The epidemiology of *Chlamydia trachomatis* and *Mycoplasma genitalium* in young Australian women.

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ABSTRACT

Chlamydia trachomatis is the most common notifiable sexually transmissible infection in young Australian women and has considerable public health consequences, yet the true burden of disease caused by chlamydia remains unknown. There are also no population data for Mycoplasma genitalium, another emerging sexually transmissible infection in young women. This thesis aims to address two issues relevant to C. trachomatis and M. genitalium. The first aim was to determine the effectiveness of an intervention in general practice to increase chlamydia testing rates, and the second aim was determine the community burden of both C. trachomatis and M. genitalium in young women in Australia.

Chapter 4 describes the C-Alert study which was a randomised controlled trial to determine the effectiveness of a computer alert in general practice on C. trachomatis testing rates in young women. The computer alert increased testing by 27% [AOR:1.27 (95%CI: 1.11-1.45)], and this small but significant increase suggests alerts might be beneficial along with other interventions to increase C. trachomatis testing in general practice.

Chapters 5, 6, 7, 8, 9 and 10 describe the CIRIS study which was a cohort study involving 1116 young Australian women. C. trachomatis prevalence at baseline was 4.9% (95%CI: 2.9-7.0) and incidence rate for the 12–month study period was 4.4 per 100 women-years (95%CI: 3.3-5.9). Prevalent C. trachomatis was associated with having had C. trachomatis previously [AOR:2.0 (95%CI: 1.1-3.9)], increased numbers of sexual partners [AOR:6.4 (95%CI: 3.6-11.3)] and unprotected sex [AOR:3.1 (95%CI: 1.0-9.5)]. Antibiotic use and older age were protective against having a prevalent infection ([AOR:0.4 (95%CI: 0.2-1.0]) and [AOR:0.9 (95%CI: 0.8-1.0)] respectively) and an incident infection ([AHR:0.1 (95%CI: 0.0-0.6]) and [AHR:0.4 (95%CI: 0.2-0.8)] respectively). Incident C. trachomatis was also associated with more partners [AHR:4.0 (95%CI: 1.9-8.6)].
More than 20% of women with \( C.\ trachomatis \) had a re-infection during the study [20.3% (95% CI: 11.6, 31.7)] with an infection rate of 20.0 (95% CI: 11.9, 33.8) per 100 women years.

In Chapter 8, \( M.\ genitalium \) prevalence was found to be 2.4% (95%CI: 1.5-3.3) and incidence rate was 1.1 per 100 women-years (95%CI: 0.4-1.6). Prevalent \( M.\ genitalium \) was associated with Indigenous status [AOR:4.5 (95%CI: 1.4-14.9)], increased numbers of partners [AOR:2.2 (95% CI:1.0-4.6)] and unprotected sex [AOR:16.6 (95%CI: 2.0-138.0)]. Incident \( M.\ genitalium \) was associated with recruitment from sexual-health clinics [HR:4.5 (95%CI: 1.0-14.7)], having more partners [HR:5.2 (95%CI: 1.0-26.5)] and having had a \( C.\ trachomatis \) infection [HR:4.2 (95%CI: 1.1-16.5)].

In Chapter 9, a psychosocial analysis found that testing was acceptable to women and women who tested positive were less affected by having a positive result than negative women anticipated they would be. Chapter 10 describes the rate of induced abortion [rate: 2.1 per 100 women-years (95%CI: 1.4-3.2)], which was an incidental finding.

