m away (Becker, Glass et al. 1998). Garnett and Anderson 1993 reviewed the degree of mixing between and within core and non-core partnerships...
Katherine Turner

Chapter 3 - Sexual mixing patterns and gonorrhoea
groups, based on the contact tracing and geographic  residence. They found a high
degree of mixing within core leading to within group transmission, which maintains
gonorrhoea in the population (Garnett and Anderson 1993a). Kerani and colleagues
define spatial bridgers as individuals with local and distant partners, although no
distinction was made between people who travelled to their partner or who had distant
partners travel to them (Kerani, Golden et al. 2003). Spatial bridgers were not typical
high risk individuals; they had higher socioeconomic status and were older than other
STI patients. Spatial bridgers therefore may be important especially in reintroducing
infection to low prevalence populations and undermining targeted local interventions
(Kerani, Golden et al. 2003).

Ethnicity

Ethnicity is an important factor in determining partner choice, and several studies have
demonstrated that individuals preferentially choose partners from the same ethnic
background (Aral, Hughes et al. 1999). Differences in disease incidence in ethnic
groups persist, even when other confounding factors are accounted for, such as access to
healthcare, behaviour, condom use or socioeconomic status. (Aral 2000) This may be in
part due to sexual segregation. In the USA black women were found to mix more
 assortatively with black men than their male partners, whereas white men were more
likely to have partners who are white women (Aral, Hughes et al. 1999). A similar
pattern is observed in the UK (Low, Sterne et al. 2001). People strongly select partners
 on the basis of country of birth and even more so if parental country of birth is factored
in (Barlow, Daker-White et al. 1997).

Implications of different mixing patterns for disease control and policy
decisions

Mixing patterns have important implications for control interventions. In a highly
assortative situation there is saturation of disease within the high activity class, so the
threshold for an intervention within that group to have an impact on disease incidence
may be higher than if mixing is random. Conversely, targeted interventions will be more
effective if mixing is highly assortative, since those STIs will be more highly
concentrated within the high risk group identified. Discordant partnerships represent
sexual bridges, which in turn facilitate the spread of infection from one group to another
(Anderson, May et al. 1991; Aral 2000). Two processes can therefore be identified:
mixing within groups (assortativity) and mixing between groups (disassortativity).
Individuals who form both types of partnerships act as functional bridges, linking groups with different risk characteristics and extending the population available for a bacterium to infect.

**Inequality in disease burden**

The population under study in this chapter has several characteristics associated with a high risk of gonorrhoea infection. They are young (16-24 years old) and live in an urban area with high levels of poverty and deprivation, and associated high unemployment and low educational achievement. Over a quarter of the population is composed of ethnic minority groups.

This uneven distribution of gonorrhoea is characteristic of the sexually transmitted infections. The overall prevalence in the UK and USA is low (although about 10 times higher in the USA), but this masks the much higher risks experienced by some groups (CDC 2000b; HPA 2003a). In both the UK and USA, gonorrhoea and chlamydia are more common amongst people from Black ethnic groups. These differences in STI incidence persist in statistical analyses even if socioeconomic status and behaviour are controlled for (CDC 2000b; HPA 2003a). Many studies of disease have described variations in prevalence or incidence in different ethnic groups, but have done little to explore the ultimate causes of the observed differences (Bhopal 1997).

UK studies in Leeds (Lacey, Merrick et al. 1997), Birmingham (Shahmanesh, Gayed et al. 2000), Coventry (Winter, Sriskandabalan et al. 2000) and London (Low, Daker-White et al. 1997) have shown higher incidence in Black ethnic groups compared to White or Asian groups for both gonorrhoea and chlamydia. Chlamydia appears to show less dramatic differences in incidence than gonorrhoea, which may be due to differences in prevalence. The difference in gonorrhoea incidence in urban areas in England is 10 to 20-fold between Black and White populations (Lacey, Merrick et al. 1997; Low, Daker-White et al. 1997) (Hickman, Judd et al. 1999). More detailed analyses showed that within the Black population, incidence of gonorrhoea among people from Black Caribbean backgrounds are higher than among Black Africans (Low, Sterne et al. 2001), with similar incidence in White and Asian populations.

In the United States as a whole, gonorrhoea incidence in 2000 were 30 times higher in non-Hispanic Blacks than in Whites (827 versus 28 cases per 100,000), despite 20 years of declining difference (CDC 2000b). A survey of US military recruits found that black women were over three times more likely to be infected with chlamydia than their white
counterparts, after controlling for state of origin, age and behaviour (Gaydos, Howell et al. 1998). In the USA, HIV is more common in African Americans, as is gonorrhoea. In the UK, HIV is more common in Black Africans, but gonorrhoea is less common than in Black Caribbeans (De Cock and Low 1997). Gonorrhoea is a co-factor for HIV transmission (CDC 2001). Therefore those groups with high gonorrhoea incidence are at increased risk of HIV, although the specific risk depends on the prevalence within the local network.

Socioeconomic status and education play an important role in determining an individual’s ability to choose safer behaviours or partners as well as their ability to seek and obtain appropriate care following infection. Sexually transmitted infections are associated with low socioeconomic status, unemployment and poor education, which can overall be considered a measure of “social capital” (Holtgrave and Crosby 2003). Black Caribbean and Black African populations (although there are important differences, e.g. Black Africans have more education and lower risk of gonorrhoea) in the UK and African Americans in the US experience higher levels of poverty and lower levels of education than their white counterparts (Pfeffer 1998). This may lead to a social context in which STIs thrive (Adimora and Schoenbach 2002). There is little or no evidence for differences between ethnic groups in biological susceptibility to infection, although it is possible that differences in the relative prevalence of other STIs such as HSV-2 or chancroid may modify this somewhat (Fleming, McQuillan et al. 1997). Population based studies in the US and UK have demonstrated that these groups remain sexually segregated (Laumann and Youm 1999) and others have shown that ethnic disparities in gonorrhoea incidence persist even after controlling statistically for measures of social and economic status (Ellen, Kohn et al. 1995; Hickman, Judd et al. 1999) and sexual behaviour (Ellen, Aral et al. 1998).

Other possible explanations for the observed differences in disease burden, include access to care, discrimination and age at sexual debut. Several authors have suggested that a major cause of the disparity is due to poorer access to care experienced by ethnic minorities with high disease incidence (Ellen, Aral et al. 1998; Moran, Aral et al. 1989). In the US there is differential use of public STD clinics, with black people more often attending public clinics, which report a higher proportion of cases and do more aetiological tests (Zenilman 2000). However in the UK health services are free to all. Discrimination and stigmatisation are also reasons why people from ethnic minorities may fear and distrust public health workers (Zenilman 2000). Other differences may
exist in sexual behaviour, such as age at sexual debut, which may modify the risk of different groups (Aral 2002b).

In recent years, attention has turned to network-based explanations, involving social context and mixing patterns (Aral 1999; Aral 2002b; Ghani, Swinton et al. 1997; Laumann and Youm 1999; Rothenberg, Sterk et al. 1998; Stoner, Whittington et al. 2000; Youm and Laumann 2002). An individual’s risk is determined by their sexual network, specifically the risk profile of their partner, in addition to their own individual characteristics. Sexual mixing patterns can act either to increase the risk of an individual by linking to a higher risk population or can protect a population from infection from external sources through sexual segregation (Aral 2000). High levels of undiagnosed asymptomatic infection within a segregated population could generate differences in incident infections (Winter, Sriskandabalan et al. 2000) and also in recurrent infections which have been found to be higher in ethnic minorities (Fortenberry, Brizendine et al. 1999). An important research question is therefore how much influence can mixing patterns within a specific network structure have on modifying an individuals risk of infection above and beyond their own risk factors?

**Is ethnicity a valid epidemiological measure?**

Using race or ethnicity as an indicator for health issues, in particular for such socially stigmatised diseases such as STIs, is a sensitive issue. The subject of ethnic differences in STIs is politically sensitive and has been the subject of considerable debate over how it should be treated. Some would argue that ethnicity is at best a meaningless categorisation or at worst, further discriminates against minority populations (Osborne and Feit 1992). Historically, differences in disease incidence have been recognised since the second world war, but research has been plagued by racism (De Cock and Low 1997; Zenilman 2000). Continuing inequality in health burden has lead to the UK government setting targets for improving the health of ethnic minorities (Adler 1997). To do this it is necessary to understand the proximate and ultimate causes of disease. Therefore Bhopal and others have called for a move from “black box” epidemiology, simply describing observed differences, to studies based on inequalities in care and provision of culturally sensitive, acceptable and accessible health care for all (Bhopal 1997).

A distinction should be drawn between ethnicity, which reflects social and ancestral identity and race, based on biological or genetic differences (Pfeffer 1998; Senior and
There are methodological concerns about using ethnicity in epidemiological research. What is the unit of measurement for ethnicity? Is it accurate and objective? The most objective approach is voluntary self-report. The groups included in surveys may contain heterogeneous populations which may obscure significant differences within a group. Most attention has been given to diseases which impose a greater burden on a minority group. This may be misleading, since not all minority groups are at equal risk, some have a lower risk and some a higher risk than the general population. The “majority” group may also incorporate other disadvantaged groups e.g. the Irish in the UK (Aral 2002b) and may be too broad to be meaningful (Pfeffer 1998).

Ethnicity can be an epidemiologically useful measure, but it must be used carefully (Aral 2002b; Bhopal 1997; Zenilman, Shahmanesh et al. 2001). Recommendations and actions taken as a result should be sensitive to social and cultural setting (Fenton, Johnson et al. 1997). Bhopal recommends that assumptions should be made fully explicit, the characteristics explored should be relevant to health, such as lifestyle, and differences observed should be used to generate testable causal hypotheses applicable to planning and delivery of healthcare (Bhopal 1997).

In the study in South East London, Low et al distinguish specific ethnic groups and show that simply combining minority groups for convenience or to make statistically significant sample sizes is inadequate (Low, Daker-White et al. 1997). This may mask even greater differences in disease incidence or different causal factors for similar incidence of disease. The surveys of the population used voluntary self-assessment (Low, Sterne et al. 2002). Despite the many demonstrations of ethnic differences in STIs, few attempts have been made to quantify the effects of mixing patterns, with mathematical models, parameterised by empirical data (Morris 1995).

It is clear that many factors contribute to the variability in disease distribution across the total population, many of which are highly interrelated, making interpretation of observed data difficult. The effects of different indicators of risk may not simply add to increasing risk of disease; instead the risk to an individual or population is highly non-linear as factors combine.

**Objectives**
The objectives of the study described in this chapter are to define the extent to which sexual mixing patterns by ethnicity and rates of partner change affect gonorrhoea incidence, and to assess how preventive interventions might affect the endemic prevalence of disease. Empirical data were used from observational studies in South East London, which has a high proportion of black Caribbean and African residents and where gonorrhoea incidence is six to seven times higher than the national average (Low, Daker-White et al. 1997). This data was used, together with extensive investigation of model outputs under different parameter value combinations, to choose the most appropriate parameters for a simple deterministic model of gonorrhoea transmission in young people.

In a modelling framework it is possible to vary individual parameters systematically and analyse the relative importance of different variables. After validating the mathematical model by comparing the outputs with observed incidence of disease, the impact of different intervention strategies in this simulated population are explored.

**Method**

**Sources of data on sexual behaviour**

The data were obtained from a population-based cross-sectional survey of 16 to 25 year olds from three ethnic groups in the former Lambeth, Southwark and Lewisham Health Authority area in South East London. Here incidence of gonorrhoea is six to seven times higher than the national average (Low, Daker-White et al. 1997; Low, Sterne et al. 2001), as illustrated in Figure 3.1. These data were used to parameterise a simple deterministic model of gonorrhoea transmission to better define the extent to which observed mixing patterns by ethnicity might affect STI incidence and to assess how interventions focused on specific ethnic groups might affect the endemic prevalence of disease. The study area comprised the quintile of electoral wards with the highest gonorrhoea incidence, which formed a contiguous area in the west of the health authority (Low, Sterne et al. 2001). The survey was adapted from the National Survey of Sexual Attitudes and Lifestyles 2000 (Johnson, Mercer et al. 2001) and included 469 participants (a response rate of 58%).
Mixing patterns

Mixing by ethnicity

Mixing matrices were constructed to show partner choice by ethnic group for heterosexual men and women from White, Black Caribbean and Black African ethnic groups. These are shown in Table 3.1 and were constructed from a question regarding the ethnicity of the last partner. Additional information could have been obtained about the variance in partner choice if additional information is used from details about the ethnicity of previous partners, but these questions were not fully completed.

Mixing by activity and calculation of partner change rate

Heterogeneity in rates of sexual partner change is crucial in determining the persistence of sexually transmitted diseases. As in the NATSAL survey, the distribution in behaviour was highly skewed, with most reporting few partners and a few reporting many partners (Johnson 1994; Low, Sterne et al. 2002). The behavioural data from South East London were used to calculate rates of partner change for each individual, illustrated in Figure 3.2. Table 3.2 shows summary measures of sexual activity for the study population. The variance in the average number of partners per year for Black Caribbean men and women was greater than for the other ethnic groups even though the median numbers of partners per year were similar.

The study population was stratified by sexual activity to provide a basis for the activity of the theoretical model populations. There is no standard way in modelling to stratify the population according to risk behaviour. Therefore an objective, but arbitrary division was used, where each of the four groups contribute the same total number of partnerships (25%). The total number of partnerships formed per year across the whole population was calculated using the following formula:

\[
\frac{\text{Total number of lifetime partners}}{(\text{Age now} - \text{age at first sex})}
\]

The total population was sorted by rates of partner change and assigned to an activity class accordingly. The highest activity class, 1, represented the lowest proportion of the population (4.6%) and the lowest activity class, 4, has the highest proportion (70.9%), with the intermediate classes (2 and 3) making up 8.7% and 15.8% of the population, respectively. These proportions were applied to each of 6 subgroups stratified by gender (male and female) and ethnic group (white, black Caribbean and black African). A group specific average rate of partner change was then calculated for each, giving a total
Chapter 3 - Sexual mixing patterns and gonorrhoea

of 24 subgroups (2 genders x 3 ethnic groups x 4 activity levels) with differing rates of partner change (Table 3.3).

In a closed population the numbers of partnerships formed by men and women must be equal. As has been found in many other studies (Johnson 1994; Wadsworth, Wellings et al. 1993), a discrepancy existed between the total number of partnerships reported by men and women, with men reporting approximately 1.5 times as many partners as women. A parameter ($\nu$) was defined to control the extent that female rates of partner change are increased and male rates of partner change decreased so that the number of partnerships contributed by each sex balance. The outcome of balancing partnerships is complicated by this. In models of interacting populations, where partner numbers have to balance, the impact on adjusted contact matrices can be quite large, particularly in small populations.
**Figure 3.1** Rates of gonorrhoea in South East London in different ethnic groups

Key
- W - White
- BC - Black Caribbean
- BA - Black African
- BO - Black other
- A - Asian

Table 3.1  Mixing matrix. Probabilities of sexual partner choice, by sex and ethnicity

<table>
<thead>
<tr>
<th>Partner ethnicity</th>
<th>Male respondent</th>
<th>Female respondent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black Caribbean</td>
<td>Black African</td>
</tr>
<tr>
<td>Black Caribbean</td>
<td>0.63</td>
<td>0.34</td>
</tr>
<tr>
<td>Black African</td>
<td>0.06</td>
<td>0.43</td>
</tr>
<tr>
<td>White</td>
<td>0.31</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* Due to the small sample size of white men, there were no reported contacts with black women, which resulted in inconsistencies and an undefined probability of mixing between white men and black women, so a small probability was assigned to white males mixing with black females.

Table 3.2 Reported rates of partner change and numbers of lifetime partners of 16-25 year olds in South East London

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Partners per year, mean)</td>
<td>(Partners per year, mean)</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(range)</td>
</tr>
<tr>
<td>N=105</td>
<td>2.2 (0-5)</td>
<td>1.4 (0-4)</td>
</tr>
<tr>
<td>Black Caribbean</td>
<td>N=75</td>
<td>N=117</td>
</tr>
<tr>
<td>Black African</td>
<td>1.0 (0-5)</td>
<td>0.8 (0-8.3)</td>
</tr>
<tr>
<td>White</td>
<td>1.4 (0-5)</td>
<td>1.1 (0-8.3)</td>
</tr>
<tr>
<td>Black Caribbean</td>
<td>N=117</td>
<td>N=89</td>
</tr>
<tr>
<td>Black African</td>
<td>1.3 (2-6)</td>
<td>0.7 (1-0)</td>
</tr>
<tr>
<td>White</td>
<td>1.0 (0-5)</td>
<td>0.3 (0-4)</td>
</tr>
<tr>
<td>Black Caribbean</td>
<td>N=49</td>
<td>N=47</td>
</tr>
<tr>
<td>Black African</td>
<td>1.2 (2-6)</td>
<td>0.7 (1-0)</td>
</tr>
<tr>
<td>White</td>
<td>1.3 (2-6)</td>
<td>0.7 (1-0)</td>
</tr>
</tbody>
</table>

Figure 3.2  Rates of partner change calculated from reported data

### Table 3.3 Average rates of partner change per year of four activity classes calculated from sexual behaviour survey

<table>
<thead>
<tr>
<th>Activity class</th>
<th>% of population</th>
<th>Mean rate of partner change (sd)</th>
<th>Index Male</th>
<th>Index Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Black Caribbean</td>
<td>Black African</td>
</tr>
<tr>
<td>1 (High)</td>
<td>4.6</td>
<td>7.5 (1.7)</td>
<td>9.9 (1.8)</td>
<td>7.3 (1.2)</td>
</tr>
<tr>
<td>2</td>
<td>8.7</td>
<td>3.9 (0.8)</td>
<td>6.7 (0.9)</td>
<td>4.5 (0.8)</td>
</tr>
<tr>
<td>3</td>
<td>15.8</td>
<td>2.2 (0.4)</td>
<td>3.8 (0.8)</td>
<td>2.3 (0.4)</td>
</tr>
<tr>
<td>4 (Low)</td>
<td>70.9</td>
<td>0.5 (0.5)</td>
<td>1.0 (0.8)</td>
<td>0.5 (0.6)</td>
</tr>
</tbody>
</table>

Notes: Rate of partner change calculated as the reported number of lifetime partners divided by the number of years since sexual debut. Those in their first year of sexual activity were assumed to have been sexually active for 6 months. Activity classes formed by splitting total number of partnerships formed into quartiles. % of population shows the proportion of population in each activity class. Due to the small sample size, a single individual (black African male) with very high rates of partner change (17.5 partners per year, compared with the next highest in his group of 8.5 partners per year) had a disproportionate effect on the diagnoses of infection predicted by the model. Recalculation of partner change rates excluding this individual generated incidence very close to those observed, so the rates excluding this individual were used in further analyses.

Gonorrhoea diagnoses

Data from previously published studies (Low, Daker-White et al. 1997; Low, Sterne et al. 2001) were used to calculate the rate of gonorrhoea in the study area for the age group 16 to 25 years in each ethnic group. Census data was used to estimate the population size. Figure 3.1 illustrates the diagnoses of gonorrhoea reported in South East London in 1997.

Estimation of model parameters

The estimation of the remaining parameters was largely informed by previous work on the transmission of gonorrhoea by Garnett et al in Newark New Jersey (Table 3.4) (Garnett, Mertz et al. 1999). The duration of infection was varied between 2 weeks and 6 months for men and 1 month and 12 months women. Recovery rates were assumed to be identical for each ethnic group, as there is no evidence to suggest any biological differences. In practice, however there may be differences in treatment seeking behaviour and access to care.

It is widely agreed that transmission of gonococci is less efficient from female to male, than vice versa, but the exact probabilities are not well established (Garnett, Mertz et al. 1999). The transmission probability per sexual partnership was varied between 0.4 and 0.6 for transmission from males to females and between 0.3 and 0.5 for transmission from females to males (Garnett, Mertz et al. 1999; Hook and Handsfield 1999). The exact values used for transmission and duration will affect the absolute magnitude of the epidemic but, since they are identical for the different ethnicities, the relative distribution of disease by ethnicity will not be altered.

The rate of entry and exit into the population was determined by the average length of time that individuals remain in the model population, i.e. 10 years (from 15-24 years), giving an entry/exit rate to/from the sexually active population of 0.1 per year.

Mathematical model

Deterministic models must explicitly describe the probability of forming partnerships between groups and must balance partnership formation exactly. Network models deal implicitly with the problem of balancing partnerships, but the need to use algorithms to sensibly describe partner choice remains.

A simple deterministic model of gonorrhoea was developed, based on previous work (Anderson and May 1991; Garnett, Mertz et al. 1999; Hethcote and Yorke 1984; Turner
Chapter 3 - Sexual mixing patterns and gonorrhoea and Garnett 2002). The model represents an exclusively heterosexual population aged 16 to 25 years stratified according to gender, sexual activity (based on rate of partner change) and ethnicity. The model population was closed, assuming that all sexual contacts were chosen from within the specified age class and the study area where the survey was conducted. The mathematical equations describing the model are given below, along with further definitions of the parameters.

Mixing matrices were used to describe the distribution of contacts of individuals of a particular activity class and ethnic group with individuals of the opposite sex according to ethnic groups and activity classes. An alternative method of describing the mixing pattern uses a single parameter to define the probabilities for each element of the mixing matrix, with reference to that predicted by random mixing. This parameter can vary the pattern of mixing from random to assortative.