These results demonstrate there is a significant proportion of \( C.\ trachomatis \) and \( M.\ genitalium \) in young women in Australia that is not captured by current testing methods. These results provide the first population based incidence and re-infection data for young women in Australia. This will be crucial in the design and measuring the effectiveness of a chlamydia screening program and further inform discussion about \( M.\ genitalium \) control.
DECLARATION

This is to certify that:

i. the thesis comprises only my original work towards the Doctor of Philosophy except where indicated in the Preface,

ii. due acknowledgement has been made in the text to all other material used,

iii. the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Jennifer G Walker       21st January 2011
PREFACE

Contribution of author, Jennifer Walker

This thesis comprises of two studies which were designed, implemented and managed by Jennifer Walker. In particular, Jennifer was responsible for the following as part of her candidature:

- The design each study, the development of questionnaires and ethics applications.
- The recruitment of all the clinics in the C-Alert study and management the recruitment of all the clinics in the CIRIS study.
- The management of the recruitment and follow up of all the women in the CIRIS study.
- The management of the team of research assistants who recruited and followed up the participants during the study.
- The management of the mail outs for the CIRIS study and the other associated clerical duties.
- The management of all the women who tested positive as a result of the CIRIS study, including organising consultations, treatment and follow up.
- Data entry and management of the data for both studies including the bulk of the analysis of the results.
- The collation of the material required for the C-Alert general practitioners’ education pack and CIRIS participants’ recruitment packs.
**Contribution of others**

The C-Alert study was led by Professor Christopher Fairley and supervised by a team of investigators including: Associate Professor Jane Hocking, Professor Jane Gunn, Dr Marie Pirotta, Associate Professor Lyle Gurrin, and Associate Professor Rob Carter. This study was funded by an NHMRC grant.

The CIRIS study was led by Associate Professor Jane Hocking and supervised by a team of investigators and including: Professor Kit Fairley, Associate Professor Sepehr Tabrizi, Dr Catriona Bradshaw, Associate Professor Marcus Chen, Professor Basil Donovan, Professor John Kaldor, Dr Kathleen McNamee, Dr Marian Currie, Mr Hudson Birden, Professor Francis Bowden, Professor Jane Gunn, Dr Marie Pirotta, Associate Professor Lyle Gurrin, Professor Veerakathy Harindra, and Professor Suzanne Garland. The study was funded by the Department of Health and Ageing as part of the Chlamydia Targeted Grants Funding.

Dr Catriona Bradshaw, Professor Kit Fairley and Associate Professor Marcus Chen provided clinical treatment and management of the women who tested positive during the study. Other clinical staff at the Melbourne Sexual Health Centre offered their clinical services and advice as well when required.

Associate Professor Sepehr Tabrizi and the staff at the Department of Molecular Microbiology at the Royal Women’s Hospital in Melbourne conducted all the testing for the CIRIS study including molecular analyses.

Associate Professor Jane Hocking, Rachelle Gerber, Dr Stella Heley, Dr Tim Read and Claire Foreman produced, wrote, directed and performed in the C-Alert DVD for the general practitioner education kit.

Dr Sandra Walker collected and collated the data for the C-Alert trial and assisted with the analysis. Sandra also had a major role in the development of the psychosocial questions for the final CIRIS questionnaire. Sandra Walker and Eve Urban were involved in the day to day running of the CIRIS study ensuring the study was conducted smoothly, ethically and efficiently. Sandra and Eve also were involved in recruiting clinics, managing some staff and data entry.
A team of research assistants recruited participants for the CIRIS study including: Debbie Edwards, Ros McLennan, Marilyn Hines, Jo Horn, Maree White, Bernie Monaghan, Eliza Marks, Rose Goodenough, Kaz Krajlic, Gabrielle Le Brocq, Jennifer Coyle, Karla Kalen, Leigh Hodgkinson, Jo Ruppin, Di Baker, Christine Hou, Christina Brieglab, Helen Tang, Tara Young, Christine Selman, Stefannie Lummas, Donna Cleall, Rachel Ujma, Hongxia Shao, Stephenie Neblett, Eris Smyth, Annie Green, Leonie Baker, Stephanie Lenko, Paula Nathan, and Kavitha Somasundaram. The bulk of questionnaire data entry was done by Mika Tsukiyama.
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Firstly I would like to thank my principal supervisor Associate Professor Jane Hocking who has been an exceptional supervisor during the period of my candidature. Jane’s knowledge of chlamydia, and her ability to steer large and complex research projects has been implicit in the success of both projects in my PhD. Also, Jane has encouraged me to challenge myself during the PhD, and helped me keep my sense of humour along the way.

I was also privileged to have Professor Christopher (Kit) Fairley as a supervisor. Kit’s clinical experience and global understanding of STI research has been invaluable. Kit has been kind, supportive and practical with his supervision and was particularly helpful with the management of the large group of staff employed to work on the CIRIS project and managing the large cohort of young women in the study.

I would like to also thank my other supervisors, Dr Catriona Bradshaw and Associate Professor Lyle Gurrin. Catriona has always been available for advice for which I was particularly grateful when managing CIRIS participants’ clinical outcomes, she was also intrinsic to the *Mycoplasma genitalium* component of this thesis. Lyle was invaluable to my understanding of how to manage to statistical analysis for both my projects. Jane and Lyle taught me the importance of being able to do my own analysis and were there to help me through challenging obstacles.

I would also like to thank Associate Professor Sepehr Tabrizi, Dr Jimmy Twin, Nicole Taylor and the laboratory staff at the Molecular Microbiology Laboratory at the Royal Women’s Hospital who conducted all the chlamydia and *Mycoplasma genitalium* testing and molecular analyses for this thesis.

Importantly, I would like to thank Dr Sandra Walker and Ms Eve Urban for their diligence, enthusiasm, and hard work during the project. Sandra and Eve worked tirelessly on the projects in this thesis, managing data and study participants and I am eternally grateful for their assistance with this.

The bulk of my candidature was spent at the Melbourne Sexual Health Centre in the which was a very supportive environment where all the staff were incredibly generous with their time, answering my questions, providing clinical support to CIRIS participants, and providing excellent feedback for all my presentations. Staff in particular who I would like to thank include: Associate Professor Marcus Chen, for his clinical and research experience, Rosey Cummins for assisting with recruiting participants for the CIRIS study, Suzanne Amisano, James Unger and Brad Morgan
who managed the complex administrative tasks associated with both the projects, and Jun Kit Sze for his IT support. Special thanks also to Dr Jade Bilardi, a fellow PhD student, who provided much needed moral and practical support during my candidature.

I have also been supported by the staff at the Centre for Women’s Health, Gender and Society, where I spent the last six months of my candidature.

My PhD would have been impossible without the support of funding from the Commonwealth Department of Health and Ageing and the National Health and Medical Research Council, Australia. I was also fortunate to be the recipient of two University of Melbourne scholarships during my candidature: the Ronald John Gleghorn Scholarship and a Faculty of Medicine, Dentistry and Health Sciences Research Scholarship. I was able to present my research findings at a number of conferences with the support of the University of Melbourne ‘PHIRST’ scholarship as well as twice receiving The Royal Australasian College of Physicians’ Scholarship to attend the Australasian Sexual Health Conferences in 2009 and 2010.

I would also like to thank the clinics that were involved in both studies. I am very grateful to them for taking the time to involve themselves in these studies particularly considering the current challenges facing general practice. I am also indebted to the young women who took part in the CIRIS study and the tremendous effort they made entrusting me with their personal material in the interest of making a valuable contribution to women’s health.

I have received enormous support from my family and friends during the process of doing this thesis, and would particularly like to acknowledge my parents, Angus and Alison McIntosh, and my sisters Louise, Fiona and Sally as well as Vicki Walker. Most importantly I would like to thank Thornton and Polly who have supported me through this from the beginning and I promise I will be home more often from now on.
RESEARCH OUTCOMES AND OUTPUTS

Primary publications


SECONDARY PUBLICATIONS


Conference papers


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<thead>
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIRIS</td>
<td>Chlamydia Incidence and Re-Infection Study</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>FCU</td>
<td>First Catch Urine</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GUM</td>
<td>Genito-Urinary Medicine</td>
</tr>
<tr>
<td>MD</td>
<td>Medical Director</td>
</tr>
<tr>
<td>MOMP</td>
<td>Major Outer Membrane Protein</td>
</tr>
<tr>
<td>NAAT</td>
<td>Nucleic Acid Amplification Technique</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PID</td>
<td>Pelvic Inflammatory Disease</td>
</tr>
<tr>
<td>RACGP</td>
<td>Royal Australian College of General Practitioners</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SAS</td>
<td>Self Administered Vaginal Swab</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually Transmitted Infections</td>
</tr>
</tbody>
</table>
CHAPTER 1.