A quantitative measure of the pattern of mixing according to sexual activity group ($\varepsilon_2$) was defined. This measure can be varied from random mixing ($\varepsilon_2 = 1$), in which activity classes form partnerships at random based on numbers of partnerships supplied by the group, to assortative ($\varepsilon_2 = 0$), in which individuals in a particular activity class only mix with individuals from the corresponding class of the opposite sex (although the partner may be of a different ethnicity). The value of this parameter has a significant effect on the epidemiology of gonorrhoea in the model. A range of values was used to assess the robustness of the results to the assumptions made.
### Table 3.4 Parameter definitions used in model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Range of values used</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>Entry rate. To maintain a constant population size, the entry and exit rates are assumed to be equal.</td>
<td>0.1 per year (average length of stay in model population 10 years)</td>
</tr>
<tr>
<td>$\beta_k$</td>
<td>Transmission probability of infection to sex $k$</td>
<td>Best fit 0.4 (female to male) Best fit 0.6 (male to female)</td>
</tr>
<tr>
<td>$\delta_k$</td>
<td>Recovery rate from infection</td>
<td>Best fit for male and female 2 months duration (recovery rate, 6 per year)</td>
</tr>
<tr>
<td>$\rho_{klmst}$</td>
<td>Mixing matrix, element $klmst$ is probability that, individual of sex $k$ in activity class $l$, ethnicity $s$, when they form a partnership, it will be with a member of activity class $m$ and ethnicity $t$, of the opposite sex, $k'$.</td>
<td>See below</td>
</tr>
<tr>
<td>$c_{kl}$</td>
<td>Partnership formation rate of individual of sex $k$, activity class $l$, ethnicity $s$ (see below)</td>
<td>See below Calculated from Table 3.3</td>
</tr>
<tr>
<td>$\varepsilon_1, \varepsilon_2$</td>
<td>Pattern of mixing: $\varepsilon_1$ by ethnicity; $\varepsilon_2$ by activity. (0=fully assortative, 1= random)</td>
<td>Mixing according to activity varied from $0 \leq \varepsilon_2 \leq 1$ Ethnicity mixing defined explicitly from reported behaviour – choice of last partner</td>
</tr>
</tbody>
</table>
Model details

A deterministic, compartmental model of a bacterial STI, in a population stratified by sex, activity class (4) and ethnicity (3) was used.

Subscripts $k$, $l$ and $s$ refer to sex, activity class and ethnicity, respectively. In the case of sex, $k=0$ for men, $k=1$ for women while $k'$ refers to the opposite sex to $k$ and for activity $l$ defines the class (from 1 to 4), according to average rate of partner change per year, $c_{kls}$. Ethnicity $s$ defines the group (1 to 3) that an individual falls into. The letters $m$ and $t$ define the activity class and ethnicity, respectively of an individual of the opposite sex ($k'$) with whom a partnership is formed. The subscripts stratify the state variables, which are as follows:

- $X_{kls}$ - population of susceptibles of sex $k$, activity class $l$ and ethnicity $s$
- $Y_{kls}$ - population of hosts infected of sex $k$, activity class $l$ and ethnicity $s$.

The ordinary differential equations which define the model are:

$$\dot{X}_{kls} = \mu N_{kls} - \lambda_{kls} X_{kls} + \delta_k Y_{kls} - \mu X_{kls}$$  \hspace{1cm} (1)

$$\dot{Y}_{kls} = \lambda_{kls} X_{kls} - \delta_k Y_{kls} - \mu Y_{kls}$$  \hspace{1cm} (2)

The force of infection, $\lambda_{kls}$, the group specific incidence per susceptible, can be calculated from the transmission probability, $\beta_k$; contact rate, $c_{kls}$; the proportion of infected individuals and the mixing pattern $\rho_{klmst}$ as follows:

$$\lambda_{kls} = c_{kls} \beta_k \sum_{t=1}^{4} \sum_{m=1}^{4} \rho_{klmst} \left( \frac{Y_{kms}}{N_{kms}} \right)$$  \hspace{1cm} (3)

Other parameters used in the model are defined in Table 3.4. The average rate of partner change for each group is determined by the reported sexual activity levels obtained from the sexual behaviour survey (Table 3.3).

The mixing matrix $P$ has to take account of both ethnicity and activity, which complicates the calculation. $\rho_{klmst}$ is an element of $P$, which defines the probability that, when an individual of sex $k$ in activity class $l$ and ethnic group $s$, forms a partnership, it will be with a member of activity class $m$, ethnicity $t$ of the opposite sex, $k'$. The values of $\rho_{klmst}$ depend on the overall pattern of mixing and can vary from fully assortative, to proportionate for both ethnicity ($\epsilon_1$) and activity ($\epsilon_2$).
Chapter 3 - Sexual mixing patterns and gonorrhoea

The following equations describe the elements of the mixing matrix in this model in the absence of external information:

\[
\rho_{klms} = \left( \frac{\sum_{u=1}^{4} N_{k'ut} c_{k'ut}}{\sum_{v=1}^{4} \sum_{w=1}^{4} N_{k'ut} c_{k'ut}} \right) + \left( 1 - \varepsilon_1 \right) \delta_{st} + \left( 1 - \varepsilon_2 \right) \delta_{ln} \]

Where \( \delta_{st} \) and \( \delta_{ln} \) are identity matrices, such that \( \delta_{ij} = 1 \) when \( i=j \) and \( \delta_{ij} = 0 \) when \( i \neq j \). \( \varepsilon_1 \) is the degree of assortativity by ethnicity and \( \varepsilon_2 \) is the degree of assortativity by activity class (for fully assortative mixing, \( \varepsilon_1 = 0 \); for random mixing, \( \varepsilon_1 = 1 \)).

If any of the mixing patterns are known or can be estimated from data, the equations above can be simplified accordingly. A mixing matrix \( M_{kls} \) was estimated from the behavioural data (NCSR 2001), which defines the probability that a person of sex \( k \), ethnicity \( s \) will choose a partner of ethnicity \( t \). This was then input directly into the equation to calculate the overall mixing matrix:

\[
\rho_{klms} = M_{kst} \left( \frac{N_{k'ut} c_{k'ut}}{\sum_{u=1}^{4} N_{k'ut} c_{k'ut}} \right) + \left( 1 - \varepsilon_2 \right) \delta_{ln} \]

5.

Model constraints: Balancing the numbers of sexual partnerships in the model population

In common with other behavioural surveys, the numbers of partnerships reported by heterosexual men exceed that reported by women in South East London (by about 1.5 times) (see Table 3.2). In a mathematical model of a closed population, it is necessary that the number of partnerships formed by sex \( k \) exactly match those of the other sex. Various constraints apply to ensure that the total number of partnerships between males and females in this closed population balance (Garnett and Anderson 1993b). There are various methods for balancing partnerships, as described elsewhere (Garnett and Anderson 1994a; Uche and Anderson 1996). For this fairly straightforward case, where there is no disease-induced mortality and the population falls within one age group (hence no significant sex difference in the average age of partner), several conditions are imposed by the model formulation to ensure that the numbers of partnerships formed by men and women in reciprocal groups are equal. Parameters are explicitly defined for both sexes, which enables the calculation of both of the mixing matrices.
The total numbers of partnership formed by one sex must equal those formed by the other, i.e.

$$\rho_{kmls} c_{kl} N_{kl} = \rho_{k'l'm's'} c_{k'nl} N_{k'n'l}$$  \hspace{1cm} \text{(6)}$$

However, this may not hold true when empirical data are used to estimate the matrices. Therefore the discrepancy between the reported number of partnerships reported by men and women is calculated.

The term for this discrepancy, $B_{lmst}$ is defined as:

$$B_{lmst} = \frac{\rho_{kmls} c_{knl} N_{knl}}{\rho_{kmls} c_{kl} N_{kl}}$$  \hspace{1cm} \text{(7)}$$

(If the numbers of partnerships balanced, each element of B would equal unity.)

A parameter $\nu$ is defined, which determines how each sex varies its activity levels to balance the total number of partnerships. If $\nu$=0, sex k doesn’t change and k’ is forced to change activity levels and vice versa if $\nu$=1. For $\nu$=0.5, both sexes adjust equally. This then allows the adjusted contact rates for each sex to be calculated, such that the adjusted contact rate, $c_{klmst}$ is:

$$c^{*}_{klmst} = c_{kl} B_{lmst}^{\nu}$$  \hspace{1cm} \text{(8)}$$

and for the opposite sex, k’:

$$c^{*}_{k'l'm's'} = c_{k'nl} B_{lmst}^{-(1-\nu)}$$  \hspace{1cm} \text{(9)}$$

These adjusted values are then used in the model to define the contact rates for each sex which are used to determine the force of infection.

This process was done twice, with male and then female reported behaviour used as the denominator in Equation 7. Since the size of the population and reported rate of partner change were different by gender and the balancing uses exponents rather than linear change, the adjusted contact rate matrices are slightly different.

The model was developed to allow the introduction of various treatment or intervention strategies during the simulation. These could be targeted at specific groups or cover the whole population. For an intervention to have an effect on incidence of infection it must act to reduce the actual or effective reproductive number of infection by decreasing the transmission probability, $\beta$ (e.g. using condoms), decreasing the contact rate, c, (e.g. changing sexual behaviour), or decreasing the duration $D$, of infection (e.g. screening...
Chapter 3 - Sexual mixing patterns and gonorrhoea programmes, treatment of infection or contact tracing). Initially the impacts of interventions such as improved access to care, recognition of symptoms or risk behaviours, and screening, all of which decrease the duration of infection were investigated. The impacts of these interventions were investigated, both for a population-wide approach and high-risk approach, targeted to Black Caribbean males, females or both. An assumption was made that the interventions resulted in a decreased duration of infection of 40% in those targeted and that coverage of 25% of the target population was achieved.

**Fitting the model**

The output from the model was compared with the observed incidence data, to obtain best fit estimates for these three parameters. Maximum likelihood analysis was used to quantify the fit of the model output to data and determine 95% confidence intervals. Incidence is binomially distributed (individuals either get infected or not during the year). The equation for the likelihood (Edwards 1972) is:

\[
L = \binom{n}{x} p^x (1-p)^{n-x} \]

which gives a log likelihood of:

\[
\ln L = \ln \binom{n}{x} + x \ln p + (n-x) \ln(1-p) \]

where \(n\) is the population, \(x\) is the number of cases observed per year and \(p\) is the model probability of infection per year (incidence).

A multivariate analysis was conducted by a systematic search of the parameter space to examine the effects of the parameter values on the model fit (the maximum likelihood was assessed by minimising: \((-2)*\ln L\) ). The following variables were varied whilst holding the other variables constant: transmission probability (from 0.4 to 0.6 for male to female transmission and from 0.3 to 0.5 for female to male transmission (Hook and Handsfield 1999)), duration of infectiousness (one to 10 months for men and two to 12 months for women (Garnett, Mertz et al. 1999; Hook and Handsfield 1999)).

For several parameters there were no estimates which could be made, either from the data or from published literature. The pattern of mixing by activity class (\(\varepsilon_2\)), the degree to which males and females change rate of partner change to accommodate the reported behaviour of the opposite sex (\(\nu\)) and the proportion of female cases of gonorrhoea not
Chapter 3 - Sexual mixing patterns and gonorrhoea

reported (α) were all unknown. It is believed that, due to the high frequency of asymptomatic infection in females, that many cases remain unreported. Estimating the extent of this underreporting is therefore of interest. It is assumed that male cases are a more accurate reflection of incidence, therefore diagnoses of males are used to fit model incidence to. The values of ε2, ν and α were varied systematically. The pattern of mixing by activity group, ε2 was varied from 0 to 1, in steps of 0.1, from random to assortative. Balancing partnerships, ν was varied from 0 to 1, in steps of 0.1, from assuming male reporting is accurate and increasing female partner change rates to balance, to the reciprocal situation. Finally the proportion of female cases which are reported α, was varied from 100% to 50%, in steps of 10%, assuming 100% reporting to 50% reporting of female cases.

Table 3.5 summarises the parameter combinations examined. A total of just over 1 million parameter combinations were examined. The best fitting model provided the most likely values of these parameters, although there is a high degree of covariance in the combinations which gave fits close to the best fit due to the effect on prevalence and incidence. For example when the balancing parameter changes the average contact rate changes (when the male reported contact rate is favoured the average rate of partner change increases) and hence the incidence changes correspondingly. Similarly, the mixing pattern affected the incidence and prevalence. These effects meant that as one parameter changes towards increasing incidence, the best fit occurs when another favours a reduction in incidence.
**Table 3.5 Parameter combinations tested for maximum likelihood analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values (displayed in order from lowest $R_0$ to highest)</th>
<th>Best fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration in men ($\delta$)</td>
<td>0.5, 1, 2, 3, 4, 6 months</td>
<td>2 months</td>
</tr>
<tr>
<td>Duration in women ($\delta$)</td>
<td>1, 2, 4, 6, 8, 12 months</td>
<td>2 months</td>
</tr>
<tr>
<td>Transmission from men to women ($\beta$)</td>
<td>0.4, 0.45, 0.5, 0.55, 0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Transmission from women to men ($\beta$)</td>
<td>0.3 0.35, 0.4, 0.45, 0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Mixing by activity ($\varepsilon_2$)</td>
<td>0.001, 0.1, 0.2, 0.3….,0.9, 1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Balancing partnerships (starting from matching to male reporting behaviour, $\nu=0$, male denominator in Equation 7)</td>
<td>0, 0.1, 0.2…..0.9, 1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Balancing partnerships (starting from matching to male reporting behaviour, $\nu=1$, female denominator in Equation 7)</td>
<td>1.0, 0.9……..0.1, 0.0</td>
<td></td>
</tr>
<tr>
<td>Underreporting of female cases ($\alpha$)</td>
<td>50%, 40%, 30%, 20%, 10%, 0%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Results

The model predictions were compared with observed diagnoses of gonorrhoea in the population of 15-24 year olds in South East London (Low, Daker-White et al. 1997; Low, Sterne et al. 2001). Model outcomes were qualitatively very similar to each other, with higher incidence in Black Caribbean and lower incidence in White and Black African groups. This result was robust across a wide range of parameters. The best fit scenario is illustrated by sex and ethnic group in Figure 3.3, together with the observed incidence of gonorrhoea in the study population and 95% confidence intervals, calculated as points. The left-hand column (of each set) shows the observed diagnoses of gonorrhoea and the right-hand column shows the model output for the best fitting set of parameters. The incidence predicted by the model for White and Black African groups were higher than those observed.

Also in the best fitting scenario, mixing by activity class was assortative and balancing sexual partnerships was intermediate between male and female reported behaviour. The overall best fit was obtained when partnerships were adjusted with a bias towards male reported behaviour, when mixing was close to assortative and when 80% of female cases of gonorrhoea are reported. The parameter combination which gave the minimum likelihood was used to investigate the outcome of intervention strategies.

Figure 3.4 shows the likelihood profiles for each parameter (where the lower values indicate a better fit), with the likelihood for each value of the parameter in question minimised across all other parameters (including using male or female as the denominator in equation 7). The method for balancing partners can give slightly different results when males or females are taken as the denominator (see Equation 7) and the discrepancy in behaviour calculated. This is because there are slightly different proportions of men and women in the different ethnic groups, who report different numbers of partners. Both alternatives were investigated to test for equivalence in the method of balancing partners. The horizontal line on each graph indicates points within the 95% confidence interval (assuming a $\chi^2$ distribution with 1 degree of freedom).

The scenarios which gave the best fit to model data also produced model prevalence close to the limit of persistence, which fits with previous estimates of the $R_0$ of gonorrhoea as being close to 1 and only above 1 in high activity groups (Brunham, Nagelkerke et al. 1994; Hethcote and Yorke 1984). There is also covariance of the parameters controlling the mixing by activity and how partnerships are balanced, shown
Chapter 3 - Sexual mixing patterns and gonorrhoea

diagrammatically in Figure 3.5. As balancing sexual partnerships tends towards male
testing, the average contact rate of the population increases and consequently the
prevalence of infection increases. As mixing by activity becomes more random,
partnership formation has to be biased towards that reported by males to produce
incidence closest to that observed. These two measures are closely correlated.
Depending on the values of the other parameters chosen which control R0, i.e. duration
of infection and transmission probability, the combination of mixing and balancing
varies and the prevalence corresponding to the best fit incidence also varies.

“Differential homophily”, i.e. the degree of preference for partners similar to oneself, is
shown by both sexes of different ethnic groups in the study population. Table 3.6 shows
the degree of differential homophily, i.e. the ratio between the numbers of reported
partners of different ethnic groups and the expected partnerships if mixing was both
proportional to numbers of partnerships contributed by each group. Black Caribbean
and Black African women were more likely to form partnerships with those of the same
ethnic group than their male counterparts. For white women, the pattern was closer to
random mixing than for white men.

Impact of intervention

Having established that the model produces results consistent with the observed data,
the impact of different intervention strategies was investigated. The total prevalence of
disease predicted by the models is close to the limit of persistence, i.e. the reproductive
number is close to unity. The parameters obtained from the sensitivity analysis as
providing the closest fit were used for modelling interventions. Each strategy was
assumed to achieve 25% coverage in the target population, and cause a decrease of 40%
in the duration of infection. The results are illustrated in Figure 3.6.

Unsurprisingly, the strategies that affect the whole population have the greatest impact
on incidence. Implementing screening, thus reducing duration of infection, caused a
reduction of 45% in annual incidence a year after the intervention is introduced.
However, reaching the entire population is expensive, inefficient and difficult. By
targeting the population at highest risk however i.e. Black Caribbeans (about 20% of the
total population in this community), the total incidence can still be reduced by 35%.
Even if only one sex is targeted, significant reductions in incidence can be achieved, e.g.
decreasing the duration of infection in females reduces the overall incidence by 20%.
To evaluate the relative impact of the different interventions simulated, the number of individuals needed to treat (intervene in) in order to prevent one case of gonorrhoea was calculated for the different scenarios; interventions in the whole population or targeted interventions in the highest risk groups. The number needed to treat is shown in Figure 3.7. Screening the whole population is much less effective than targeting the group (i.e. Black women) most at risk.
Figure 3.3  Model predictions compared with observed diagnoses of gonorrhoea

Notes: Model output with the best fit to the observed data, using maximum likelihood methods. Estimated parameter values: transmission probability higher from male to female (0.6) than from female to male (0.4), duration of infection 2 months in males and females, 20% underreporting in females, close to assortative mixing (by activity) ($\epsilon_2$ =0.2) and partnerships balanced towards those reported by men ($v=0.2$).
Figure 3.4  Likelihood profiles from maximum likelihood analysis for unknown parameters

Panel a) Mixing by sexual activity class

Panel b) Balance between number of partnerships reported by men and women

Panel c) Underreporting of female infections

Panel a) mixing by level of sexual activity: varies from $\varepsilon_2=0$, assortative to $\varepsilon_2=1$, random. Panel b) balance between number of sexual partners per year reported by men and women: varies from $v=0$, male rate remains unchanged to $v=1$, male rate changes to balance that of women. Panel c) degree of underreporting of female cases: varies from 0%, all female cases reported to 50%, half of female cases not reported.

The dotted line is the best fit maximum likelihood value + 3.814. Points below the line are statistically equivalent fits to the data, points above the line are worse, compared with the best fit value. Where no data point is shown, the maximum likelihood is too high to be shown on the y axis.
The effect of shifting the balance of partnerships formation rates towards that reported by men effectively increases the average rate of contact in the population and thus increases the $R_0$. Under assortative patterns of mixing the overall level of infection may be low, but a few people bear the brunt of disease.
### Table 3.6 Differential homophily shown by both sexes and different ethnicities

<table>
<thead>
<tr>
<th>Partner ethnicity</th>
<th>Male respondent</th>
<th></th>
<th>Female respondent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black Caribbean</td>
<td>Black African</td>
<td>White</td>
<td>Black Caribbean</td>
</tr>
<tr>
<td>Black Caribbean</td>
<td>0.63</td>
<td>0.34</td>
<td>0.0 (0.01)*</td>
<td>0.77</td>
</tr>
<tr>
<td>Black African</td>
<td>0.06</td>
<td>0.43</td>
<td>0.0 (0.01)*</td>
<td>0.13</td>
</tr>
<tr>
<td>White</td>
<td>0.31</td>
<td>0.23</td>
<td>1.00 (0.98)*</td>
<td>0.10</td>
</tr>
</tbody>
</table>

* Figures for white men used the same estimated values for the distribution of partnerships as in Table 3.1.

Notes: Table shows the ratio between the number of reported partnerships and the number expected if mixing was proportional to reported numbers of partnerships contributed by each group. For like with like mixing (along the diagonals), the higher the value, the greater the degree of homophily.
Figure 3.6  Impact of different treatment strategies on the epidemiology of disease

Percentage of population in each ethnic group for each sex (Male; White (70.86), Black Caribbean (18.59), Black African (10.55); Female; White (69.85), Black Caribbean (19.73), Black African (10.42))

Caribbean (18.59), Black African (10.55); Female; White (69.85), Black Caribbean (19.73), Black African (10.42)
Figure 3.7 The relative impact of interventions on the incidence of disease in the population

Number of people needed to receive intervention to prevent one infection, assuming decrease in duration of infection by 40% and coverage of 25% in the population targeted.