CLINICAL ASPECTS AND EPIDEMIOLOGY OF GENITAL CHLAMYDIA TRACHOMATIS INFECTION IN WOMEN

This literature review is separated into two chapters. The first of these, Chapter one, describes the biology of \( C. \) trachomatis, the clinical presentation of women infected with \( C. \) trachomatis, how \( C. \) trachomatis is diagnosed, the epidemiology of \( C. \) trachomatis, and methods for controlling \( C. \) trachomatis in young Australian women. Chapter 2 describes the biology of \( M. \) genitalium, the clinical presentation of \( M. \) genitalium and the epidemiology of \( M. \) genitalium.

1.1 Literature review

Genital \( Chlamydia \) trachomatis is the most commonly notifiable sexually transmissible infection in young women in Australia and international research suggests \( Mycoplasma \) genitalium is likely to affect young Australian women similarly. The extent of \( Chlamydia \) trachomatis and \( Mycoplasma \) genitalium in young women in Australia is unknown, although both potentially have significant public health implications.

1.1.1 Terminology

The term ‘chlamydia’ will refer to genital \( Chlamydia \) trachomatis throughout this PhD, and will be limited to chlamydia in women unless indicated otherwise. Chlamydia in this thesis will not include \( Lymphogranuloma \) venereum (LGV) unless stated specifically. \( Mycoplasma \) genitalium is referred to as \( M. \) genitalium throughout the thesis.
1.2 Biology of chlamydia

Chlamydiae are obligate intracellular bacteria which are differentiated from viruses because they contain both RNA and DNA and have a cell wall like gram-negative bacteria. Chlamydiae cannot be cultured on artificial media and are unable to synthesis high-energy compounds including amino acids, vitamins and co-factors and are therefore reliant on host cells to supply ATP and necessary nutrients for growth and replication.

Figure 1-1  *Chlamydia trachomatis* bacteria inside a cell (Biomedical imaging unit Southampton General Hospital/SPL)(Low, 2007)
1.2.1 Life cycle

Chlamydiae have a unique biphasic life cycle involving two highly specialized morphological forms; an infectious extracellular form – the elementary body, and a metabolising intracellular form - the reticulate body (Jones and Batteiger, 2000, Schachter and Stephens, 2008). Chlamydiae are obligate intracellular bacteria which are differentiated from viruses because they contain both RNA and DNA and have a cell wall like gram-negative bacteria. Chlamydiae cannot be cultured on artificial media and are unable to synthesis high-energy compounds including amino acids, vitamins and co-factors and are therefore reliant on host cells to supply ATP and necessary nutrients for growth and replication.

The elementary body attaches to a host cell in the extracellular fluid and enters the cell, where it converts to its intracellular reticulate structure forming a chlamydial inclusion. The reticulate body is able to metabolise within the host cell, multiply and then convert back into elementary bodies, which are then released from the cell into the extracellular fluid. The multiple new elementary bodies then infect host cells and begin the life cycle again (Jones and Batteiger, 2000, Schachter and Stephens, 2008). A complete cycle can take between 36 and 96 hours (Corsaro et al., 2003) (Figure 1-2).
Figure 1-2 The life cycle of *Chlamydia trachomatis*. [RB: reticulate body; EB: elementary body] (Everett, 2010).
1.2.2 Taxonomy

Until recently, chlamydiae classification has been in the order *Chlamydiales* and family *Chlamydiaceae* based on the unique phenotypic structure of the organism (Skerman, 1980). The reclassification of the taxonomy of the family *Chlamydiaceae* based on genotype, now includes the ‘chlamydia–like’ genus *Chlamydophila*, despite objections to this by some chlamydiologists (Everett et al., 1999, Schachter et al., 2006) (Figure 1-3). The genus *Chlamydia* includes the pathogenic species: *Chlamydia trachomatis*, *Chlamydia suis*, *Chlamydia muridarum*, *Chlamydia psittaci* and *Chlamydia pneumonia* (Everett et al., 1999, Jones and Batteiger, 2000).
Figure 1-3  The revised taxonomy for the Order Chlamydiales.

1a represents the recent taxonomic revision of the Order Chlamydiales,

1b represents the taxonomy of the order Chlamydiales prior to revision (Everett, 2010)
1.2.3 Serovars: distribution and clinical presentations

*C. trachomatis* has many serovars and variants within these serovars (Stothard et al., 1998, Dean and Millman, 1997, Stevens et al., 2010). Serovars L1, L2, L2a and L3, cause *Lymphogranuloma venereum* (LGV), serovars A, B, Ba and C cause ocular trachoma (‘trachoma’), and serovars B, Ba, and D, Da, E, F, G, Ga, H, I, Ia, J and K cause ocular and genital diseases in adults and children as well as infant pneumonia (Stevens et al., 2004, Stothard et al., 1998, Schachter and Stephens, 2008). The most common serovars found in women with genital tract infections are E, F and G in Australia and internationally (Lister et al., 2005, Suchland et al., 2003).

Recently, a new variant of chlamydia has been discovered in Europe which evades detection by some of the commercial diagnostic assays such as the COBAS Amplicor system (Roche Molecular Systems, Branchburg, NJ). In response to this, The European Surveillance of Sexually Transmitted Infections network (ESSTI) and the European Centre for Disease Prevention and Control (ECDC) have developed an initiative to study the characteristics and monitor the extent of the new strain (Ripa and Nilsson, 2006).

New technology is continually being developed to identify more specific genotypes and identify multiple genotypes present within one specimen (Morre et al., 1998, Frost et al., 1991, Stevens et al., 2004). Increasingly specific diagnostic tests provide more information in relation to determining sexual networks, treatment efficacy and potentially vaccine development (Stevens et al., 2010, Geisler et al., 2003, Morré et al., 2000). At this stage it is not known if there are differing patterns of virulence or clinical presentation within these strains, however studies are continually working on links between different strains and severity and infectiousness (Byrne, 2010). Although one study has reported a difference in clearance rate of different serovars with serovars B, D, E, H, I, J, and K had a having a decreased clearance rate compared with serovars F and G (Molano et al., 2005).
1.3 Diagnosis of chlamydia

Diagnostic procedures for chlamydia have changed radically in the last 20 years, up until recently, cell culture was the only diagnostic test (Stamm et al., 1983, Black, 1997, Lees et al., 1988, Centres for Disease Control and Prevention, 2002, Østergaard, 2002). Despite having a very high specificity (near 100%), cell culture diagnosis has many drawbacks when applied to large scale chlamydia testing including: the length of time it takes to produce a result (up to five days), specialised cold chain transport is required to retain viability of the specimen, and the sensitivity of the test is dependent on laboratory expertise and can range between 40 and 100% (Black, 1997).

Newer tests became available in the 1990s called ‘antigen detection tests’ which detect antigens specific to the lipopolysaccharide antigens or the major outer membrane protein (MOMP) component in the outer layer of the organism. The tests included enzyme immunoassays test (EIA) and the direct fluorescent antibody test (DFA) (Østergaard and Møller, 1995, Johnson et al., 2002) and they both had the advantage over cell culture as they do not require specific handling and they can be applied to rapid testing environments such as in remote areas (Johnson et al., 2002, Østergaard, 2002). Unfortunately, EIA is not as specific as cell culture, can test positive in the presence of Escherichia coli, Bacteroides sp. and Staphylococcus aureus and its specificity decreases with age (Østergaard and Møller, 1995). Also, the DFA tests use fluorescein-conjugated antibodies which rely on the expertise of the microscopist to be able to differentiate specific chlamydia fluorescent particles from non-specific fluorescent particles (Black, 1997, Østergaard, 2002).