Percentage of population in each ethnic group for each sex (Male; White (70.86), Black Caribbean (18.59), Black African (10.55): Female; White (69.85), Black Caribbean (19.73), Black African (10.42))
**Discussion**

In this chapter previously published models of gonorrhoea transmission dynamics have been further developed to explore the details of a particular dataset. The focus of the study was ethnic disparities in gonorrhoea incidence and the results derived from the model show how such disparities can arise from small differences due to the feedback inherent in the system. Empirical data from South East London, where sexual behaviour and disease incidence was well described, was used to parameterise the model as far as possible. This, coupled with extensive analysis of the effect of varying different parameters provided insight into the reasons for the observed disparities in disease incidence in this population.

The outcomes from the mathematical model are consistent with the observed data across a range of parameters. A large proportion of the ethnic difference in diagnoses of gonorrhoea in this South London population could be accounted for using a limited number of simple parameters. By using a mathematical model of the dynamics of gonorrhoea transmission it was possible to incorporate the effects of sexual mixing and illustrate their role in contributing to ethnic disparities in diagnoses of infection.

The model illustrates how small differences in behaviour i.e. the variance in activity or in attending clinics can become magnified by the feedback found within an infection transmission system. More data are needed on the patterns of mixing by activity and how this relates to other mixing patterns, such as age or ethnicity. Differences in recovery rate or transmission probability, for example, due to poor access to healthcare or behavioural differences, are often postulated to explain differences in disease burden. In the model including these largely unquantified effects would exacerbate the differences in disease burden and strengthen the effects of targeted therapy, whilst obscuring the effects of sexual behaviour and partner choice in determining disease epidemiology. Socioeconomic factors may influence the incidence of STIs through behaviour, but standard statistical techniques will not identify the influence of this behaviour. The model can be used to explore interactive effects which might otherwise stay hidden. The consistency of the model predictions with the observed data, suggests that additional differences may be less obvious than might be expected.

In all scenarios the prevalence corresponding to the best fit is close to the limit of persistence. This suggests that the $R_0$ of gonorrhoea is close to 1. In the best fitting scenario in terms of duration and transmissibility, the values taken by mixing by activity
and balancing partnerships are towards the extremes of assortativity and match reported male behaviour. The overall prevalence of disease is determined by the reproductive number of the organism, which in turn depends upon the mixing patterns of the population. When different values for the mixing between activity classes ($\varepsilon_2$) are used, the distribution of infection within the different activity classes will be altered. If the parameter estimates are reasonable, the model suggests that the disease is close to not persisting. The best fitting model is in a sensitive region of the parameter space, therefore slight changes in parameters which determine the reproductive number ($R_0$) of the infection can have a substantial impact. A low $R_0$ means that, in a deterministic scenario, the model is sensitive to small changes in parameter values. Therefore whilst the results are robust across a range of parameters, additional analysis is necessary to determine whether the parameters chosen are close to those which actually occur in the study population.

The investigation of the relative impact of different potential interventions to reduce the levels of gonorrhoea showed that interventions targeted at the group at highest risk, i.e. Black Caribbeans would be nearly three times as effective as those implemented in the whole population (Figure 3.7). This is due to the dynamic feedback effects which help to maintain an STI in a population. Targeted interventions can have large effects both within the target group and in the overall population. Inequities in access to healthcare can be evened out, as well as the whole population benefiting from the intervention directly or indirectly. To ignore the differences in disease burden on the grounds of political correctness is to do disservice to those populations most at risk. Community-based action which empowers minority groups in matters of their health is urgently needed (Fenton 2001; Hughes, Brady et al. 2001; Low and FitzGerald 1998).

Two factors were crucial in determining the distribution of disease within the population: heterogeneity in the rate of partner change (which was greater in Black Caribbeans than in other groups) and partner choice (which was dependent on the choices of the whole population). Overall prevalence is determined by variety of factors which influence the reproductive number. When the average contact rate among the whole population is quite low, as seems to be the case for this population, it acts as a limiting factor on the persistence of disease and the prevalence is determined by the degree of mixing between activity groups (if all other factors are kept constant). Average behaviours do not explain the distribution of gonorrhoea in this highly heterogeneous population. Instead, the behaviour of a few individuals within a minority
population, combined with the pattern of partner choice by the whole population, had a
disproportionate effect on the overall burden of disease experienced by that group.

The model used was an approximation of the interactions of the whole population. For
simplicity a closed population was assumed. The reality is more complex. External
partnerships are possible, e.g. between young women and older men or partnerships
outside the geographic region. Ignoring age mixing would overestimate the prevalence
of gonorrhoea in young men compared to young women. Disease incidence in girls
occurs primarily within this age group, but for men the distribution of disease is more
evenly spread up to older ages. Intervention programmes should take account of this and
may need to involve older men as well. However, the sexual behaviour survey showed
that only 15% of women had older male partners so the effect of this on predicted
incidence would be small. There were no data from which to estimate the rate of
partnership formation with individuals outside the geographic region. Studies from
Baltimore however, show that the average linear distance between the residences of
non-cohabiting sexual partners was only 100m (Becker, Glass et al. 1998).

The sample sizes for some of the behavioural data, especially for white men and women
were small. In future work it would be important to include other sources of behavioural
data. The ethnicity of the last partner alone was used to determine the mixing matrix in
the model, possibly increasing the likelihood of choosing a regular/long-term partner in
the same ethnic group and thereby biasing the matrix used towards assortativity.

Incidence figures in the cross-sectional surveys were based on attendance at sexually
transmitted diseases clinics. Differences in healthcare facility use by different ethnic
groups might influence the distribution of disease observed. For simplicity, no measure
of concurrent sexual partnerships was included in the model, although this has been
shown to be important in theoretical studies (Morris and Kretzschmar 1997). The survey
data suggested that concurrency was more common in the Black Caribbean population,
which would further exacerbate the ethnic disparity seen in this population.

The pattern of mixing between individuals in different activity classes also varies
according to ethnicity (Aral, Hughes et al. 1999; Laumann and Youm 1999). In the
general population in the United States of America, African Americans with low risk
sexual behaviour have been shown to be more likely than whites to have partners with
high risk behaviour (Laumann and Youm 1999). In studies in Seattle amongst
individuals with gonorrhoea, the direct links between high and low prevalence groups
were most common between African American men and low prevalence women (Aral,
In mixing matrices obtained from the model some evidence was found to support this hypothesis, with the probability of women in the lowest activity group having a male partner from the highest activity group being slightly higher for black Caribbean than white women. However the possibility of large differences by ethnicity in the probability of forming partnerships with other activity classes was not explored explicitly.

The best fit to the observed data occurred when sexual mixing between activity classes was assortative, but this was sensitive to assumptions about the average rate of partner change. Modelling studies in sexually transmitted diseases clinic attenders as well as the USA general population study by Laumann (Laumann, Gagnon et al. 1994) and these have found near random or weakly assortative mixing (Garnett, Hughes et al. 1996; Garnett, Mertz et al. 1999). This may be as a result of biases in reporting, under representing high risk behaviours in those infected. Alternatively stochastic effects may be important in restricting contacts with the core group, for example due to spatial segregation. Thus, in the model presented here, assortative mixing may be required to restrict the spread of gonorrhoea, whereas in a stochastic network simulation mixing which is less assortative might provide a better fit.
Chapter 4  Epidemiology of reinfection with gonorrhoea

Summary

In this chapter the importance of reinfection to the epidemiology of bacterial sexually transmitted infections is investigated. Both chlamydia and gonorrhoea often occur repeatedly in the same individual. This has implications for the health of the patient, since reinfection is associated with an increased risk of future complications. Reinfection also impacts on the wider epidemiology of infection, because the prevalence at which infection saturates in a high risk groups is increased compared to the case when reinfection is not possible and troughs in incidence which could lead to fade out of infection are minimised.

Using data collected in London, the frequency of reinfection is calculated. A mathematical model of reinfection is developed to compare with the observed data and obtain insights into the natural history of reinfection. Usually, reinfection occurs a short time after initial infection, but does sometimes occur many years afterwards. A few individuals were diagnosed multiple times within the five year timeframe of the data collection.

This study aims to use mathematical models, together with observed rates of reinfection, to analyse the effect of different network structures as described by mixing patterns on rates of reinfection.

Two mathematical models of gonococcal reinfection were developed. An analysis of the effect of varying the degree of assortative mixing (i.e. like with like) on the rate of reinfection was carried out to determine whether this difficult to measure parameter can be estimated using other epidemiological characteristics of the disease, in this case the rate of reinfection.
Introduction

Patients diagnosed with bacterial STIs, especially gonorrhoea and chlamydia, are often infected multiple times. Patients with gonorrhoea or chlamydia may re-attend a clinic with the same diagnosis due to transmission from an untreated partner (either existing or new) or treatment failure, due to resistant infection or relapse. In this chapter reinfection is considered a repeat infection acquired from another person, as illustrated in Figure 4.1. Infection due to treatment failure, persistent or resistant infection will be termed relapse.

A proportion of cases of STIs occur in those who have previously had an STI and these may make up a significant fraction of the case load of a GUM clinic. Reinfections with chlamydia and gonorrhoea represent approximately one third of cases of these infections diagnosed at GUM clinics in the UK (HPA 2003a). In the USA in 2000, 47% of patients with gonorrhoea reported a history of infection (CDC 2002b). The risk of suffering long term effects of infection, such as PID and infertility, increases with the number of reinfections (Hughes, Brady et al. 2001). An interesting approach was taken by Fortenberry et al who considered all STIs and found that over 40% of adolescent women at an STD clinic reattended within a year with the same or a different infection (Fortenberry, Brizendine et al. 1999).

Multiple diagnoses can be used to identify those at risk of complications in the future. Patients who are infected repeatedly are likely those participating in current high risk behaviour and are potentially members of the “core group” (Hughes, Brady et al. 2001). Identifying individuals with repeat infections provides a point of contact for interventions and a group likely to obtain the most benefit from prevention efforts. Finally, reinfection is a biologically meaningful measure of the impact of control strategies. As such, reinfection is an endpoint which can be used to quantify and test the relative success of different arms of randomised controlled trials (Golden, Whittington et al. 2001; Schillinger, Kissinger et al. 2003). Those infected once tend to be reinfected, so their incidence is higher than others. They can therefore provide a smaller sample size for trials than a random selection of the population. Alternatively, a trial may be specifically designed to prevent reinfection itself. If more general interventions reduce the overall incidence then infections may become more concentrated in the core, and reinfections may become relatively more common, whilst decreasing in absolute numbers.
Figure 4.1  Mechanisms of reinfection

A - Reinfection from existing, untreated partner.
B – Reinfection from a new, infected partner.
Rates of reinfection with gonorrhoea and chlamydia

Studies of rates of reinfection are difficult to compare since many are conducted over different time periods, with different study populations. However it is clear that reinfection is common and constitutes a significant fraction of cases of STIs. In the UK, of those attending STI clinics, approximately one third of those diagnosed with gonorrhoea had a previous gonorrhoea diagnosis (HPA 2003a).

In the US and UK, projects to survey gonorrhoea isolates (GISP and GRASP, respectively) are underway, which are primarily used to track trends in antimicrobial resistance, but also collect other valuable data, including past history of infection (CDC 2000a; Paine, Fenton et al. 2001). In the US, GISP 2001 reported that approximately 48% (Range: 45% - 50%) of participants (who are comprised of the first 25 men with urethral gonorrhoea reporting to STD clinics in 26 cities each month) had ever previously had gonorrhoea. Approximately 20% of these (Range: 17.2% - 23.6%) had a diagnosis within the previous 12 months (CDC 2002b). These proportions were quite stable from 1991 – 2001. The GRASP survey in the UK 2002 (which collects consecutive isolates from sentinel surveillance sites in the UK from both men and women) showed somewhat lower proportions ever infected, with 27% of patients reporting a previous gonorrhoea diagnosis in 2002. Women were least likely to report a history of gonorrhoea (22%), followed by heterosexual men (27%) with homosexual men the most likely to have a history of infection (36%) (GRASP 2002).

Various different study designs have been used to examine the likelihood of reinfection following treatment for chlamydia. Retrospective or prospective cohort studies analyse historical data and identify repeat infections or reported history. For example Hughes et al conducted a retrospective cohort study and showed that 14% of patients with an acute STI attended again within a year. (Hughes, Brady et al. 2001). Prospective studies enrol a cohort and can arrange testing at intervals after initial treatment and may identify a higher proportion of asymptomatic infections especially in females. For example, Whittington et al followed young women treated for chlamydia, and tested one and four months after the initial diagnosis. Overall they found 13% were infected by the second test (Whittington, Kent et al. 2001). A passive prospective study would identify symptomatic reinfections when they attend again.

These different approaches have different strengths and weaknesses. Retrospective studies can investigate large datasets, but are restricted with respect to the questions that
can be addressed. Cohort studies are time-consuming and expensive, and therefore usually only involve small numbers of people. They are sometimes able to quantify the time to reinfection, but more commonly are able to determine a time interval for reinfection to have occurred. Cohort studies can assess the probability of reinfection more accurately by retesting a known cohort at specific time intervals. Clinic based calculations of reinfection may underestimate rates of reinfection if patients do not return to the same clinic for subsequent diagnoses. Only 36% of women with repeat chlamydia diagnoses in a US study were diagnosed in the same health care setting and only half of those were diagnosed in the same type of clinic (Xu, Schillinger et al. 2000a). In the same study young girls were the least consistent in their clinic use (Xu, Schillinger et al. 2000b). Conversely, in prospective studies of reinfection, compliance may be biased by those with symptomatic reinfections or known risk behaviour who may be more likely to attend follow-up appointments, compared with those without symptoms and who don’t perceive themselves to be at risk, leading to overestimates of the rate of reinfection. In the prospective cohort study of chlamydia reinfection by Whittington et al, less than 70% of those enrolled attended at least one follow-up appointment. (Whittington, Kent et al. 2001)

As well as the proportion of people who are likely to get reinected at some stage, it is also important to know the timing of reinfection events and their distribution. Burstein and colleagues followed 3000 inner city adolescents treated in a variety of clinic settings for an average of 33 months. For those initially infected, the median time to reinfection was 6 months and slightly longer (7 months) for those initially tested negative for chlamydia (Burstein, Zenilman et al. 2001).

**Risk factors for reinfection**

Several studies have identified risk factors for reinfection with gonorrhoea or chlamydia. For gonorrhoea, Hughes et al, found that in UK GUM clinic attendees, young age, Black Caribbean ethnicity, female gender, previous diagnosis of STI and high rates of partner change were important determinants of repeat infection (Hughes, Brady et al. 2001). Similarly, in the US, risk factors for reinfection were young age, female gender and Black ethnic group. Not surprisingly these variables are risk factors for any infection as well as for repeat infection. Gunn et al found that the strongest predictor of subsequent infection was recent or current infection with gonorrhoea or chlamydia and an increased number of past episodes increased the future risk (Gunn, Fitzgerald et al. 2000).
A large study in Washington State followed 32,000 women after their treatment for chlamydia. It was found that 15% had at least one reinfection within 3 years. For those less than 20 years old, 17% were reinfeected within 2 years. Hughes et al also report that teenage females are more likely to have repeated infections; 20 - 30% of this group are diagnosed with an acute STI within 18 months of initial diagnosis (Hughes, Brady et al. 2001) and that 12-15 year olds re-attend soonest. Many studies have demonstrated that adolescents have a higher rate of reinfection than older patients but few have provided evidence to explain this observation. Possible reasons for a higher probability of reinfection in young people are biological factors e.g. greater susceptibility to infection; social factors, e.g. poorer adherence to therapy, lower ability or power to inform partners and ensure their treatment and sexual network factors e.g. young people may be involved in densely connected networks, with a high turnover of partners and relatively high prevalence.

**Reinfection with gonorrhoea**

In gonorrhoea, resistance to antimicrobials may lead to treatment failure. Risk factors for resistant infection depend on the stage of the epidemic of antimicrobial resistance. Ciprofloxacin was recommended as first line therapy in the UK in 1989. In the next few years, when most strains were sensitive, risk factors for resistance included acquiring infection abroad, since resistance to ciprofloxacin was already very high in other countries, especially in the Pacific rim and Asia (CDSC 2003; Ison, Woodford et al. 1998). More recently ciprofloxacin resistance has spread endemically in the UK and therefore risk factors are less clearly defined (HPA 2003a). Gonococcal isolates have been reported with resistance to a wide variety of antimicrobials and are increasing in frequency (Chapter 1, Table 1.2). Persistent gonococcal infection i.e. infection which apparently clears but remains in a latent form and can reactivate at a later date, does not appear to occur.

The evidence for acquisition of immunity to gonorrhoea is equivocal. Recent human challenge studies suggest complex mechanisms. There may be some strain specific immunity, but this is unlikely to provide cross protection (Plummer, Simonsen et al. 1989; Schmidt, Schneider et al. 2001). Ross et al found no evidence of strain specific immunity, when they compared circulating strain types with strains isolates from first and subsequent infections (Ross, Moyes et al. 1995). In general, individuals remain susceptible to future infections following successful treatment. The production of antibodies in response to gonorrhoea infection is limited and no higher in those with a
history of infection (Russell, Hedges et al. 1999). The same study notes that the origin of immune cells in the genital tract is obscure and a better understanding will be necessary if therapies are to be developed which support the natural immune response (Russell, Hedges et al. 1999).

Reinfection with chlamydia

Persistent chlamydial infection has been reported to occur in some people, potentially for many years (Dean, Suchland et al. 2000). The exact proportion of treated infections which are not cleared through standard therapy is thought to be small, although few studies have carefully followed individuals treated for more than a few weeks. In one study, patients treated with doxycycline for 7 days were followed up for 20 weeks and no recurrent infections were detected by PCR (after one week) or by culture methods (except one woman who was reinfected) (Workowski, Lampe et al. 1993). Stamm suggests that similar studies could be carried out with single dose azithromycin therapy, to see if a single dose therapy permits persistence (Stamm 2001).

Reinfection with a different strain can be taken as definitive evidence of a new infection, if infections with more than one strain do not occur or will always result in the same strain being cultured. However, many true reinfections are likely to occur with the same strain, through repeated contact with the original source or due to infection with the most common strain in circulation in the local community (Stamm 2001). It is not known whether persistent infections have any particular characteristics in terms of human or pathogen biology and epidemiology. (Dean, Suchland et al. 2000; Suchland, Eckert et al. 2003).

Antimicrobial therapy may promote persistence in *C. trachomatis* (Dreses-Werringloer, Padubrin et al. 2000). In contrast to *N. gonorrhoeae*, there as yet appears to be very little, if any, clinically significant antimicrobial resistance of *C. trachomatis*. Somani and colleagues recently reported clinically significant chlamydia resistance (Somani, Bhullar et al. 2000). Given the increasing intensity of chlamydia case-finding through screening over the last 10 years, perhaps this recent emergence of resistance is not surprising. The evolutionary aspects of the emergence of drug resistance are considered in Chapter 5.

There is some evidence for acquisition of immunity to chlamydia, although the biological mechanism is not well understood (Schachter, Cles et al. 1983). In guinea pigs, experimental studies showed that treatment with doxycycline inhibits the
development of an effective immune response and may reduce acquired immunity (Su, Morrison et al. 1999).

**Comparison of gonorrhoea and chlamydia reinfection**

Reinfection with chlamydia has features which differ from reinfection with gonorrhoea, but also many similarities. A patient with gonorrhoea is more likely to fail therapy due to drug resistance than someone with chlamydia, but a patient with chlamydia is more likely to relapse due to persistent infection. For both pathogens there is some evidence for the acquisition of strain-specific immunity, but there is better evidence regarding immunity to chlamydia than to gonorrhoea and the protection against future infection with the same strain is greater for chlamydia (Ross, Moyes et al. 1995; Schachter 1999; Schachter, Cles et al. 1983; Sparling 1999).

In a recent study of network characteristics of those with chlamydia and gonorrhoea infections, those with co-infections and repeat infections were disproportionately represented in the large (i.e. more densely connected) components of the network (Potterat, Muth et al. 2002). Nearly 75% of repeat and 60% of co-infections occurred in medium to large networks.

Two randomised controlled trials have investigated interventions designed to reduce the rate of reinfection, through patient delivered therapy (PDT). Index patients are given treatments to give to their partner or facilities are put in place for their partner to collect treatment from a pharmacy (Golden, Whittington et al. 2001; Schillinger, Kissinger et al. 2003). The rationale for this approach is that providing treatment for partners will increase the proportion of partners who get treated or reduce the delay in obtaining their treatment. Treating both partners within a short space of time should reduce the probability of reinfection from an untreated partner. Thus, reinfection rates in index cases can be used to measure the success of the intervention.

To date two groups have reported the results from such randomised controlled trials. The first (Schillinger, Kissinger et al. 2003) reported a lower proportion of women reinfected with chlamydia 4 months after initial diagnosis. A total of 12% were reinfected in the PDT arm compared with 15% in the control arm, in which patients referred their partners for treatment. However this difference was not statistically significant. The second trial (Golden 2003; Golden, Whittington et al. 2001) investigated the impact of PDT for the partners of patients (men and women) with gonorrhoea and/or chlamydia. Overall they found a statistically significant reduction in
Chapter 4 - Reinfection with gonorrhoea

the rate of reinfection of index patients (9.9% PDT vs. 13% standard care), but the intervention was more successful in preventing gonorrhoea reinfections (3.4% PDT vs. 10.6%) than chlamydia (13.2 vs. 10.6%) (Golden 2003; Golden, Whittington et al. 2001). Of those reporting no sexual intercourse between tests, the rate of apparent reinfection for women with chlamydia was 6%, only one woman was reinfected with gonorrhoea and no men were reinfected with either pathogen. This suggests that persistent chlamydial infection may affect the ability of an RCT to detect a significant change in the rate of reinfection. In addition, patients with chlamydia are more likely to refer their partners without additional interventions than are gonorrhoea patients, so the margin for improvement may be greater with gonorrhoea.