The most dramatic change to chlamydia diagnostics has occurred in the mid 1990s with the development of nucleic acid amplification tests, which detect DNA or RNA sequences specific to chlamydia (Johnson et al., 2002, Black, 1997).

1.3.1 Nucleic acid amplification tests (NAATs)

The introduction of nucleic acid amplification tests (NAAT) has revolutionised chlamydia testing. NAAT testing has the advantage of producing a result quickly and
specimens do not require specialised handling as they can detect non-viable organisms. NAAT testing is considered the new ‘gold standard’ in chlamydia diagnostics and has led to the possibility of testing on a much greater scale within the general population (Bowden et al., 2002) (Black, 1997, Johnson et al., 2002, Schachter et al., 2003).

The premise of NAAT testing is the identification and amplification of DNA/RNA specific to the organism. Amplification can be successful from a single strand of nucleic acid sequence from a first catch urine sample (FCU) in men, or FCU, vaginal or endocervical swabs in women (Schachter, 2001a, Johnson et al., 2002, Black, 1997). Many commercial assays are available for chlamydia testing and differ depending on the nucleic acid sequences they target. The four main types of NAATS include: polymerase chain-reaction-based test (PCR), ligase chain reaction-based (LCR) which target sequences in the chlamydial cryptic plasmid, transcription-mediated amplification test (TMA) which detect a specific ribosomal RNA target, and strand displacement–based test which amplifies chlamydia DNA sequences in the cryptic plasmid of chlamydia (Schachter, 2001a, Schachter, 2001b, Johnson et al., 2002) (Figure 1-4). LCR is no longer available for chlamydia testing.
Figure 1-4  A schematic representation of a major chlamydia particle with different targets for diagnostic tests: major outer membrane protein (MOMP), lipopolysaccharide (LPS), chlamydia plasmid (DNA and RNA), chlamydia chromosome (DNA and RNA) (Land, 2010).
One of the main criticisms of NAAT testing is their cost (Johnson et al., 2002). Methods for reducing the cost of large scale testing have been developed such as pooling samples into batches which are tested together, then retesting all the individual samples within the pooled samples if the batch tests positive (Johnson et al., 2002, Schachter, 2001a, Currie et al., 2004).

1.3.2 Sensitivity and specificity of NAAT tests

The U.S Centre for Disease Control (CDC) guidelines recommend NAAT testing for chlamydia partially because the sensitivity of the NAAT tests exceeds non-NAAT tests (Johnson et al., 2002). The sensitivities of the various tests range between 49% and 100% and depend on the type of test used and specimen taken (Johnson et al., 2002, Black et al., 2002, Østergaard, 2002, Watson et al., 2002) The most sensitive of the NAAT tests is LCR (Schachter, 2001b), and the one most affected by inhibitors is PCR (Schachter, 2001b). In a head-to-head analysis, endocervical specimens tested with NAAT exceeded the non amplified nucleic acid amplification test by 19.7% (95% confidence interval [CI] = 12.9%, 26.6%) for LCR, and 12.4% (95% CI = 2.1%, 22.7%) for PCR, and urine specimens demonstrated slightly lower sensitivities than endocervical specimens when the LCR and PCR tests were performed (83.4% versus 91.4% and 79.5% versus 84.0%) (Black et al., 2002). Comparing the sensitivities of culture tests against NAAT testing, using an endocervical specimen, the sensitivity of the NAAT LCR test exceeded the culture test by 10.8%, and by 6.1% using a urine sample (Black et al., 2002). A recent review of the sensitivities and specificities of the most commonly used commercial assays is outlined in Table 1-1 (Land, 2010).