**Estimation of parameters**

The crucial parameters for determining the role of reinfection in the epidemiology of infection cannot be derived from routine data. It is important to know whether reinfection has any impact on the parameters which determine the effective reproductive number ($R_t$) of the organism. These parameters include the transmission probability of an infection which may be reduced due to incomplete immunity, the duration of subsequent infections, which may be shortened due to better recognition of symptoms and awareness of the possibility of infection and the contact rate of the individual which may be modified transiently or permanently following infection. There is some evidence for a degree of acquired immunity as discussed but the extent of immunity or the level of cross protection from other strains has not been quantified. There is also a possibility that previous infection may have caused cellular damage and rendered the individual more susceptible to future infection, i.e. an enhancement effect.

Most studies of reinfection have considered repeat attendances at the same clinic, with the attendant difficulties of loss to follow-up when cases reattend elsewhere. It is not known if the clinical profile of infection changes with repeated episodes of infection or if this has an effect on the timing or likelihood of a patient seeking treatment.

The characteristics of those who become reinfected have been well defined and a mathematical model should be able to incorporate an epidemiologically meaningful measure of the profile of those at risk for reinfection or not.

In contrast, the timing of reinfection is not well described. For the purposes of designing new interventions or trials, the timing of reinfection in relation to the method of follow-up is important.
Various studies have estimated the time to reinfection for chlamydia or gonorrhoea but most have been over a relatively short period of time (Javanbakht, Smith et al. 2003; Jolly and Wylie 2002; Orr, Johnston et al. 2001; Whittington, Kent et al. 2001), although a few have been conducted for 2 or more years (Burstein, Zenilman et al. 2001; Mehta, Erbelding et al. 2003; Rietmeijer, Van Bemmelen et al. 2002; Xu, Schillinger et al. 2000a). The findings presented here indicate that reinfection may still occur many years after the initial infection although at what point, if ever, risk becomes equivalent to the general population is not clear.

Method

This chapter uses two deterministic mathematical models, together with observed rates, in an analysis of rates of reinfection.

Empirical data

The empirical data presented consists of gonococcal isolates collected at St Mary’s Hospital, in London between 1995 and 2001 by Prof Cathy Ison and Dr Iona Martin (Imperial College London).

In order to distinguish epidemiologically meaningful reinfection (i.e. reinfection from an infected, untreated partner) from treatment failure or infection at multiple sites, reinfection is defined as a second infection occurring more than one month following treatment for an initial infection. The same patient may be listed more than once on the same day or soon after with infection at different anatomical sites, so these are considered as a single event.

Overall, nearly a quarter (23.6%) of infections diagnosed at St Mary’s occurred in women. This proportion did not change during the data collection (Figure 4.2). Between 1995 and 2001 the number of isolates collected at St Mary’s increased in line with London-wide increases. In Figure 4.2 the number of isolates collected at Mary’s are compared with London overall (shown on different scales). In 2001 there were 809 isolates collected at St Mary’s, in London there were 9378 diagnoses of gonorrhoea reported to the Health Protection Agency from KC60 data which are lab confirmed diagnoses (HPA 2003b).

Mathematical model of reinfection

Two deterministic mathematical models of gonorrhoea reinfection were developed, a simple model of reinfection and a modified version, incorporating a refractory period
when treated individuals cannot transmit or acquire infection. An analysis of the effect of varying the degree of assortative mixing (i.e. like with like) on the rate of reinfection was carried out to determine whether it can be estimated using other epidemiological characteristics of the disease, in this case the rate of reinfection.

These two models describing reinfection with gonorrhoea are presented and illustrated as flow diagrams in Figure 4.4 and Figure 4.5. They are based on a simple one pathogen susceptible-infected-susceptible (SIS) and a susceptible-infected-recovered-susceptible (SIRS) deterministic model. The model structures make it possible to track infections over time to calculate the proportion of the population who get reinfected. Within an activity class exposure is the same across individuals and is a function of the pattern of sexual partner change and mixing.
Figure 4.2  Proportion of gonorrhoea diagnosed in females.
Diagnoses at Marys

Year


Diagnoses across London


Diagnoses of gonorrhoea at St Mary's Hospital compared with all London diagnoses.
Figure 4.4 Flow diagram of reinfection model 1
Figure 4.5  Flow diagram of reinfection model 2 with refractory period
Mathematical model 1 – simple reinfection

The model describes a population stratified by gender and partner change rate and whether an infection is the first, second or third (or greater) time an infection has occurred. Individuals enter the susceptible population at a rate $\mu$ and can then acquire infection repeatedly. Recovery from infection occurs at a rate $\sigma$ and once an individual recovers they are assumed to be immediately susceptible to reinfection. The flow diagram for this model is given in Figure 4.4.

The state variables are as follows:

- $X_{0kl}$ - population of naïve susceptibles of sex $k$, activity class $l$
- $Y_{1kl}$ - population of hosts infected for the first time of sex $k$, activity class $l$
- $X_{1kl}$ - population of susceptibles (previously infected once) of sex $k$, activity class $l$
- $Y_{2kl}$ - population of hosts infected for the second time of sex $k$, activity class $l$
- $X_{2kl}$ - population of susceptibles (previously infected twice) of sex $k$, activity class $l$
- $Y_{3kl}$ - population of hosts infected for the third or greater time of sex $k$, activity class $l$
- $X_{3kl}$ - population of susceptibles (previously infected three or more times) of sex $k$, activity class $l$

In order that the model system is closed, the last two compartments, corresponding to infection and recovery three or more times, cycle between infected and susceptible.

Subscripts $k$ and $l$ refer to sex and activity class, respectively. $k=0$ for men, $k=1$ for women. The subscript $l$ defines the activity class (from 1 to 4), according to average rate of partner change per year, $c_{kl}$.

The ordinary differential equations which define the model are:

1. $\dot{X}_{0kl} = \mu N_{kl} - \lambda_{kl} X_{0kl} - \mu X_{0kl}$
2. $\dot{Y}_{ikl} = \lambda_{kl} X_{(i-1)kl} - \sigma Y_{ikl} - \mu Y_{ikl}$ (for $i = 1, 2$)
3. $\dot{X}_{ikl} = \sigma Y_{ikl} - \lambda_{kl} X_{ikl} - \mu X_{ikl}$ (for $i = 1, 2, 3$)
4. $\dot{Y}_{3kl} = \lambda_{kl} (X_{2kl} + X_{3kl}) - (\sigma + \mu) Y_{3kl}$

The force of infection, $\lambda_{kl}$, (the group specific incidence per susceptible) can be calculated from the transmission probability from sex $k'$ to sex $k$ ($\beta_{kl}$), contact rate ($c_{kl}$) the proportion of infected individuals ($\Sigma Y_{ikl} m'/N_{k'l}$, where $\Sigma Y_{ikl} m'$ is the sum of those infected $i = 1, 2$ or 3 and $N_{k'l}$ is the total population of sex $k'$, activity class $m$) and the
mixing pattern between different activity groups $\rho_{klm}$ (where letter $m$ defines the activity class of an individual of the opposite sex ($k'$) with whom a partnership is formed) as follows:

$$\lambda_{kl} = c_{ui} \beta_k \sum_{m=1}^{\delta} \rho_{klm} \frac{\sum_{i=1}^{3} Y_{ik'm}}{N_{k'm}}$$

Parameters used in the model are further defined in Table 4.1.

$\rho_{klm}$ is an element of $P$, which defines the probability that, when an individual of sex $k$ in activity class $l$, forms a partnership, it will be with a member of activity class $m$ of the opposite sex, $k'$. The values of $\rho_{klm}$ depend on the overall pattern of mixing by partner change rate, and can vary from fully assortative ($\epsilon_1=0$) to proportionate ($\epsilon_1=1$).

The following equation describes the mixing matrix:

$$P_{klm} = \left( \epsilon_1 \frac{N_{k'm}^c k'm}{\sum_{u=1}^{4} N_{k'u}^c u} + (1 - \epsilon_1) \delta_{lm} \right)$$

where $\delta$ is the identity matrix, such that $\delta_{lm} = 1$ when $l=m$ and $\delta_{lm} = 0$ when $l \neq m$. 
Table 4.1  Table of parameters used in mathematical models 1 and 2 of reinfection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Values used</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>Entry rate. To maintain a constant population size, the entry and exit rates are assumed to be equal.</td>
<td>0.1 per year (average length of stay in model population 10 years)</td>
</tr>
<tr>
<td>$\beta_k$</td>
<td>Transmission probability of infection to sex $k$ per contact</td>
<td>Probability per contact 0.5 (Male to Female) 0.35 (Female to Male)</td>
</tr>
<tr>
<td>$\sigma_k$</td>
<td>Recovery rate from infection</td>
<td>1.5 per year (female) – mean duration 8 months. 2 per year (male) – mean duration 6 months.</td>
</tr>
<tr>
<td>$P_{klm}$</td>
<td>Mixing matrix, element $\rho_{klm}$ is the probability that, when an individual of sex $k$ in activity class $l$ forms a partnership, it will be with a member of activity class $m$ of the opposite sex, $k'$.</td>
<td>See below</td>
</tr>
<tr>
<td>$c_{kl}$</td>
<td>Partnership formation rate of individual of sex $k$, activity class $l$ (see below)</td>
<td>See below</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Pattern of mixing: $\varepsilon$ by activity (0=fully assortative, 1=random)</td>
<td>Mixing according to activity varied from $0 \leq \varepsilon \leq 1$</td>
</tr>
</tbody>
</table>
Mathematical model 2 – including a refractory period

In the second model, a third state is introduced, the refractory period \( (Z_{ikl}) \), which represents the period following diagnosis and treatment of an infection, in which individuals are not infectious or susceptible to infection with gonorrhoea and therefore do not contribute to the force of infection. This could be due either to a lasting benefit effect of antibiotic therapy or abstention from sex or complete condom use during for a week, as recommended. Protection from reinfection is assumed to be complete during this period. The flow diagram for this model is given in Figure 4.5.

The state variables for the modified model are as follows:

- \( X_{0kl} \) - population of naïve susceptibles of sex \( k \), activity class \( l \)
- \( Y_{1kl} \) - population of hosts infected for the first time of sex \( k \), activity class \( l \)
- \( Z_{1kl} \) - population of hosts refractory following first infection, sex \( k \), activity class \( l \)
- \( X_{1kl} \) - population of susceptibles (previously infected once) of sex \( k \), activity class \( l \)
- \( Y_{2kl} \) - population of hosts infected for the second time of sex \( k \), activity class \( l \)
- \( Z_{2kl} \) - population of hosts refractory following second infection, sex \( k \), activity class \( l \)
- \( X_{2kl} \) - population of susceptibles (previously infected twice) of sex \( k \), activity class \( l \)
- \( Y_{3kl} \) - population of hosts infected for the third or greater time of sex \( k \), activity class \( l \)
- \( Z_{3kl} \) - population of hosts, refractory following third (or more) infection(s), sex \( k \), activity class \( l \)
- \( X_{3kl} \) - population of susceptibles (previously infected three or more times) of sex \( k \), activity class \( l \)

As in the previous model, the requirement for closure means, after the third infection individuals in the population cycle between the final three compartments, corresponding to infection, recovery and refraction three or more times.

In the equations describing model 2, subscripts \( k \) and \( l \) refer to sex and activity class, respectively. In the case of sex, \( k=0 \) for men, \( k=1 \) for women while \( k' \) refers to the opposite sex to \( k \) and for activity \( l \) defines the class (from 1 to 4), according to average rate of partner change per year, \( c_{klr} \). The letter \( m \) defines the activity class of an individual of the opposite sex \( (k') \) with whom a partnership is formed by a person of sex \( k \), activity class \( l \).
Two additional parameters are included to control movement to and from the refractory period in model 2. These are a relapse rate, $\gamma$, which accounts for treatment failure (resistance or persistence) not counted as reinfection and the duration of stay in the refractory period $\alpha$ i.e. the time following diagnosis when a patient is not infectious or susceptible to further infection. They continue to form sexual partnerships but are assumed to have short term immunity and use condoms or refrain from intercourse during the refractory period.

The ordinary differential equations which define the model are:

$$\dot{X}_{0kl} = \mu N_{kl} - \lambda_{kl} X_{0kl} - \mu X_{0kl}$$  \hspace{1cm} (2.1)

$$\dot{Y}_{ikl} = \lambda_{kl} X_{(i-1)kl} - (\sigma + \mu) Y_{ikl} + \gamma Z_{ikl} \quad (\text{for } i = 1, 2)$$  \hspace{1cm} (2.2)

$$\dot{Z}_{ikl} = \sigma Y_{ikl} - (\alpha + \mu + \gamma) Z_{ikl} \quad (\text{for } i = 1, 2, 3)$$  \hspace{1cm} (2.3)

$$\dot{X}_{ikl} = \alpha Z_{ikl} - (\lambda_{kl} + \mu) X_{ikl} \quad (\text{for } i = 1, 2, 3)$$  \hspace{1cm} (2.4)

$$\dot{Y}_{3kl} = \lambda_{kl} (X_{2kl} + X_{3kl}) - (\sigma + \mu + \gamma) Y_{3kl}$$  \hspace{1cm} (2.8)

The force of infection, $\lambda_{kl}$, and the mixing matrix, $\rho_{klm}$, are as defined for model 1.
Results

Between 1995 and 2001 a total of 3911 infections were diagnosed in 2860 individuals. The gender was known for 2670 of whom, 24% (631) were female. This proportion has stayed roughly constant since 1995. During the study, on average of 5.0% (Male, 5.3%, Female 3.8%) of patients diagnosed with GC in a London GUM clinic were diagnosed two or more times, and 0.4% (0.4% Male, 0.4% Female) three or more times within each year. Cumulatively over the seven years of the study, 11.5% of patients were diagnosed two or more times, and 2.5% diagnosed three or more times. The number of people diagnosed with 1, 2, 3 or more infections over the course of the study is given in Table 4.2
Table 4.2  Number of people reinfected and diagnosed at St Mary’s, London between 1995 and 2001

<table>
<thead>
<tr>
<th>Number of infections</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>3256</td>
</tr>
<tr>
<td>≥2</td>
<td>447</td>
</tr>
<tr>
<td>≥3</td>
<td>23</td>
</tr>
<tr>
<td>≥4</td>
<td>15</td>
</tr>
</tbody>
</table>

Initial infection 1995-1999 (median = 1997)

Earliest diagnosis July 1995

Last diagnosis July 1999
The mean and median times to reinfection were calculated crudely for each year. This was taken as the time between the most recent diagnosis and the previous diagnosis and in an alternative calculation, between the most recent diagnosis and the first ever diagnosis. This is illustrated in Figure 4.6. The left hand column for each year shows the time since the most recent occurrence, the right hand column the time since first diagnosed. The lower shaded section of the column indicates the median time to reinfection and the whole column the mean. Error bars indicate the maximum and minimum time to reinfection in each year.

The time to reinfection was calculated for the first reinfection to create a survival curve for time remaining without reinfection. Figure 4.7 shows the fraction becoming reinfected following index infection as a survival curve. The median time to reinfection amongst those who were reinfected was 15 months. The longest time to first reinfection observed within the study was 70 months. However given that isolates were only collected for 72 months and that half of observed infections were documented more than 15 months after the first isolate was collected, those diagnosed with gonorrhoea may remain at elevated risk for several years afterwards. In general, most reinfections observed occurred soon after, with 25% occurring within 6 months. This is shown more clearly as a hazard function in Figure 4.8, where there is a high hazard initially, which drops and levels off to a fairly constant low risk after approximately 1 year. In calculating the hazard only those infections included sufficiently early to be able to acquire an infection at the particular time are included in the denominator. Thus as time progresses, fewer individuals are included and confidence in the hazard decreases.
Figure 4.6  Mean and median time to reinfection since first occurrence and most recent occurrence for those who have previously been infected in each year of the study

(Error bars indicate the range)
Figure 4.7 Kaplan-Meier survival curve, showing the time to reinfection in St Mary's, London.
Figure 4.8 Hazard function, showing the time to reinfection in St Mary's.

Median time to recovery
Model 1 - simple reinfection scenario

Model 1 fails to capture the pattern of reinfection, primarily because reinfection occurs too rapidly. Reinfection is overestimated in the deterministic model but because of the difficulties identifying a repeat infection, is likely to be underestimated in observed data. Figure 4.9 illustrates the effect of changing the mixing pattern on the proportion of reinfections which occur. Model simulations show that as mixing becomes more random, the frequency of reinfection decreases. Those who become reinfected have a higher average rate of partner change than those who are singly infected.

Model 2 – with refractory period

Because of the overestimate of reinfection a second model is introduced to examine the effect of a refractory phase due to treatment of infections. It is assumed that those treated change their behaviour or gain benefit from antimicrobial therapy for 4 weeks following diagnosis of an STI that renders them not susceptible to infection for the duration of the refractory period. Introducing this stage also allows the introduction of a rate of treatment failure or relapse to investigate.

With this scenario, more realistic proportions of the yearly incidence of repeat infections are obtained, as shown in Figure 4.10.

The results suggest that reduced susceptibility to reinfection has to be present for a time following treatment. This is without allowing in the model for reinfection from the initial partner. However, chance may slow down reinfection in a sexual partner network.
Figure 4.9 Model 1 result, proportion of infections which are reinfections per year.
Proportion of infections in group 1, 2, 3

- Assortative
- Random

1 month refractory period
5% relapse

Prevalence of infection

Proportion of infections in group 1, 2, 3

First infection
2 infections
3 or more infections

Prevalence

Mixing

Figure 4.10 Model 2 results with refractory period, proportion of infections which are reinfections per year

Chapter 4 - Reinfection with gonorrhoea
Katharine Turner
Discussion

Reinfection represents an important component of the epidemiology of gonorrhoea and of chlamydia, but gaps remain in knowledge of the extent of reinfection and timing of reinfection events. This chapter presents new data and a mathematical modelling approach to improve understanding of the population level factors including mixing patterns and rates of partner change which can affect the risk of reinfection. There remains a lack of knowledge on the natural history of reinfection with gonorrhoea. Mathematical models can be used to investigate the expected outcome of different rates of relapse and acquired immunity which may allow these parameters to be quantified with more accuracy.

In this chapter the frequency and timing of reinfection in St Mary’s clinic, London from was calculated and the implications for models of gonorrhoea investigated. Reinfection with gonorrhoea occurs frequently, and about 5% of people return within a year of diagnosis, overall 20% of those diagnosed at St Mary’s will be reinjected. Multiple reinfections were also quite common. Fifteen people returned four or more times during the course of the data collection at intervals greater than one month. The average time to reinfection was 15 months. These values are comparable with rates of reinfection obtained in studies in similar settings (Mehta, Erbelding et al. 2003).

The pattern of reinfection observed is complex. The risk of reinfection is highest soon after treated infection, as is anticipated if most reinfection events occur due to reinfection from untreated partners. However, reinfections were also observed several years after initial infection which implies that some individuals who have been infected with gonorrhoea remain at elevated risk for a substantial period. Infections occurring several years later are unlikely to be acquired from the original source of infection. This implies that these infections represent a new source, either from a newly infected existing partner (which would indicate overlapping partnerships) or from a new partner who is infected. Both scenarios suggest continued high risk and potential membership of a core group. Since Hethcote and Yorke’s seminal work on gonorrhoea transmission dynamics and even before it has been recognised that members of core groups are prime targets for intervention efforts.

Limitations of method

Empirical data from one clinic will tend to underestimate the proportion of reinfection due to the availability of other sources of care, including other clinics or GPs and
movement of people away from the area. Many of the parameters required for a model
or reinfection with gonorrhoea remain poorly characterised, for example the variation in
time before seeking care, variability in the incubation period and the effect of contact
tracing and treatment of partners on the probability of future infections. At present it is
difficult to determine whether a reinfection is due to failure of treatment, contact with
an untreated partner or due to a contact with a new infected partner. Patients who have
acquired an STI from one sexual partner are more likely to be in higher risk networks
and may therefore be more likely to form future partnerships with infected or high risk
partners.

It is difficult to quantify how many reinfection events are missed in the empirical study,
due to a proportion of people seeking treatment elsewhere. The rates of reinfection
reported are likely to be an underestimate. In the USA, people seeking care in public
STI clinics comprise higher risk demographic groups than the general population at risk
for STIs and reinfection rates based on this population may overestimate reinfection. In
the UK, where free care is available to all this may not be true to the same extent.
However, there are other sources of care which may be utilised, in particular men who
reported having had an STI diagnosis were more likely to report attending a GUM clinic
than women (Johnson, Mercer et al. 2001). There may be some gender differences in
the risk of reinfection, and further analysis should be undertaken to evaluate these and
the effect of sexual orientation on the rate of reinfection.

This analysis did not incorporate age, but this would be useful additional work, as most
studies of reinfection have found that age correlates strongly with risk of reinfection
with both gonorrhoea and chlamydia, which occurs more often and more rapidly among
young people. Burstein and colleagues found in a study of chlamydia in 12-18 year olds
that 14 year olds had the highest rate and, in a later study in a wider age range of women
12-60, showed the same pattern of higher risk in younger women (Burstein, Gaydos et
al. 1998; Burstein, Zenilman et al. 2001). Similarly for gonorrhoea, rates are high in
young people (Orr, Johnston et al. 2001).

More data are needed for model parameterisation, for example in the rate of treatment
failure due to resistant infection may change over time and under different treatment
guidelines. If treatment does not clear the infection but does resolve symptoms, then
infections may last for much longer than anticipated. There is some evidence that
treatment of chlamydia may lead to asymptomatic infection, (Dreses-Werringloer,
Padubrin et al. 2000) and that it is possible that a similar effect may occur if gonorrhoea
is treated sub-optimally. Modelling can help to predict the effects of different outcomes of treatment and the effects of resistant or persistent infection. This theoretical aspect is explored further in Chapter 5.

Using a standard susceptible-infected-susceptible model of gonorrhoea, it was initially found that reinfection occurred much more rapidly than was suggested by empirical data. It is reasonable to assume that, following successful treatment, people do not become immediately exposed and susceptible to infection. To mimic the definition of reinfection as occurring more than one month after initial diagnosis, this protected period was set to one month. During this time, individuals are not susceptible to infection. This has the effect of reducing the pool of susceptibles (especially in the highest activity groups) which therefore results in a reduction in the effective $R_0$ of gonorrhoea and a reduction in the prevalence and rate of reinfection. This effect brought the rate of reinfection down to a more realistic level. The evidence suggests that individuals change their behaviour at least temporarily following diagnosis with an STI (Fortenberry, Brizendine et al. 2002). Treatment may induce a benefit for some days afterwards, depending on the pharmacokinetics and pharmacodynamics of the drug used and dosing regime.

If reinfection could be modelled accurately with good parameter estimates, then by fitting rates of first, second and greater infections per year the mixing patterns within the population could be estimated. This has not been possible as yet, since too many of the parameters are poorly quantified. However, it does represent a novel approach which could be taken, together with data on coinfection to characterise populations at risk who would benefit from targeted interventions and also to monitor the epidemiology of STIs and indirectly measure changes in sexual behaviour for example in mixing patterns or the distribution of sexual activity.

The model of reinfection has not been explicitly fitted to data due to the uncertainty in the parameter estimates made. However, additional sensitivity analyses could be carried out to determine the relative effect of varying parameters which are not well quantified, such as resistance, proportions of asymptomatic infections, protective acquired immunity. There is some evidence that there is incomplete strain-specific immunity (Plummer, Simonsen et al. 1989), two or more strain models such as that developed in Chapter 2 (gonorrhoea and chlamydia) and Chapter 5 (2 strains of gonorrhoea) as well as other work on strain structure in viral and bacterial populations (Castillo-Chavez, Hethcote et al. 1989; Ferguson, Anderson et al. 1999; Gupta and Galvani 1999) could
be extended to investigate the specific properties of gonorrhoea strain structure and immunity. Risk of reinfection is intimately linked with partnerships and infection status of partners, so the next stage in this work is to explore individual based models with explicit partnerships. This will enable different mechanisms of reinfection to be determined as well as the effect of novel intervention approaches, such as partner delivered therapy.

Molecular typing provides another empirical approach to understanding the source of reinfections and more generally the epidemiology of gonorrhoea. (Ghani, Ison et al. 1996; Ward, Ison et al. 2000) Genetic typing could also be used to identify sources of reinfections, either new infections, resistant infections or reinfections from untreated partners (Martin and Ison 2003).
Chapter 5  
Evolution of gonorrhoea and chlamydia

Summary

The evolution of any sexually transmitted organism will be influenced by prevailing epidemiological interactions. The level of competition between organisms and the selective pressures imposed on the pathogens are determined by the prevalence of infection and the use of interventions.

A deterministic, compartmental mathematical model of two strains of gonorrhoea with a range of properties is used to illustrate some of the key relationships between epidemiology and evolution. The epidemiology of an STD can be categorised according to a series of ‘phases’ which provide a framework within which to discuss its influence on evolution.

The basic reproductive number is a measure of fitness which, within constraints imposed by what is biologically possible, will be optimised by selection. Additionally, if there is strong interference between infections the speed of replication as measured by transmissibility can be an important component of fitness. When treatment is introduced it imposes an enormous selective cost. The optimum strategy for an organism to overcome treatment, either through drug resistance or cryptic infections, depends upon whether the method for identifying patients is passive (treating symptoms alone favours asymptomatic organisms) or active (screening favours resistant organisms).

The use of mathematical models of competing strains of infection allows theoretical predictions for the outcome of evolution under a range of assumptions about potential phenotypes. The course of pathogen evolution has implications for the success of interventions, but the predictions presented need to be tested at the level of the community in carefully monitored interventions.
Introduction

The current diversity of sexually transmitted infections is the consequence of evolution. For any infectious organism this evolution is profoundly influenced by the epidemiological factors which constrain its environment. The organisms within an infection interact with one another and with the individual host. Likewise, within the host population, infections compete, altering their reproductive success.

For any organism, evolution is shaped by the mechanisms that introduce variation into the genome, the ways in which genes spread through populations and the challenges which limit populations and thereby the success of different genes. The sequence of bases in DNA and RNA encoding the regulation and synthesis of enzymes and structural molecules is the raw material for evolution. On replication, molecular mechanisms of base substitution and deletion, or recombination and re-assortment, configure this genetic raw material. Then selection and neutral drift act to determine the distribution of different sequences in future generations. Chances for genetic recombination, genetic drift and natural selection are a function of the population dynamics of organisms and, for infectious diseases, population dynamics is the main focus of epidemiology. The phase of an epidemic plays many roles in controlling evolutionary pressures, which will be explored here in the context of sexually transmitted infections (STIs).

As described elsewhere, an epidemic can be divided into five phases characterising growth and decline of a population of infectious organisms (Garnett 2002; Wasserheit 1992). These are:

Phase I – The growth period, as the invasion of host population occurs;
Phase II – The peak of the epidemic and hyper-endemic phase when no controls have yet been imposed;
Phase III – A decline phase as controls are introduced and take effect;
Phase IV – A new endemic phase i.e. the steady state prevalence and incidence when controls are acting;
Phase V – Elimination, and potentially eradication. These phases could be applied to the global or local spread of an infectious organism.

By definition, STIs are caused by pathogens, whose evolution is intimately tied up with the disease they induce, their ability to spread in new hosts and their response to
immunity and treatment. It is inevitable that when the relationship between the evolution and epidemiology of STIs is considered, the concern will be with the phenotypes of the organisms (the actual expression of the characteristics encoded gene which is influenced by both genes and the environment) and how these phenotypes influence their reproductive success. The pressures imposed on the sexually transmitted infection can be considered at each epidemiological phase in turn.

The founder effect will be important in phase I when an infection enters a host population and spreads with little competition (Anderson and May 1991). The founder effect is defined as the establishment of a new population by a few original founders, which carry only a fraction of the genotypes of the parental population (Mayr 1963). Particular genotypes will become common because they were present when the STI was introduced into the population. With small local outbreaks, as are currently observed in industrialised countries for bacterial STIs, there will be repeated episodes where founder infections become common in particular locations causing fluctuations in the common genotypes within a community, country or region. Likewise, for infections within the host those organisms present in the infecting dose may be a limited subset of the infectious population allowing for random shifts in the genes represented in the pathogen population.

At a hyper-endemic steady state (Phase II), saturation of the infection in the population has occurred, when pre-emptive infection, or acquired immunity, reduces the reproductive success of each infection. It is in this phase that the transmissibility of the infection and the ability to persist in the individual host, avoiding acquired or innate immunity, would be optimised. This will generate and hone mechanisms to avoid the immune defences of the individual host and the host population. Examples of these mechanisms are antigenic variation as observed in gonorrhoea, chlamydia and HIV (Ward, Ison et al. 2000) (Nowak 1991; Stephens, Wagar et al. 1988), low levels of exposed antigens as appears to be the case for syphilis (Schouls 1992), latent state in an immune privileged site with continual reactivation as in the case of HSV-2 (Corey 1999) or minimal contact with systemic immunity as appears to be the case with minimally invasive infections like HPV (Galloway 1999). Competition at this endemic prevalence may be particularly intense, especially if there is a group with a high risk of acquiring and transmitting infection, as is often the case for STIs where continual re-exposure can occur for some individuals. The ability to invade an already infected host
becomes a selective advantage in such circumstances, but concomitantly it becomes an
advantage for the original infection to prevent further infection.

The key measure for evolutionary fitness is the reproductive success of the organism,
i.e. its representation in future generations. Normally the reproductive success (the
number of viable offspring) of the individual organism or gene is measured. However,
in infectious disease epidemiology one can also think in terms of the reproductive
success of the infection, a colony of related individuals, and the reproductive number
\((R_0)\) (Anderson and May 1991).

The basic reproductive number \((R_0)\) is defined as the average number of new infections
arising from one index case in an entirely susceptible population. The value of the
reproductive number at a given time \(t\) \((R_t)\) determines whether the related organisms are
increasing \((R_t > 1)\) or decreasing \((R_t < 1)\) their representation at that time. The basic
reproductive number \(R_0\) applies only in the absence of density dependent constraints, in
Phase I, the invasion of a susceptible population. The influences on the reproductive
number, in addition to the proportion of the host population susceptible, consist of three
main elements: the duration of infectiousness, the pattern of contact within the host
population and the likelihood of transmission on contact. An increase in duration of
infectiousness or transmissibility would increase the fitness of a pathogen.

While it is possible to hypothesise about optimum evolutionary strategies, the early
academic consensus, that parasites should evolve to become benign, illustrates the
potential pitfalls of such speculation. It was assumed that increasing the longevity of
the host would also improve the fitness of parasites by maximising the parasites own
survival (McKeown 1988). However, this fails to take into account the potential
correlation between pathogenesis and virulence\(^1\).

A trade off is likely between the duration of infection and infectiousness, which may be
associated with severity of disease (Anderson and & May 1982; Bull 1994; Lipsitch
2001). Biological explanations for the link between virulence and pathogenicity have
been explored and may include increased replication, which increases pathogenicity but
also increases fitness in terms of ability to withstand host immune defences and
increased probability of transmission (Lipsitch and Moxon 1997; Lipsitch and Nowak

\(^1\) Virulence has been defined differently across disciplines. To the clinical microbiologist virulence is the
ability to invade the host causing disease, whereas to the evolutionary biologist virulence is a measure of
an organisms ability to replicate and be transmitted to new hosts. The latter definition is used here.
Katherine Turner

Chapter 5 - Evolution of gonorrhoea and chlamydia

1995). The level of disease associated with an infection will depend upon this trade off and the biological mechanisms damaging the host.

Support for the earlier view was invoked from the severe symptoms and high mortality observed for many emerging infections are seen, which then decline as the epidemic progresses. The first recorded outbreaks of syphilis, caused by *Treponema pallidum*, in the fifteenth century involved severe symptoms and rapid progression to death (Quetel 1990). Subsequently, disease progression has slowed and symptoms reduced in intensity (Garnett, Aral *et al.* 1997). The myxoma virus strains, which cause myxomatosis in rabbits, were released in Australia in 1950. The initial virus was associated with a 90% fatality rate, but was soon supplanted by strains with a lower level of virulence (Anderson and & May 1982; Fenner 1965). In both cases an intermediate level of virulence was maintained as the optimum in the trade of between transmission and survival.

In the later phases of an epidemic (III, IV and V) following the introduction of interventions, very different selective pressures will apply. The characteristics of an infection that allow it to be targeted by an intervention become more significant, and will be selected against. In the case of treatment, this selective pressure could be for drug resistance or to avoid being identified (i.e. selection against the characteristics that identify cases for treatment). Under the selective pressures of an intervention new optimum characteristics are selected for, and the most successful organisms are likely to have a different phenotype from those most successful in Phase II.

Selection of traits such as drug resistance or asymptomatic infections could compromise the organism’s ability to exploit its host, avoid immunity or be transmitted. For example, in several organisms, including HIV, *Escherichia coli* and *Salmonella typhimurium* drug resistance is associated with a reduced rate of replication for some mutations, however, compensatory mechanisms have been shown to evolve rapidly in antimicrobial resistant viral and bacterial strains (Gillespie 2001; Levin, Perrot *et al.* 2000).

If the new organisms can compensate for the costs associated with resistance or asymptomatic infection then they will re-establish the Phase II prevalence, causing the failure of the intervention. However, it is likely that resistant or asymptomatic infections are less transmissible and the new steady state prevalence will be lower than that of Phase II. If the selection imposed by the intervention is sufficiently strong it will drive the population of pathogens to extinction. This is the ‘cost of selection’ defined by
Haldane (Haldane 1957), which limits the rate of change imposed by natural selection. The greater this cost the faster a sensitive gene will be eliminated and a resistant gene will dominate, but also the greater the chances of the entire population being eliminated.

In the last phase, Phase V, small, isolated populations of organisms are likely to be selected by the main traits related to their niche as pathogens and the interventions against them, but are also more likely to be susceptible to the fixation or loss of genes through genetic drift. Genetic or neutral drift is where there are random shifts in the frequency of genes and alterations to gene sequences that are selectively neutral (e.g. synonymous changes in bases which do not alter the amino acids coded for) spread through populations (Kimura 1983).

To illustrate the influence of phase of epidemic on STI evolution a mathematical model of two interacting strains is used. The model is that used by Hethcote and Yorke (Hethcote and Yorke 1984) to study gonorrhoea epidemiology, with the additional complexity derived from including two strains. First the ability of a genotype to invade a naive population (Phase I) is explored, and then its ability to invade a population where infection is hyper-endemic (Phase II). The importance of both the basic reproductive number, which determines the relative success of strains in a naive population and also the importance of causing new infections rapidly, thus out-competing rivals are highlighted. The ability of organisms to coexist and compete when they are able to exclude one another and when there is restricted cross immunity are compared. In the extreme case of no cross immunity, the two strains are entirely independent and play no role in one another’s evolutionary success. Then the changed situation in Phases III, IV and V is explored when interventions have been included. In particular, the relative merits of drug resistance and asymptomatic infection as evolutionary strategies are illustrated.
Method

Two versions of a two-strain deterministic model of gonorrhoea in a heterosexual population divided into four activity classes are used. Partnerships in this type of model occur instantaneously. A small proportion of the population (2%) are in the highest activity class, the majority (60%) are in the lowest. For simplicity in balancing the supply and demand for sexual partnerships, both sexes are assumed to have the same distribution of activity. The values of the transmission probability per sex partnership or the duration of infection for each strain are varied, to represent different phenotypes. For example, resistance to antimicrobial therapy would generate a longer duration of infection compared to sensitive infections, when treatment is used. For all infections it is assumed that there is no acquired immunity, so recovery is to the susceptible class. In the case of dual infection, recovery may be from either or both strains.

Both models allow the parameter values describing the characteristics of strains to change during the course of the simulation. This could be to add a new strain or to represent the introduction of a treatment strategy. The impact of treatment is modelled by assigning new values for the duration of infections of the strains. The new values depend on the assumed sensitivity of the particular strain to treatment and whether the infection can be detected and treated (e.g. asymptomatic infections may go untreated for a long period of time). The impact of these changes can then be seen in the context of different phases of the epidemic, depending when the switch is made.

The models are illustrated in Figure 5.1 where the flow of people between categories is shown. In the first model, model 1, (Figure 5.1a) ‘super-infection’ is possible and the host population falls into four categories: susceptible; infected with strain A; infected with strain B; and infected with both strains. Infection with one strain may confer some immunity to infection against the other, with the strength of this cross protection varying from absolute (no super infection) to negligible where the strains are independent. Different strains could vary in their ability to inhibit rival strains, e.g. by faster growth in vivo, but in the following examples cross protection is assumed to be symmetrical.

The second model, model 2, is a special case, with total cross-immunity, which includes the additional complexity of asymptomatic and symptomatic infections being separately represented and strains having an associated propensity to generate symptoms (Figure 5.1b). Asymptomatic infections are widely assumed to be less transmissible than
symptomatic infections, e.g. due to a lower intensity of infection or lower replication rate. However it may also be the case that symptomatic infections are transmitted less frequently due to increases in treatment seeking behaviour, decreases in sexual contacts or increases in condom use. There is no good quantitative evidence to indicate which of these factors is most important and the balance between the two conflicting assumptions is likely to vary in different populations with differing access to education and healthcare. A term has been included in the model to allow the transmissibility of asymptomatic infections to be modified (either increased or decreased) relative to symptomatic infections, depending on available empirical evidence, but this term is not utilised in the examples given here.

Model 2 has five categories: susceptible (X); asymptomatic infections with strain A (A\textsuperscript{a}); symptomatic infections with strain A (A\textsuperscript{s}); asymptomatic infections with strain B (B\textsuperscript{a}); and symptomatic infections with strain B (B\textsuperscript{s}). The probability that when an infection occurs it remains asymptomatic differs between the strains (strain A: 80% asymptomatic and 20% symptomatic; strain B: 40% asymptomatic and 60% symptomatic infections. Mathematical descriptions of the models and the parameters used are presented.
Figure 5.1 Flow diagrams describing the categorisation of infections in two strain models of gonorrhoea

(a) model 1 – a two strain model with superinfection. (b) Model 2 – a two strain model incorporating asymptomatic and symptomatic infection.
Mathematical models

Model 1 - Two-strain model, including superinfection

Model incorporates two strains, two sexes and four activity classes with the possibility of super-infection.

Subscripts refer to the sex and activity class. In the case of sex, $k=0$ for men, $k=1$ for women while $k'$ refers to the opposite sex to $k$ and for activity $l$ defines the class (from 1 to 4), according to average rate of partner change per year, $c_{kl}$. The superscripts $A$, $B$ associated with parameters identify the strain of the infection and $C$ a dual infection.

The subscripts stratify the state variables, which are as follows:

- $X_{kl}$ - population of susceptibles of sex $k$ and activity class $l$
- $A_{kl}$ - population of hosts infected with strain A of sex $k$, activity class $l$
- $B_{kl}$ - population of hosts infected with strain B of sex $k$, activity class $l$
- $C_{kl}$ - population of hosts infected with strains A and B of sex $k$, activity class $l$
- $N_{k,l}$ - total population, sex $k$, activity class $l$

In order to simplify the equations first define the force of infection ($\lambda$) is defined for each strain (A and B) and for coinfection. The force of infection is the product of the transmissibility of the strain ($\beta$), the contact rate ($c$) and the proportion of the total population infected with the strain, contacts with whom are determined by the mixing matrix ($\rho_{klm}$). The force of infection is equivalent to the incidence rate per susceptible.

Thus for an individual of sex $k$, activity class $l$, the forces of infection for strains A or B, or coinfection C are:

$$\lambda_{kl}^A = c_{kl} \beta_k^A \sum_{m=1}^{4} \rho_{klm} \left( \frac{A_{k'm}}{N_{k'm}} \right)$$

$$\lambda_{kl}^B = c_{kl} \beta_k^B \sum_{m=1}^{4} \rho_{klm} \left( \frac{B_{k'm}}{N_{k'm}} \right)$$

$$\lambda_{kl}^C = c_{kl} \beta_k^C \sum_{m=1}^{4} \rho_{klm} \left( \frac{C_{k'm}}{N_{k'm}} \right)$$

The equations describing the model are as follows:

$$\frac{dX_{kl}}{dt} = \mu N_{kl} - X_{kl} \left( \lambda_{kl}^A + \lambda_{kl}^B + \lambda_{kl}^C \right) + \sigma_k^A A_{kl} + \sigma_k^B B_{kl} + \sigma_k^C \left( 1 - (\omega^A + \omega^B) \right) C_{kl} - \mu X_{kl}$$
Parameter definitions used in models (for two general strains, A and B) are given in Table 5.1.

\( P_{klm} \) is a mixing matrix, whose elements \( \rho_{klm} \) are the probability that an individual of sex \( k \) in activity class \( l \) will form a partnership with a member of activity class \( m \) of the opposite sex. The value of \( \rho_{klm} \) depends on the pattern of mixing and could vary from fully assortative, where partnerships only form within the same activity group to random, where partnerships form randomly between different activity classes.

\[
\rho_{klm} = \varepsilon_0 \delta_{lm} + (1 - \varepsilon_0) c_{k,m} \frac{N_{k,m}}{\sum_{l=1}^{4} c_{k,l} N_{k,l}}
\]

\( \delta_{lm} = 1 \) when \( l = m \) and \( \delta_{lm} = 0 \) when \( l \neq m \).

It is necessary that the number of partnerships formed by sex \( k \) match those of the other sex. For the sake of simplicity in these models both sexes are divided into classes of identical size and activity levels. The models can include a range of mixing patterns between activity classes (from fully assortative to random).

The rate of partner change for each activity class is given in (Table 5.2).
### Table 5.1 Table of parameters used in the mathematical models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Default value</th>
<th>Range of values used in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>Entry rate to maintain a constant population size, the entry and exit rates are assumed to be equal.</td>
<td>0.02 per year</td>
<td>n/a</td>
</tr>
<tr>
<td>$\beta^A_k, \beta^B_k$</td>
<td>Transmission rate of strain A or strain B to sex k per contact</td>
<td>0.5 per contact</td>
<td>$0 &lt; \beta &lt; 1$</td>
</tr>
<tr>
<td>$\sigma^A_k, \sigma^B_k$</td>
<td>Recovery rate from asymptomatic infection with A or B per year (recovery rate = 1/duration)</td>
<td>$\sigma = 2$ per year</td>
<td>With treatment, recovery depends on efficacy of treatment and the average time taken to seek treatment.</td>
</tr>
<tr>
<td>$\gamma^A, \gamma^B$</td>
<td>Proportion of contacts with superinfected individuals, which result in transmission of A or B only. (If $\gamma^A + \gamma^B = 0$, then all contacts result in transmission of superinfection, if $\gamma^A + \gamma^B = 1$, then all contacts with coinfected individuals result in the transmission of a single strain.</td>
<td>$\gamma^A = \gamma^B = 0.4$</td>
<td>$0 \leq \gamma \leq 1$</td>
</tr>
<tr>
<td>$\omega^A, \omega^B$</td>
<td>Proportion of those recovering from superinfection that remain infected with strain A or B. The extreme cases are when either all recovery is from mixed infection to the susceptible class ($\omega^A = \omega^B = 0$); or all recovery is from single infections ($\omega^A + \omega^B = 1$). In the examples given in the text, 40% of recovery from coinfection is from a single strain (equally split between the two strains), and 60% is recovery to the susceptible class directly, e.g. due to treatment.</td>
<td>$\omega^A = \omega^B = 0.2,$</td>
<td>$0 \leq \omega \leq 0.5$</td>
</tr>
</tbody>
</table>
### Parameter Definitions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Default value</th>
<th>Range of values used in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\phi^A, \phi^B$</td>
<td>Protective effect of infection with strain A, or strain B on likelihood of transmission of different strains (total protective effect, no coinfection ($\phi^A=\phi^B=0$) to no protective effect ($\phi^A=\phi^B=1$)). An enhancing effect of transmission due to prior infection could also be given by $\phi^A$ or $\phi^B &gt; 1$.</td>
<td>$\phi^A = \phi^B = 0.5$</td>
<td>$0 \leq \phi \leq 1$ for protective effect, or $\phi &gt; 1$ for enhancing effect.</td>
</tr>
<tr>
<td>$P_{klm}$</td>
<td>Mixing matrix, element $p_{klm}$ is probability that individual of sex $k$ in activity class $l$ will form a partnership with a member of activity class $m$ of the opposite sex.</td>
<td>See below</td>
<td>n/a</td>
</tr>
<tr>
<td>$c_{kl}$</td>
<td>Contact rate of individual of sex $k$, activity class $l$ (see below)</td>
<td>See below</td>
<td>n/a</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Pattern of mixing (0=fully assortative, 1= random)</td>
<td>1 (random)</td>
<td>$0 \leq \epsilon \leq 1$</td>
</tr>
<tr>
<td>Activity class</td>
<td>Rate of partner change (per year)</td>
<td>Proportion of population in class</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>
Relation between $R_0$ and recovery rate and transmissibility

When varying the transmissibility or recovery rate, the following formula is used to for calculations to keep $R_0$ constant:

$$R_0 = \frac{\beta c}{\mu + \nu}$$

$R_0$ is the reproductive number (defined as the average number of new infections caused by an index case), $\beta$ is the transmission coefficient, $c$ is the contact rate, $\mu$ is the entry rate into the population and $\nu$ is the recovery rate, which is related to the duration of infection as follows:

$$\nu = \frac{1}{D + \mu}$$

Model 2 - Two strain model, including asymptomatic and symptomatic infections

Model incorporates two strains, two sexes, four activity classes with asymptomatic and symptomatic infection.

Formulae to accompany two-strain model incorporating asymptomatic and symptomatic infections with no superinfection. Superscript 'a' or 's' denotes asymptomatic and symptomatically infected populations respectively, e.g. $A^a_{kl}$ is the population infected with strain E who are asymptomatic. Capital superscripts indicate the strain as before.

The force of infection ($\lambda$) is again defined, for strains A and B, assuming no coinfection:

$$\lambda^A_{kl} = c_{kl} \beta^A_k \left( \psi^A \sum_{m=1}^{4} \rho_{klm} \left( \frac{A^a_{km}}{N^a_{km}} \right) + \sum_{m=1}^{4} \rho_{klm} \left( \frac{A^s_{km}}{N^s_{km}} \right) \right)$$

$$\lambda^B_{kl} = c_{kl} \beta^B_k \left( \psi^B \sum_{m=1}^{4} \rho_{klm} \left( \frac{B^a_{km}}{N^a_{km}} \right) + \sum_{m=1}^{4} \rho_{klm} \left( \frac{B^s_{km}}{N^s_{km}} \right) \right)$$
The equations describing the model are as follows:

\[
\frac{dX_{kl}}{dt} = \mu N_{kl} - X_{kl} \left( \lambda^A_{kl} + \lambda^B_{kl} \right) + \sigma_{k}^A A_{kl}^a + \sigma_{k}^A A_{kl}^s + \sigma_{k}^B B_{kl}^a + \sigma_{k}^B B_{kl}^s - \mu X_{kl}
\]

\[
\frac{dA_{kl}^a}{dt} = \theta^A X_{kl} \lambda_{kl}^A - \sigma_{k}^A A_{kl}^a - \mu A_{kl}^a
\]

\[
\frac{dA_{kl}^s}{dt} = (1 - \theta^A) X_{kl} \lambda_{kl}^A - \sigma_{k}^A A_{kl}^s - \mu A_{kl}^s
\]

\[
\frac{dB_{kl}^a}{dt} = \theta^B X_{kl} \lambda_{kl}^B - \sigma_{k}^B B_{kl}^a - \mu B_{kl}^a
\]

\[
\frac{dB_{kl}^s}{dt} = (1 - \theta^B) X_{kl} \lambda_{kl}^B - \sigma_{k}^B B_{kl}^s - \mu B_{kl}^s
\]

The models were solved numerically using a standard fourth order Runge-Kutta method.
Table 5.3  Additional parameters for model 2, including asymptomatic infection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Default value</th>
<th>Range of values used in the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta^A, \theta^B$</td>
<td>Percentage of infections with A or B which are asymptomatic.</td>
<td>$\theta^A = 0.8$ $\theta^B = 0.4$</td>
<td>n/a</td>
</tr>
<tr>
<td>$\psi^A, \psi^B$</td>
<td>Transmissibility of asymptomatic infections as a percentage of symptomatic infections transmissibility. (If $\psi=0$, then only symptomatic infections are transmitted, if $\psi=0.5$, the transmissibility of asymptomatic infections is 50% that of symptomatic, for $\psi=1$, transmissibility of both infections is the same. Potentially there could be an increase in the relative transmissibility of asymptomatic infections, due to lack of awareness of infections, and therefore no change in sexual behaviour (e.g. condom use or abstention).)</td>
<td>1 (No difference between asymptomatic and symptomatic infections)</td>
<td>n/a</td>
</tr>
<tr>
<td>$\sigma^A_{a_k, b_k}$</td>
<td>Recovery rate from asymptomatic infection with A or B per year (recovery rate = 1/duration)</td>
<td>$\sigma = 2$ per year, i.e. average duration of 6 months without treatment, decreasing to 10 per year, i.e. 1.2 months duration with treatment.</td>
<td>With treatment, recovery depends on efficacy of treatment and the average time taken to seek treatment.</td>
</tr>
<tr>
<td>$\sigma^S_{a_k, b_k}$</td>
<td>Recovery rate from symptomatic infection with A or B per year (recovery rate = 1/duration)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

**Competition between strains during phases I and II**

Phase I and II describe the Initial spread of infection in a naïve population and the early endemic situation. The outcome of competition between strains is investigated in the presence and absence of superinfection (model 1).

Theory is used, as illustrated by model results, to predict the result of competition between strains during the initial spread and saturation of infection (Phase I and II). First, if there is cross protection the outcome of competition between strains will be determined by their relative $R_0$. The strain with the higher $R_0$ will dominate and drive other strains to extinction. Recent studies of HIV, for example, suggest that HIV-1 will eventually competitively exclude HIV-2 (Anderson and May 1996).

This general rule of competitive exclusion with a higher $R_0$ applies for a deterministic large population approximation, when there is total cross immunity. However, it is possible that despite a lower basic reproductive number a strain with a higher transmissibility (and by implication shorter duration of infectiousness) could spread first, only to eventually be overtaken by the strain with a higher basic reproductive number associated with a lower transmissibility but longer duration, which could persist at an extremely low prevalence early in the epidemic (Lipsitch and Nowak, 1995). In smaller populations the first strain drives another strain to extinction before the overall reproductive number is made to count. If two strains have the same basic reproductive number, which is likely if they are genetically very similar, they will coexist. However, a strain introduced when another is already endemic can only invade if it has a higher $R_0$ than the existing strain.

Figure 5.2 illustrates the importance of transmissibility (in model 1), during the initial phase of the epidemic (total cross immunity), with the course of epidemics illustrated in Figure 5.2a, and the equilibrium prevalence in Figure 5.2b. Both strains have the same $R_0$ (to permit coexistence) but different transmission parameters. The transmissibility of strain B is increased and, in compensation, its duration of infection decreased, while parameters for strain A were held constant. When the strains are identical in transmissibility and reproductive number they cause similar numbers of cases. When B is less transmissible the initial increase of strain B is slower and it ultimately causes fewer cases. This is reversed as the transmissibility of B exceeds that of A. The total number of infections is the same in each case since the $R_0$ of both strains is constant.
High transmissibility in the growth phase enables a strain to establish itself in the available ecological niche quickly and is a selective advantage.

The results described above apply to mutually exclusive strains, but it is quite possible that multiple strains coexist within infections. The simplest case, with two strains, is explored first and ‘superinfection’ is defined as infection with more than one strain. The evolutionary outcome of superinfection will depend upon which organisms are transmitted to contacts and when recovery occurs.

Superinfection can occur in two ways; by serial acquisition i.e. acquisition of one strain followed by the separate acquisition of another strain, or by the concurrent transmission of both strains from a superinfected individual. Both are biologically feasible and may lead to different outcomes in terms of competition between the two strains. Serial transmission may present more difficulties for the invading pathogen, since it not only has to overcome the host defences, but also has to establish itself in the face of competition from the resident strain. To transmit to a pre-infected individual a strain may need to have a higher replication rate or occupy a different ecological niche which avoids direct competition in the host. Alternatively pre-infection may actually aid further infections, by altering the host environment to be more hospitable to invading bacteria e.g. by changing the pH or causing inflammation. Different strains could conceivably have differing success in male and female hosts, which could allow both to persist. The order of serial infection may be important, with a hierarchy of invasiveness of different strains. However, in the current model this level of complexity is not explored.
Figure 5.2  Competition between strains

The outcome of spread of 2 strains in the absence of superinfection with the same basic reproductive number for each strain but variation in the transmission coefficient of Strain B. Graph a – the time course of the epidemic as a whole and the epidemic of strain B. The bars show the equilibrium prevalence of the two strains. Graph b – The equilibrium percentage of strains that are B as a function of its transmission probability. ($\beta_A = 0.5$, $\sigma_A = 2$; $\beta_B = 0.1,..,0.9$, $\sigma_B = 0.3,..,3.62$)
The timescale over which multiple infecting organisms coexist is important. If a strain can out-compete a rival before the next opportunity for transmission, then superinfections will be less important in the overall prevalence of infections. Instead there would be a hierarchy of replacement and direct competition between strains, where ability to dislodge a rival from a host would play a role in the success of competing strains. Assuming that superinfection lasts long enough to be transmitted directly to another individual, what actually happens within the next infected individual will be the result of competition between the strains for resources. Another important interaction, which gonococci in particular are capable of, is the exchange of genetic material, potentially resulting in the evolution of novel strains in a short space of time. *N. gonorrhoeae* are competent for gene transfer or plasmid exchange all the time, so it seems highly likely that this is an important mechanism for this organism. In these models, however it is assumed that strains remain distinct during superinfection.

Recovery from superinfection may be faster than from single infections, e.g. due to a greater host immune response or increased likelihood of symptoms and hence treatment seeking behaviour. Alternatively, superinfections may be more difficult for the host to clear, e.g. due to increased replication by the competing strains. Recovery from superinfection may be to the susceptible class, e.g. if effective treatment is obtained, or to single infection with either strain, e.g. if competition between strains removes one strain, or if strains have different sensitivities to antimicrobial treatment. The recovery rate from superinfection may be faster or slower than for single infections and may be dependent on the recovery rates of the individual strains present.

If cross immunity is relaxed and superinfection can occur, various outcomes are possible, depending on the selective pressures acting on the system and the characteristics of the two competing strains (Anderson 1994; Anderson and May 1996). The equilibrium prevalence of the two strains is explored in Figure 5.3 where there is only a moderate level of cross protection so that coexistence of strains in the population will be frequent. Three sets of possibilities are explored: (1) both strains are transmitted concomitantly from a superinfection and recovery is from both strains simultaneously, e.g. all recovery is due to treatment and both strains are equally susceptible. In this case superinfection becomes the sole form of infection despite cross protection unless it causes more rapid recovery, giving an advantage to single strain infections. (2) Both strains are transmitted together but recovery from superinfection involves the removal of one strain before recovery from the other strain becomes possible. For example, this
could be due to within-host competition, where one strain rapidly drives the other to extinction and there is some kind of hierarchy of invasiveness, or alternatively there is a differential response to treatment. Here superinfection can increase the average duration of infections and the relative recovery rates of single and dual infections determines their relative frequency with a longer duration of infection for a strain providing a greater advantage than a comparable higher transmissibility. (3) Transmission from a superinfected host always generates a single infection. This could be due to stochastic effects or differences in transmissibility of the two strains. Here superinfection is much less common.

Stronger cross protection decreases the overall prevalence of infection (with no cross protection, no potential infections are prevented). With no superinfection, an invading strain may only invade if its $R_0$ is higher than the existing strain. Superinfection relaxes the impact of phase of an epidemic on the outcome of competition between strains, as the timing of a strain entering the population no longer determines its relative success. Additionally, a strain with a lower $R_0$ may invade and coexist with the more infectious strain. The relative proportions are determined by the $R_0$ of the two strains and with some cross protection the relative duration of infection is critical because long infections prevent proportionately more infections with the opposite strain than short ones.
Figure 5.3  The equilibrium prevalence of individual infections and coinfection with two strains

Using model 2, for a range of assumptions about the biology of superinfection. Intermediate cross immunity $\phi_A=\phi_B=0.5$ throughout. Transmission: either $\beta_A=\beta_B=0.5$ or $\beta_A>\beta_B$ ($\beta_A=0.5$, $\beta_B=0.2$), and $\beta_C=\beta_A$ or $\beta_C=\beta_B$. Recovery: either $\sigma_A=\sigma_B=0.5$ or $\sigma_A>\sigma_B$ ($\sigma_A=2$, $\sigma_B=0.788$) (greater recovery rate implies shorter duration). Transmission of both strains from superinfection: ($\gamma_A=0$), except last two columns ($\gamma_A=0.5$).
In phases III and IV, controls take effect resulting in declining incidence and prevalence. The impact of the introduction of a resistance phenotype is investigated (model 1). The implementation of effective treatments or changes in host behaviour imposes new selective pressures in the ongoing competition between host and parasite. This may select for novel traits, such as resistance, or for increases in the likelihood of asymptomatic infection. The success of different evolutionary strategies for the pathogen depends upon a trade-off between the costs and benefits of the phenotypic change. Possible evolutionary strategies are constrained by the mechanisms available to the organism from within its own gene pool or drawn from other organisms through recombination or the transfer of plasmids (Condit 1990). Because of rapid replication and various genetic mechanisms e.g. DNA transfer, the evolution of bacteria can be extremely rapid. If competition between strains for hosts is intense, small advantages in reproductive fitness can quickly translate to large changes in frequency distributions of different strains (Levin and Bergstrom 2000; Lipsitch 2001). Frequent population bottlenecks, e.g. during transmission to a new host and bacterial population expansion in a host provide fertile conditions for the rapid evolution and distribution of new strains.

In Phases III/IV of an epidemic, the implementation of controls can therefore exert a strong selective pressure on the bacterial populations resulting the in the evolution of novel strains. Treatment of symptomatic gonorrhoea infections has led to the evolution of resistant strains. E.g. *Neisseria gonorrhoea* strains resistant to penicillin were isolated 30 years after the introduction of the drug (Phillips 1976). Following the introduction of other antimicrobial compounds new resistant strains have appeared, e.g. to tetracycline (MMWR 1985) and fluoroquinolones (Fox, Knapp *et al.* 1997). There has been general theoretical work modelling the evolution and spread of resistance in bacteria which has concentrated on non-specific consumption of antibiotics and nosocomial infection (Austin 1999; Lipsitch and Levin 1997; Stewart, Antia *et al.* 1998). Here the impact of treatment on two competing strains is modelled.

Figure 5.4 illustrates the impact of treatment on two competing strains, with no superinfection. In Figure 5.4a before treatment, both strain A and B have the same parameters and so each contributes 50% of total prevalence. Strain A is sensitive and
Chapter 5 - Evolution of gonorrhoea and chlamydia

strain B resistant to treatment. When treatment is implemented, the recovery rate of the susceptible strain A is greatly increased, lowering its effective reproductive number. Strain B rapidly outcompetes A, and drives it to extinction. If treatment reduces the reproductive number of A to less than one it will become extinct, whether or not there is competition from another strain. Even if the basic reproductive number ($R_0$) has not been reduced to less than one, competition between strains can drive the sensitive strain A from the population when there is complete cross protection. Despite the reduction in prevalence of the sensitive strain the total prevalence of gonorrhoea is eventually restored because the resistant strain is released from competition.

The effect of resistant infection being introduced rather than being common at the outset is illustrated in Figure 5.4b. Again the reproductive numbers of A and B are identical in the absence of treatment but A is sensitive to treatment and B resistant. In the absence of treatment, strain B would not be able to invade. Two alternatives are illustrated, first, when treatment has no effect on B it invades and rapidly spread, replacing A, and re-establishing prevalence. Second, treatment has some effect on strain B, e.g. due to retreatment after initial treatment failure. Here B is still able to invade, but somewhat more slowly and with a lower final prevalence, due to a lower effective reproductive number. Which alternative is most likely depends upon the mechanism of resistance, the other costs it imposes and the availability of second line drugs.

Resistant strains are able to rapidly out-compete sensitive strains when there is no superinfection due to the introduction of a significant difference in the effective reproductive number. Without superinfection, two strains can only coexist if they have the same $R_0$. When superinfection is permitted, the situation becomes more complicated and is discussed in detail elsewhere (Anderson 1994; Anderson and May 1996). Competition between strains is no longer absolute and strains with different basic reproductive numbers can coexist in a host population.
Figure 5.4  Impact of treatment on resistant and susceptible strains during Phases III and IV of an epidemic in the absence of superinfection (i.e. total cross immunity)

Graph a – the resistant stain is present when infection is introduced. Before treatment: $R_0A = R_0B$; transmissibility (per contact) $\beta_A = \beta_B = 0.5$; recovery (individuals per year) $\sigma_A = \sigma_B = 2$. After treatment: transmissibility $\beta_A = \beta_B = 0.5$; recovery $\sigma_A = 10$, $\sigma_B = 2$.

Graph b – resistant strain (strain B) introduced with 1 infected individual of each sex at the same time as treatment. Before treatment: $R_0A = R_0B$; transmissibility (per contact) $\beta_A = \beta_B = 0.5$; recovery (individuals per year) $\sigma_A = \sigma_B = 2$. After treatment, transmissibility $\beta_A = 0.5$, $\beta_B = 0.5$; recovery $\sigma_A = 10$, $\sigma_B = 2$, $\sigma_B = 4$.
Competition between strains during Phases III, IV and V – Model 2

During phases III, IV and V controls take effect. The model used includes resistance phenotypes and asymptomatic infections (model 2).

During Phases III, IV and V, in the presence of treatment asymptomatic infections may play an extremely important role in determining the success of a strain. The effect of different treatment strategies is investigated, on competition between strains with different asymptomatic and resistant phenotypes using model 2.

In Figure 5.5 both strains have the same basic reproductive number prior to treatment and the same transmission/duration parameters, but strain A generates a higher proportion of asymptomatic infections (80:20 asymptomatic: symptomatic) compared to B (40:60). For the purposes of this discussion, it is assumed that the recovery rates, for a particular strain, of both asymptomatic and symptomatic infections are the same in the absence of treatment. The effect of treatment is incorporated in the model by decreasing the duration of infection of those treated, according to whether the strain is susceptible or resistant. Outcomes are shown 2 years after treatment, when levels have largely stabilised i.e. in Phase IV of the epidemic, the endemic situation after controls are introduced.

Column (a) shows the distribution of infections by strain and by asymptomatic or symptomatic infection before treatment. As expected, each strain accounts for 50% of the total infections and infections are asymptomatic and symptomatic according to the ratios above. If symptomatic infections are treated and both strains are sensitive to drug (column b) there is a modest decrease in the overall prevalence. While symptomatic infections decrease quite dramatically prevalence is maintained by asymptomatic infections. The proportion of prevalent infections that are asymptomatic increases for strain A to 95% and for strain B to 83%. Strain A has a higher probability of causing asymptomatic infection and consequently a greater proportion of those infected are untreated and the proportion of all infections caused by A increases to over 90%.
Figure 5.5 The impact of treatment targeted at symptomatic or all infections on the equilibrium prevalence of strains with different levels of resistance and propensities to cause asymptomatic infections.

Column a: No treatment - Transmissibility $\beta^A = 0.5; \beta^B = 2$. Column b: Treatment of symptomatic infections $\sigma^A = \sigma^B = 10$. Column c: Treatment of all infections $\sigma^A = \sigma^B = 8$. Column d: All infections treated - Recovery rates of treated infections $\sigma^A = 10, \sigma^B = 4$. Column e: Symptomatic infections only treated - Recovery rates of treated infections $\sigma^A = 10, \sigma^B = 4$.

Treatment regime

- No treatment
- Treatment of symptomatic infections, both strains susceptible
- Treatment of both asymptomatic and symptomatic infections, both strains susceptible
- Treatment of both asymptomatic and symptomatic infections, B-resistant
- Treatment of symptomatic infections only, B-resistant

Population infected 2 years after treatment introduced out of total population of 10000
The impact of the introduction of a screening programme, or comparable strategy e.g. contact tracing and partner notification, which results in the treatment of both asymptomatic and symptomatic infections is illustrated in column (c). If treatment decreases the basic reproductive number of strains A and B to less than one, both will become extinct. If however the basic reproductive number for each strain remains above one, both infections can persist, retaining the same proportions of A to B and asymptomatic to symptomatic infections, but at a much lower overall prevalence.

A similar scenario is illustrated in column (d) where both types of infection can be detected and treated, but strain A is sensitive and B resistant. Competition between A and B will quickly drive strain A to extinction due to a lower effective number. The recovery rate of the resistant strain B is still increased due to re-treatment with second line options so its prevalence falls.

In column (e), as in column (b), symptomatic infections alone are treated, and strain A is sensitive and B resistant, but strain A is more likely to lead to asymptomatic infections. Both strains persist for at least two years, but the propensity to cause asymptomatic infections is a greater advantage than resistance, illustrating the impact that failure to identify and treat asymptomatic infections may have. Unless there is an effective screening program to identify asymptomatic cases, surveillance data on the incidence of symptomatic gonorrhoea might show a dramatic decrease masking the continued high levels of asymptomatic infections. For columns (e) and (b) the incidence of symptomatic infections of both strains declines and eventually reaches a new equilibrium point, when strain A outcompetes B. The time taken to reach the new equilibrium is determined by the relative difference between the $R_0$ of A and B after treatment. For these particular parameters, strain A has a higher $R_0$ than B after treatment and will eventually dominate, but for different proportions of asymptomatic infections for the strains or different responses to treatment, strain B would dominate. If the benefit conferred by resistance is equivalent to the benefit gained from avoiding treatment due to a higher proportion of asymptomatic infections, i.e. if the effective reproductive numbers after treatment is introduced are the same, both strains can coexist indefinitely. If the reproductive numbers are similar, then both strains may coexist for many years before one or other dominates.

Empirical evidence of asymptomatic strains gaining a selective advantage is scarce probably because it has not been sought. In the case of gonorrhoea, where asymptomatic infections are common, particular strains may be associated with asymptomatic, or very
Chapter 5 - Evolution of gonorrhoea and chlamydia

mild infection e.g. the AHU auxotype (Crawford, Knapp et al. 1977). In Washington, the prevalence of the AHU auxotype has declined steadily from 52% in 1971 to 1074 to 0% in 1994 to 1996. This was believed to be due to increased screening efforts, resulting in treatment of more asymptomatic infections. More recently (1996 - 1997), the CU auxotype, which is also associated with asymptomatic infection, has increased in prevalence in this region, despite an overall decline in gonorrhoea rates of 80% (Whittington and Holmes 2000). The exact reasons for the changes in subtype distribution of gonorrhoea are not well understood. This CU auxotype is more likely than other auxotypes to be misdiagnosed as nongonococcal urethritis (NGU), which may account for part of the increase. Other possible explanations include: decreased screening, decreased competition between strains, or genetic drift resulting from purely stochastic events facilitated by the lower population size and the random introduction and disappearance of subtypes.
Discussion

The ecology and evolution of an infectious disease are influenced by both the natural dynamics of epidemics and the interventions used to control them. An extension of a mathematical model which includes two competing strains, with the possibility of superinfection or asymptomatic infections is used to explore the outcome of competition. The results illustrate the conditions that lead to coexistence and the optimum phenotypes of organisms according to the phase of epidemic. In the early phases of an epidemic, where the majority of contacts are with susceptible hosts, the simplest models of competition suggest that transmissibility is a key attribute. If strains can coexist within a host, the impact of transmissibility on the success of competing strains is reduced and instead, the duration of infection becomes paramount. Founder effects are also important at this stage, as once a strain is established in the population, only strains with a higher basic reproductive number ($R_0$) can invade.

The biological mechanisms allowing coinfection and its clinical consequences are poorly specified. To generate testable predictions from models including superinfection, assumptions need to be based on the biology of specific organisms. For example, there is convincing evidence (Martin and Ison 2003) that mixed infections of gonococci do occur and that two strains can be transmitted simultaneously, depending on the relationship between the course of infection and sexual exposure. However, competition between strains within the host is intense and it seems likely that one of the strains or a novel, composite descendant, resulting from gene exchange between different lineages will rapidly come to dominate in a particular host and be transmitted onwards. It is likely that intense competition between strains in high risk (core) individuals may be important in driving the evolution of novel strains.

The impact of different treatment strategies on the evolution of STIs like gonorrhoea may differ at different phases of an epidemic. Early interventions, during the growth phase, are likely to have more impact than those made once a strain is endemic. The need for identifying and treating asymptomatic infections is highlighted. Treatment of symptomatic infections only has a small effect on the total prevalence of infections (depending on the proportion of asymptomatic infections), but reduces the number of symptomatic infections. The increase in the proportion of infections that are asymptomatic may result not from genetic changes in the population of organisms, but
simply be a product of the asymptomatic infections not being curtailed in comparison to symptomatic infections.

A decrease and subsequent stabilisation in the incidence of symptomatic cases is seen in the model when only symptomatic infections are treated, therefore, the observed decline, and subsequent levelling off of reported cases, e.g. USA (CDC 1999), could be in part explained by this effect. There will be a selective advantage to organisms that are prone to cause asymptomatic infections, which could well further increase the proportion of infections without obvious symptoms. A major concern would be that such infections still have serious long-term sequelae. In the example shown, strains with a high proportion of asymptomatic infections could compete well, even against strains resistant to antimicrobial therapy. For all cases it is clear that treatment will act as a strong selective force for novel strains. Advantages in resisting or avoiding treatment will result in the rapid spread of a strain through the population and elimination of competitors.

In the simulations presented in this thesis, extreme levels of competition between strains are assumed, which in reality may not exist, due to heterogeneities in hosts or more subtle differences in the biological properties of the strains and their ability to colonise different hosts. The deterministic model assumes that partnerships are instantaneous and there is no concurrency. Therefore two features of real partnerships e.g. duration of partnership and concurrency, which have been shown to affect the epidemiology of STIs (Ghani, Swinton et al. 1997; Morris and Kretzschmar 1997) are not captured in these models. Models that include more detail and have been validated are necessary to predict the outcome of treatment strategies and informing decision-makers.

Only through careful monitoring of the genotype of organisms, the link between the genotype and the in vivo phenotype and the relationship to epidemic phase will it be possible to gain a full understanding of STD evolution. Such an understanding would underpin the construction of the detailed and well validated models necessary to predict the outcome of treatment strategies.
Chapter 6 Discussion

This chapter draws together the findings of the thesis. Several themes have emerged from the results presented and a variety of important issues in sexually transmitted disease epidemiology raised. These can be considered in terms of biology, behaviour and interventions. The future directions of research on mathematical models of STIs are discussed.

Gonorrhoea and chlamydia are an important public health problem in the developed world. Despite readily available treatment and a commitment from the UK government to control STIs, there has been a sustained increase in gonorrhoea and chlamydia diagnoses. There remains a need for better control. A better understanding of the epidemiology of these infections is necessary to allow appropriately targeted control interventions. The mathematical models presented in Chapter 2, 3 and 4 allow interventions to be compared.

There are various unique features of STI epidemiology to consider when developing mathematical models (Anderson 1999). For STIs, the course of an epidemic is determined by the rate of partner change and not population density as for other infections such as influenza or measles. There is also much more heterogeneity in individual risk than for airborne or community-acquired infections. High rates of partner change increase the effective size of the sexual network available for infection. In addition, the importance of mixing patterns (i.e. partner choice) has been recognised as a factor influencing the epidemiology of an STI (Garnett & Anderson, 1993 and Ghani, 1997).

Accurate parameter estimates are essential for realistically parameterising mathematical models, but also for determining the impact of interventions. There are ethical and practical difficulties associated with conducting experiments on human infection, although a small number of investigations are ongoing for male gonococcal infection.

Extensive parameter analysis was conducted in Chapter 3 to choose the model scenario which provided the best fit to the data. Whilst this study highlights the need for much more information for several parameters, this approach can indicate the extent to which parameter uncertainty is likely to impact on qualitative model results. In addition, this highlights areas where additional empirical research could be undertaken.

The epidemiology of sexually transmitted infections is characterised by heterogeneity. In terms of the natural history of infection, strains circulating in the population may
differ in their susceptibility to antibiotics, their ability to survive in particular anatomical sites, their ability to colonise men or women, their likelihood of causing serious disease and their chances of being detected by diagnostic tests. The emergence and spread of novel strains is the subject of Chapter 5. Maintaining surveillance and knowledge of the biology of these organisms to identify the emergence of new strains which could subvert current interventions is crucial for the future treatment and management of infections.

Probably the most interesting and most studied but least well quantified aspect of STI epidemiology is human sexual behaviour. Risk of acquiring an STI is complex. Human sexual behaviour is highly variable across a population and within an individual’s lifetime. Not all humans are at equal risk of acquiring an STI. Also not all humans with the same contact rate with new sexual partners are at the same risk. Whilst most markers of risk concentrate on individual behaviour, studies such as those by Low presented in Chapter 3 show the importance of an individual’s position in the sexual network in raising or lowering their risk of acquiring infection relative to the general population.

This heterogeneity in risk also plays a role in ensuring the continued transmission of STIs. Both gonorrhoea and chlamydia occur more often in those who are difficult to reach through standard health care programmes, due to social exclusion. The challenge for health care providers is therefore to provide appropriate interventions and to maintain those interventions to include new cohorts of young people as they become sexually active. Alongside interventions, maintaining surveillance is essential to be able to assess the efficacy of interventions.

The models presented here have attempted to incorporate some of the complexity and heterogeneity in novel frameworks and to use available data in new ways. In Chapter 2 a model including both gonorrhoea and chlamydia is presented. The aim was to investigate the possible mixing patterns by activity in the population which would give rise to the observed proportion of coinfections with both gonorrhoea and chlamydia. This proved to be difficult due to the number of poorly quantified parameters. However this approach could be pursued, validated and tested with more specific data.

The advantage of the data presented in chapter 3 was that both behavioural and epidemiological parameters were estimated for a well defined population in South East London. Extensive analysis of the impact of the parameter choices on the model outputs made the results more robust. The parameter values obtained for the duration of infection and the transmission probability are well within reasonable limits, which is
reassuring. Even a simple deterministic model may perform reasonably well in this type of analysis, given appropriate choices of complexity to be included. In this instance, the inclusion of ethnic specific choices of partner ethnicity captured some of the most relevant aspects of gonorrhoea in this population.

Another novel source of information about the epidemiology of gonorrhoea, or chlamydia is the number of people who become reinfected and the length of time between infections. As discussed in chapter 4 reinfec tion and the lack of a significant sustained immunological response to these infections, presence of asymptomatic infections and the concentration of disease within high risk individuals, means that reinfection is common. Reinfection also represents a potentially useful measure of the success of an intervention, which is relevant to the health of those in whom reinfection is prevented.

Asymptomatic infection is an important component of the epidemiology of infection with gonorrhoea and chlamydia. Unrecognised or asymptomatic infections represent a reservoir of infection which may go untreated for a substantial period of time; this may increase the probability that the infected person will develop complications. In addition, individuals without symptoms are unlikely to modify their behaviour whilst infectious, so the potential for onwards transmission of infection remains while they are infectious. Little is known about the relation between symptoms and transmissibility for either gonorrhoea or chlamydia but modelling approaches can investigate a range of scenarios.

In Chapter 5, a theoretical analysis of the different selective pressures which are exerted on populations of bacteria was undertaken. The interplay between asymptomatic and symptomatic infections and resistant and susceptible infections was explored. In general treatment selects for drug resistance and treatment of symptomatic infections selects for asymptomatic infections. Depending on the effect of treatment on the $R_0$ of a strain, either outcome may be selected for. For example treatment of only symptomatic infections may favour a predominantly asymptomatic, drug sensitive strain over a resistant but predominantly symptomatic one. Screening and contact tracing which identify and treat asymptomatic cases will tip the balance in favour of the evolution of drug resistance. Understanding these selective pressures requires constant monitoring the changes in the natural history of bacterial infections and an appreciation of the expected effects of an intervention.

Throughout this thesis, deterministic transmission models have been used to investigate the epidemiology of gonorrhoea and chlamydia. Recent interest has centred on network
formulations. Both types of modelling approach have their advantages. Deterministic models are, by definition well-defined and for a given set of parameters produce identical outputs. Individual-based network models give a range of outputs for any given set of input parameters and therefore require more analysis to interpret. In both cases the form of the model itself has unpredictable elements, such as the impact that the choice of partner matching algorithm has on the overall structure of the sexual network and whether this is true to the formation of partnerships in reality.

All models involve simplification and abstraction of the complexities that make up the sexual behaviour and transmission of STIs in a population. Whilst it may seem that there is a debate of which model is the “right” model to use, in fact the appropriateness of a model depends very much on the question one wishes to answer. A robust comparison of different methods of analysing model performance for different tasks is needed. Several authors are attempting to do this with respect to STI epidemiology and a few have compared their results to empirical data (Eames and Keeling 2002; Ghani and Garnett 2000; Morris 1997), but most have simply shown how different models perform consistently in different ways. The future of mathematical modelling of sexually transmitted infections should be characterised by close collaboration between clinical scientists and epidemiologist who collect and understand the context of data and theoreticians who can build an accurate picture.

**Future directions**

Modelling of STIs in the future will require continuation of the process of parameter estimation and model validation using good quality data. Only in this way can the field progress. Other model structures, in particular individual based network models, are emerging as important tools for understanding the social component of STI transmission and as the tools for interpreting and analysing these models continue to improve, they will surely produce fascinating, new insights into the epidemiology of STIs. An interesting feature is the apparent robustness of STIs to interventions, which is not predicted by most current models. The properties of human sexual networks hold the key to a fuller understanding of sexually transmitted disease. Further work is needed to improve the realism of such models or at least more fully validate the findings from more abstract models with real life data.
Conclusions

As outlined in chapter 1, infections with gonorrhoea and chlamydia represent a significant public health threat. However, in large part due to the difficulty in reaching those at highest risk, neither infection is well controlled. The modelling studies outlined demonstrate the need for accurate data to define the parameters which determine the reproductive number of the infection, namely, the transmission probability, the duration of infectiousness and the contact rate in the population. This thesis has used some new data and reanalysed existing data in novel ways to investigate the epidemiology of gonorrhoea and chlamydia. The main results are that realistic outputs can be achieved when empirical data are used to parameterise mathematical models. The sexual behaviour of the general population is difficult to quantify, since it is highly heterogeneous and therefore simulations based on smaller populations, such as those in Chapter 3 and 4 are useful for validating and testing hypotheses. Data were used in new ways to enable improved parameter estimation and incorporation of relevant complexity in simple models. A recurring theme in the studies presented here is the absence of good estimates of many of the parameters needed in a mathematical model. This absence of accurate information highlights what is needed from empirical studies and should promote caution in interpreting model results.

Appendix

Antibiotics used in treatment of gonorrhoea and chlamydia

This list is not intended to be exhaustive, but to illustrate the differences between the major classes of antibiotics used in the treatment of gonorrhoea and chlamydia, as described in USA and UK treatment guidelines (MMWR 1998; MMWR 2002a; Radcliffe, Ahmed-Jushuf et al. 1999). Antibiotics are either bacteriostatic, i.e. prevent reproduction and growth or bactericidal, i.e. cause death. Table 1.2 notes the first reports of clinically significant drug resistance in *N. gonorrhoeae* to various antibiotics. The MEDSCAPE drug directory was searched for the major classes of antibiotics used for treatment of gonorrhoea and chlamydia in the UK (Table A.1) and USA (Table A.2) (Medscape 2001). The chemical structures are illustrated in Table A.3.
Penicillins

Natural penicillins (penicillin G, penicillin V)
Semisynthetic penicillins, e.g. aminopenicillins (ampicillin, amoxycillin), pipericillin
Extended spectrum penicillins.

Mechanism of action

The same mechanism of action applies to natural and semisynthetic penicillins. Bactericidal, β-lactam antibiotics act by inhibition of mucopeptide synthesis in the bacterial cell wall. Penicillins are hypothesised to act as analogues of acyl-d-alanyl-d-alanine, binding reversibly to various enzymes (penicillin binding proteins or PBPs), and thereby disrupting mucopeptide synthesis. This results in osmotically unstable organisms, which normally lyse. β-lactam antibiotics are most active when cells are actively dividing and synthesising new cell walls.

Natural penicillins are normally active against non-penicillinase producing strains of *Neisseria gonorrhoeae*, but due to increasing prevalence of resistant strains CDC changed guidelines in 1989 and no longer recommends penicillins as first line therapy (MMWR 1989). Penicillin is not effective against chlamydial infections.

Structures (Table A.3)

Chemistry

Natural penicillins

Natural penicillins are produced by the fermentation of mutant strains of *Penicillium chrysogenum*. Various forms, with different side chains can be produced by the addition of specific chemicals to the culture media. Of these, penicillin V (phenylacetic acid) and penicillin G (phenoxyacetic acid) are of clinical interest. The alternative side chains (phenoxyethyl or phenyl, respectively) result in different pharmacological properties: penicillin V has more acid stability but decreased antibacterial activity compared to penicillin G.

Aminopenicillins

Aminopenicillins are semisynthetic penicillin derivatives produced by acylation of 6-aminopenicillanic acid (6-APA). They are characterised by a free amino group at the alpha position R group on penicillin nucleus. This increases the activity of aminopenicillins against gram-negative bacteria compared with natural penicillins by improving the penetration of the drug across the cell wall.
Ampicillin is the prototype aminopenicillin and is composed of penicillin G with an amino group at the alpha position on benzene ring at R on the penicillin nucleus. Amoxycillin is the p-hydroxyl analogue of ampicillin.

Piperacillin is a semisynthetic acylaminopenicillin and is the piperazine derivative of ampicillin, may be active against some strains of gonorrhoea resistant to natural penicillins.

**Resistance**

The two possible mechanisms of resistance to penicillins are: production of β-lactamase (inactivates β-lactam drugs) and intrinsic resistance (presence of permeability barrier or alterations in the target enzymes, PBPs).

Both complete and relative resistance have been reported for *N. gonorrhoeae* (Table 1.2). PPNG strains are resistant to penicillin and are usually also resistant to aminopenicillins, but may be inhibited by spectinomycin, cefotixin, cefuroxime or third generation cephalosporins. Relative resistance is due to either alterations in PBP or presence of a permeability barrier. Strains may also be resistant to aminopenicillins, tetracyclines, erythromycin and chloramphenicol, but may be susceptible to spectinomycin, cefoxitin or third generation cephalosporins. Some strain of Neisseria gonorrhoeae resistant to natural penicillins (including some PPNG) may be inhibited by acylaminopenicillins e.g. piperacillin.

**Cephalosporins**

First generation cephalosporins e.g. cefadoxil
Second generation cephalosporin, e.g. cefaclor, cefoxitin
Third generation cephalosporins e.g. cefotaxime, ceftizoxime, ceftriaxone
Forth generation cephalosporins e.g. cefepime.

**Mechanism of action**

Cephalosporins are β-lactam antibiotics, and are usually bactericidal. Thought to act as substrate analogues of acyl-d-alanyl-d-alanine in the same way as penicillins and therefore also only act on actively divided cells. Cephalosporins are structurally and pharmacologically related to penicillins.
Structures (Table A.3)

Chemistry

Cephalosporins are semisynthetic β-lactam antibiotic derivatives of cephalosporin C, which is produced by the fungus *Cephalosporium acremonium*. Cephalosporins in clinical use all contain 7-aminocephalosporanic acid (7-ACA) nucleus, which is composed of a β-lactam ring fused with a six-membered thiazolidine ring of penicillins. Aminothiazolyl methoxyimino cephalosporins (3rd generation, broad spectrum), e.g. cefixime, cefdinir, cefodoxime proxetil, cefituben, ceftraxime, ceftriaxone, ceftizoxime, contain an aminothiazolyl side chain at position 7 of the cephalosporin nucleus, which enhances their antibiotic activity and confers a high degree of β-lactamase stability.

Resistance

Although they remain effective, strains with reduced susceptibility to 3rd generation cephalosporins have been reported in the Western Pacific region (WHO 2002). 99.9% of isolates in USA in 1994 were susceptible to broad-spectrum cephalosporins (Fox, Knapp *et al.* 1997). Cefixime is not hydrolysed by beta-lactamases classified as Richmond-Sykes types Ia (P99), III (TEM-1, TEM-2, SHV-1), IV (K-1), and V (OXA-2, OXA-3, PSE-1, PSE-4, PSE-4), which includes those produced by *Neisseria gonorrhoeae*. Some authorities recommend that third generation oral cephalosporins are discouraged as this will lead to self-medication, which in turn can increase the development of resistance (van de Laar, van Duynhoven *et al.* 1997).

Resistance to earlier cephalosporins (first and second generation) may occur through several mechanisms: either the drug cannot permeate the bacterial cell wall, or the drug does not inhibit the metabolic pathways of the bacterium. Additionally resistance can occur by direct action of the bacteria on the drug, breaking it down into harmless metabolites. Production of β-lactamase is a common example of this form of resistance. The bacteria produce this enzyme, which inactivates the cephalosporin by hydrolysing the β-lactam ring. However, in practice resistance usually results from both production of β-lactamases and presence of permeability barriers.

Spectinomycin

Spectinomycin is obtained from cultures of *Streptomyces spectabilis.*
Mechanism of action

Spectinomycin is usually bactericidal in action. Appears to inhibit protein synthesis by binding to 30S ribosomal subunit.

Structures (Table A.3)

Tetracyclines

Mechanism of action

Usually bacteriostatic, but may be bactericidal in high concentrations or against highly susceptible organisms. Appear to inhibit protein synthesis by binding reversibly to 30S ribosomal subunit and inhibiting binding of aminoacyl transfer RNA to the ribosome. Additionally it appears to bind to the 50S ribosomal subunit. There is early evidence to suggest that tetracycline also alters the cytoplasmic membrane of susceptible organisms, causing leakage of nucleotides and other cellular components.

Structures (Table A.3)

Chemistry

Tetracyclines are natural and semisynthetic antibiotics derived from cultures of Streptomyces. The tetracycline nucleus (Table A.3) forms the basis of all tetracyclines currently available. Different drugs can be formed by addition of different side groups at R5, R6 and R7

Resistance

Resistance may be natural or acquired and the mechanism of resistance is usually decreased permeability of the cell surface. This may be due either to mutations or the presence of an inducible plasmid-mediated resistance factor acquired by conjugation. Plasmids carrying resistance factors may be transferred between species and may code for resistance to more than one type of antibiotic.

N. gonorrhoeae strains resistant to tetracyclines were first reported in the USA 1985 (MMWR 1985) and subsequently increased (MMWR 1987). Tetracycline resistance was reported in UK at around the same time (Beattie, Moyes et al. 1999; Ison, Gedney et al. 1987) and followed the same increasing trend. In the USA and UK treatment guidelines have been changed and tetracycline is no longer recommended as a first line therapy (MMWR 1998; Radcliffe, Ahmed-Jushuf et al. 1999).
In the Netherlands, there has been an increase in the prevalence of tetracycline resistant strains of *N. gonorrhoeae* (TRNG), even though this drug is not used to treat gonorrhoea (van de Laar, van Duynhoven *et al*. 1997). It is possible that treatment of chlamydia with tetracycline has contributed to the development and spread of tetracycline resistant gonococci. The evolution of resistant strains of gonorrhoea therefore must be seen within a wider context of treatment of associated infections such as chlamydia and other STDs, and antibiotic use in general (Austin, Kakehashi *et al*. 1997; Bonhoeffer, Lipsitch *et al*. 1997).

High level resistance to tetracycline is conferred by a 25.2MDa plasmid, derived from the 24.5MDa conjugative plasmid with an additional *tetM* determinant. (Morse, Johnson *et al*. 1986) Some strains with TRNG may be susceptible to other antibiotic agents, such as penicillins or cephalosporins (e.g. ceftriaxone). Strains which are also PPNG have been reported in the US and elsewhere. Testing for TRNG is more difficult and expensive than for PPNG, which slowed the early detection of such strains. Chromosomally mediated resistance to tetracycline also occurs and many of these strains also possess chromosomally mediated resistance to penicillin (CMRNG).

### Macrolide antibiotics

Erythromycins.

Azalides e.g. azithromycin

#### Mechanism of action

Macrolide antibiotics are usually bacteriostatic (sometimes bactericidal, but not against *N. gonorrhoeae*). Act on the 50S RNA subunit to inhibit translocation of aminoacyl transfer RNA and thus inhibit protein synthesis. This class of drugs are only effective against multiplying organisms. Penetrates gram-positive bacteria better than gram-negative bacteria. Activity decreases at low pH. Accumulates in phagocytes, which is necessary for activity against intracellular pathogens such as *Chlamydia trachomatis*.

### Erythromycins

Erythromycin is a macrolide antibiotic produced by *Streptomyces erythreus*. Erythromycin is a weak base and readily forms salts and esters with organic acids. Erythromycin penetration is better in gram positive than gram-negative bacteria.
Azalides

A subclass of macrolides, azalides have a nitrogen atom at position 9a of the lactone ring compared with other macrolides. The semisynthetic azalide, azithromycin, contains a methyl-substituted N atom at the 9a position of the macrolide ring, which distinguishes it from erythromycin. Azithromycin has an extended spectrum of activity compared to erythromycin and is more active in vitro against gram-negative bacteria, due to better penetration of the cell wall. It is also less prone to acid degradation. Resistance to macrolide antibiotics (NB no specific mention of gonorrhoea/chlamydia on the website)

- This can be natural or acquired and may occur via several mechanisms:
  - Decreased permeability of cell envelope to antibiotic
  - Plasmid-mediated active efflux of antibiotic
  - Enzymatic inactivation of antibiotic by plasmid-mediated esterases or phosphotransferases
  - Chromosomally mediated alteration of a single 50S ribosomal protein at receptor site, resulting in decreased macrolide affinity
  - Alteration of 23S ribosomal RNA of 50S ribosomal subunit by methylation of adenine to decrease macrolide affinity

Quinolones

Fluoroquinolones e.g. ciprofloxacin, enoxacin, ofloxacin

**Mechanism of action**

Fluoroquinolones are bactericidal and act by inhibiting the enzymes DNA gyrase and DNA topoisomerase IV, both of which are involved in DNA replication. Disruption of DNA replication leads to cell death (Hooper 2000).

**Structures (Table A.3)**

**Resistance**

Resistance to ciprofloxacin has increased substantially in the UK and USA in the last 5 years. In the UK resistance to ciprofloxacin reached nearly 10% in 2002, with wide local variations. The national guidelines have been changed to reflect this and ciprofloxacin is no longer recommended as first line therapy (Fenton 2003; GRASP 2003)(CDSC 2003).
<table>
<thead>
<tr>
<th>Disease R/A&lt;sup&gt;§&lt;/sup&gt;</th>
<th>Agent</th>
<th>Dose (g)</th>
<th>Method of administration</th>
<th>Number of doses per day</th>
<th>Course (days)</th>
<th>Comments relating to specific regimens</th>
<th>Follow-up and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydial infection - uncomplicated</td>
<td>Doxycycline (Tet)</td>
<td>0.1 Oral</td>
<td></td>
<td>2</td>
<td>7</td>
<td>Cheaper than Azi Contraindicated in pregnancy Retest not necessary</td>
<td>Both recommended regimes have equal efficacy Treat partners Refer contacts to GUM</td>
</tr>
<tr>
<td></td>
<td>Azithromycin (M)</td>
<td>1 Oral</td>
<td></td>
<td>Single dose (1 hr before food or 2 hrs after food)</td>
<td></td>
<td>Dosing regimen improves compliance Retest not necessary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythromycin (M)</td>
<td>0.5 Oral</td>
<td></td>
<td>4 2</td>
<td>7 14</td>
<td>GI side effects in 20-25% sufficient to cause discontinuation of treatment. Decreased efficacy compared with doxycycline or azithromycin Retest may be considered after 3 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diclofloxacine (Tet)</td>
<td>0.3 Oral</td>
<td></td>
<td>2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oflaxcin (Q)</td>
<td>0.2 Oral</td>
<td></td>
<td>2 1</td>
<td>7 7</td>
<td>Similar efficacy, better side effect profile, but more expensive than doxycycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetracycline (Tet)</td>
<td>0.5 Oral</td>
<td></td>
<td>4</td>
<td>7</td>
<td>Contraindicated in pregnancy</td>
<td></td>
</tr>
<tr>
<td>Chlamydial infection in pregnant women</td>
<td>Erythromycin (M)</td>
<td>0.5 Oral</td>
<td></td>
<td>4</td>
<td>7</td>
<td>&lt;95% effective. Side effects significant</td>
<td>Quinolones and tetracyclines are contraindicated in pregnancy. Partner notification should be discussed and documented.</td>
</tr>
<tr>
<td></td>
<td>Amoxycillin (P)</td>
<td>0.5 Oral</td>
<td></td>
<td>3 2</td>
<td>7 14</td>
<td>Similar cure rate to erythromycin and better side effect profile. Has been shown to induce latency in vitro, so may not be reliable.</td>
<td></td>
</tr>
</tbody>
</table>

R: recommending
A: advising
<table>
<thead>
<tr>
<th>Uncomplicated gonococcal infection of cervix, urethra and rectum in the adult/adolescent</th>
<th>Azithromycin (M) Not Recommended</th>
<th>1</th>
<th>Oral</th>
<th>Single dose</th>
<th>Recent data suggest Azi might be safe and effective, but insufficient to recommend as routine therapy for pregnant or lactating mothers.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>0.5</td>
<td>Oral</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ofloxacin</td>
<td>0.4</td>
<td>Oral</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicillin + Probenecid</td>
<td>2 or 3 1</td>
<td>Oral</td>
<td>Single dose</td>
<td>Applicable in areas where regional prevalence of penicillin resistant <em>N. gonorrhoeae</em> &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
<td>0.25</td>
<td>i.m.</td>
<td>Single dose</td>
<td>All three are highly active against penicillin and quinolone resistant strains of <em>N. gonorrhoeae</em> (Ia).</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>0.5</td>
<td>i.m.</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spectinomycin</td>
<td>2</td>
<td>i.m.</td>
<td>Single dose</td>
<td>Not usually used as first line therapy in United Kingdom, but valuable against imported infection from South East Asia, and/or when special considerations apply.</td>
</tr>
<tr>
<td>Uncomplicated gonococcal infection of the pharynx</td>
<td>Ceftriaxone</td>
<td>0.25</td>
<td>i.m.</td>
<td>Single dose</td>
<td>Single dose treatments using ampicillin or spectinomycin have a poor efficacy in eradicating gonococcal infection of the pharynx.</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin (Q)</td>
<td>0.5</td>
<td>Oral</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ofloxacin (Q)</td>
<td>0.4</td>
<td>Oral</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td>Gonococcal infection in pregnant women</td>
<td>Ceftriaxone</td>
<td>0.25</td>
<td>i.m.</td>
<td>Single dose</td>
<td>Quinolones and tetracyclines are contraindicated in pregnant women</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>0.5</td>
<td>i.m.</td>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicillin + Probenecid</td>
<td>2 or 3 1</td>
<td>oral</td>
<td>Single dose</td>
<td>Where regional prevalence of penicillin resistant N. gonorrhoea &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Spectinomycin</td>
<td>2 g</td>
<td>i.m.</td>
<td>Single dose</td>
<td></td>
</tr>
</tbody>
</table>

*R = Recommended therapy; A = Alternative therapy; S = Cephalosporins; M = Macrolides, including the erythromycins and azalides; P = penicillins; Q = Quinolones; Tet = Tetracyclines*
<table>
<thead>
<tr>
<th>Disease</th>
<th>R/A</th>
<th>Agent</th>
<th>Dose (g)</th>
<th>Method of administration</th>
<th>Number of doses per day</th>
<th>Length of course (days)</th>
<th>Comments relating to specific regimens</th>
<th>Follow-up and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chlamydial infection</strong></td>
<td>R</td>
<td>Azithromycin (M)</td>
<td>1</td>
<td>Oral</td>
<td>Single dose</td>
<td></td>
<td>Dosing regimen improves compliance Retest not necessary</td>
<td>Refer patients sexual partners from past 60 days for treatment Return visit if symptoms persist or recur Recommend abstention from sex for 7 days and/or until the end of the course of treatment and/or until all partners treated Patients infected with HIV should receive same treatment Quinolones and tetracyclines contraindicated in pregnancy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline (Tet)</td>
<td>0.1</td>
<td>Oral</td>
<td>2</td>
<td>7</td>
<td>Cheaper than Azi Contraindicated in pregnancy Retest not necessary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Erythromycin base (M)</td>
<td>0.5</td>
<td>Oral</td>
<td>4</td>
<td>7</td>
<td>GI side effects Decreased efficacy compared with Azi, Dox and Ofl Retest may be considered after 3 weeks</td>
<td>Expensive Equivalent efficacy to Azi and Doxy Contraindicated in pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin ethylsuccinate (M)</td>
<td>0.8</td>
<td>Oral</td>
<td>4</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ofloxacin (Q)</td>
<td>0.3</td>
<td>Oral</td>
<td>2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chlamydial infection in pregnant women</strong></td>
<td>R</td>
<td>Erythromycin base (M)</td>
<td>0.5</td>
<td>Oral</td>
<td>4</td>
<td>7</td>
<td>Repeat testing recommended 3 weeks after completion, none of these regimens is highly efficacious. Side effects of erythromycin compounds might result in patient non-compliance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amoxycillin (P)</td>
<td>0.5</td>
<td>Oral</td>
<td>3</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Erythromycin base (M)</td>
<td>0.25</td>
<td>Oral</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin ethylsuccinate (M)</td>
<td>0.8</td>
<td>Oral</td>
<td>4</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin ethylsuccinate (M)</td>
<td>0.4</td>
<td>Oral</td>
<td>4</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin (M)</td>
<td>1</td>
<td>Oral</td>
<td>Single dose</td>
<td></td>
<td>Recent data suggest Azi might be safe and effective, but insufficient to recommend as routine therapy</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>R/A</td>
<td>Agent</td>
<td>Dose (g)</td>
<td>Method of administration</td>
<td>Number of doses per day</td>
<td>Length of course (days)</td>
<td>Comments relating to specific regimens</td>
<td>Follow-up and general comments</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td>-------</td>
<td>---------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Uncomplicated gonococcal infection of cervix, urethra and rectum in the adult/adolescent</td>
<td>R</td>
<td>Cefixime (C-S)</td>
<td>0.4</td>
<td>Oral</td>
<td>Single dose</td>
<td>97.1% efficacy</td>
<td>Similar spectrum to cefixime, but not as high or sustained a bactericidal level</td>
<td>No need for retest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftriaxone (C-S)</td>
<td>0.125</td>
<td>i.m.</td>
<td>Single dose</td>
<td>99.1% efficacy</td>
<td>Safe and effective for gonorrhoea at all sites including rectal/pharyngeal</td>
<td>Partner referral important as most recurrent infections are due to reinfection rather than treatment failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ciprofloxacin (Q)</td>
<td>0.5</td>
<td>Oral</td>
<td>Single dose</td>
<td>99.8% efficacy in urogenital and anorectal infections</td>
<td>Safe and relatively inexpensive</td>
<td>Persistent urethritis, cervicitis or proctitis also may be caused by <em>C. trachomatis</em> or other organisms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ofloxacin (Q)</td>
<td>0.4</td>
<td>Oral</td>
<td>Single dose</td>
<td>98.4% efficacy</td>
<td>Urogenital and anorectal infections</td>
<td>Patients should avoid sex until therapy in completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin (M)</td>
<td>1</td>
<td>Oral</td>
<td>Single dose</td>
<td>Also effective for chlamydial infection</td>
<td>Pregnant women (see separate section)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline (Tet)</td>
<td>0.1</td>
<td>Oral</td>
<td>Single dose</td>
<td>98.2% efficacy</td>
<td>Urogenital and anorectal infections</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spectinomycin (Spc)</td>
<td>2</td>
<td>i.m.</td>
<td>Single dose</td>
<td>98.2% efficacy</td>
<td>Expensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefixime (C-S) + Probenecid</td>
<td>0.5</td>
<td>i.m.</td>
<td>Single dose</td>
<td>None offer any advantage over ceftriaxone. Limited clinical experience for gonorrhoea treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefotaxime (C-S) + Probenecid</td>
<td>0.5</td>
<td>i.m.</td>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cefotetan (C-S) + Probenecid 1 i.m. Single dose

Cefoxitin (C-S) + Probenecid 2
  1 i.m.
  1 Oral Single dose

Enoxacin (Q) 0.4 Oral Single dose

Lomefloxacin (Q) 0.4 Oral Single dose

Norfloxacin (Q) 0.8 Oral Single dose

Limited data on these alternative quinolones, none seems to offer any advantage over ciprofloxacin or ofloxacin

Contraindicated in pregnancy

Many other antimicrobials are effective against *N. gonorrhoea* but this is not exhaustive list but simply a guideline. Azithromycin 2 g orally is effective, but expensive and too often causes GI side effects to be recommended. At 1 g it is insufficiently effective (93%).

<table>
<thead>
<tr>
<th>Uncomplicated gonococcal infection of the pharynx</th>
<th>R</th>
<th>One of:</th>
<th>0.125</th>
<th>i.m.</th>
<th>Single dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>of:</td>
<td></td>
<td>Cefixime (C-S)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ciprofloxacin (Q)</td>
<td>0.5</td>
<td>Oral</td>
<td>Single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ofloxacin (Q)</td>
<td>0.4</td>
<td>Oral</td>
<td>Single dose</td>
</tr>
<tr>
<td>Plus one of:</td>
<td></td>
<td>Azithromycin (M)</td>
<td>1</td>
<td>Oral</td>
<td>Single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline (Tet)</td>
<td>0.1</td>
<td>Oral</td>
<td>2 7</td>
</tr>
</tbody>
</table>

Gonococcal infection in pregnant women | R | Treatment with recommended or alternate cephalosporin
Cephalosporin intolerant women should be prescribed a single dose of 2 g spectinomycin i.m.
If *C. trachomatis* infection is diagnosed or presumed, treatment with erythromycin or amoxycillin is recommended.

Quinolones and tetracyclines are contraindicated in pregnant women

$^8$R = Recommended therapy; A = Alternative therapy

C-S = Cephalosporins; M = Macrolides, including the erythromycins and azalides; P = penicillins; Q = Quinolones; Tet = Tetracycline
### Table A.3 Structure of antibiotics (http://www.medscape.com.)

#### Penicillins

<table>
<thead>
<tr>
<th>Penicillins</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G potassium</td>
<td>Penicillin V</td>
</tr>
</tbody>
</table>

#### Cephalosporins

<table>
<thead>
<tr>
<th>Cephalosporins</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime</td>
<td>Cefoperazone sodium</td>
</tr>
<tr>
<td>Cefpodoxime proxetil oral</td>
<td>Ceftiaxone</td>
</tr>
</tbody>
</table>

#### Aminocyclitol

<table>
<thead>
<tr>
<th>Aminocyclitol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectinomycin</td>
<td></td>
</tr>
</tbody>
</table>

#### Tetracyclines


<table>
<thead>
<tr>
<th><strong>Tetracycline</strong></th>
<th><strong>Oxytetracycline</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Tetracycline" /></td>
<td><img src="image2" alt="Oxytetracycline" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Doxycycline</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Doxycycline" /></td>
</tr>
</tbody>
</table>

### Erythromycins

<table>
<thead>
<tr>
<th><strong>Erythromycin ethyl succinate</strong></th>
<th><strong>Azithromycin oral</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4" alt="Erythromycin ethyl succinate" /></td>
<td><img src="image5" alt="Azithromycin oral" /></td>
</tr>
</tbody>
</table>

### Quinolones: Fluoroquinolones

<table>
<thead>
<tr>
<th><strong>Ciprofloxacin</strong></th>
<th><strong>Ofloxacin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image6" alt="Ciprofloxacin" /></td>
<td><img src="image7" alt="Ofloxacin" /></td>
</tr>
</tbody>
</table>
Bibliography


CDC (2003). Centre for Disease Control http://www.cdc.gov/node.do/id/0900f3ec80009e98


Cohen, M. S., B. E. Britigan, et al. (1987). Preliminary observations on lactoferrin secretion in human vaginal mucus: variation during the menstrual cycle,


Katherine Turner
Bibliography


Acknowledgements

Many people have helped in many ways during the writing of this thesis. Firstly thanks to Geoff Garnett, my supervisor, for your support and encouragement.

Nicola Low not only provided the data presented in Chapter 3, but more importantly a great deal of her time and energy and advice, for which I am very grateful.

Cathy Ison and Iona Martin kindly allowed me to use the reinfection data from St Mary’s.

Thanks also to Matt Golden for your hospitality, help and advice.

Practically everyone in DIDE has helped in some way or other, but thanks especially to Azra Ghani and Peter White for STI modelling related stuff. Steve Riley, programming genius, without him I would still be on “hello world”. Ruanne Barnabas- always there to provide expert help, advice and medical assistance or, failing that, handbags and muffins! The rest of the BAYS stalwarts, Lucy Bartley, Kamal Desai, Nick Grassly and James Lewis: cheers dudes.

All my friends deserve thanks for still being there. I’m sure Jenny and Graham will miss my late night discussions on STIs.

Thanks Sam for everything.

Many thanks to Mum and Dad and the rest of my family, for your belief in me and constant love and support. Last but definitely not least, thank you Flash and Poppy, I couldn’t have done it without you.