The specificity is high for all the tests, except for point-of-care testing which is not currently used as the low specificity limits its use in the field (Table 1-1) (Land, 2010).
Table 1-1 Sensitivities and specificities of chlamydia detection assays for the most widely used commercially available tests

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (range %)</th>
<th>Specificity (range %)</th>
<th>Detection limit (no. of organisms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAAT⁴</td>
<td>90 - 95</td>
<td>&gt;99</td>
<td>1 - 10</td>
</tr>
<tr>
<td>DFA²</td>
<td>80 - 85</td>
<td>&gt;99</td>
<td>10 - 500</td>
</tr>
<tr>
<td>EIA³</td>
<td>60 - 85</td>
<td>99</td>
<td>500 - 1000</td>
</tr>
<tr>
<td>DNA-probe⁴</td>
<td>75 - 85</td>
<td>&gt;99</td>
<td>500 - 1000</td>
</tr>
<tr>
<td>Cell culture</td>
<td>50 - 85</td>
<td>100</td>
<td>5 - 100</td>
</tr>
<tr>
<td>POC⁵</td>
<td>25 - 55</td>
<td>&gt;90</td>
<td>&gt;10 000</td>
</tr>
</tbody>
</table>

⁴ Nucleic acid amplification test. DNA based: PCR Amplicor Assay (Roche Diagnostics, Basel Switzerland), LCR (Abbott Laboratories, Abbott Park USA), currently the BD Probe tec. RNA based: TMA, AMP-CT (Gen-probe, USA), current system from Gen-Probe is named TIGRIS; NASBA (Organon Teknika, Boxtel, The Netherlands).

⁵ Direct Fluorescence Assay. Syva Micro Trak (Syva Co, USA).

⁶ Enzyme Immuno Assay. Vidas (France).

⁷ DNA-based: hybrid capture assay (Qiagen, Germany), Ampliprobe system (ImClone Systems, USA): RNA-based PAC 2 assay (Gen-Probe, USA).

⁸ Point of care test. Handilab-C (Zonda Inc, USA), Biorapid Chlamydia Ag test (Biokit, Spain), QuickVue Chlamydia test (Quidel, USA) (Land, 2010)

Despite the advantages of NAAT tests, they are not always the first choice for chlamydia diagnosis. Other tests are at times preferentially used due to increased availability, reduced cost, or ease of use. Cell culture is still the first choice when for forensic pathology due to its specificity and it is the only test where the cell isolates can be retained for evidence (Johnson et al., 2002).

**1.3.3 Chlamydia sampling methods**

NAAT testing can be achieved successfully in women either with a ‘first catch urine’ sample (FCU), self administered vaginal swab (SAS), self-collected tampon, vaginal flush, or a swab dipped in urine (Østergaard et al., 2000, Chernesky et al., 2005, Tabrizi et al., 1996, Costa et al., 2009). Endocervical swabs or first catch urine samples are commonly used depending on the clinical or research demands as the sensitivity and specificity of the different methods compare favourably (Table 1-2).
Table 1-2 Diagnostic performance of NAATs.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (range %)</th>
<th>Specificity (range %)</th>
<th>Positive predictive value (range %)</th>
<th>Negative predictive value (range %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocervical swabs</td>
<td>64-100</td>
<td>96-100</td>
<td>73-100</td>
<td>99</td>
</tr>
<tr>
<td>Urine women</td>
<td>49-100</td>
<td>98-100</td>
<td>52-100</td>
<td>96-100</td>
</tr>
<tr>
<td>Vaginal secretions</td>
<td>90-97</td>
<td>99-100</td>
<td>93-100</td>
<td>98-100</td>
</tr>
</tbody>
</table>

Source: (Østergaard, 2002)

NAAT testing techniques have increased the acceptability of chlamydia testing in young women, primarily because testing can be achieved without having a pelvic examination. (Pimenta et al., 2003a, Joffe, 1999, Wiesenfeld et al., 2000, Verhoeven et al., 2002, Harindra et al., 2003, Newman et al., 2003, Richardson et al., 2003, Tebb et al., 2004, Shafer et al., 2002, Moens et al., 2003, Ford et al., 2004b, Ford et al., 2004a, Schachter et al., 2003) Generally, given the option, women prefer to do a FCU over a self-administered swab (SAS) if there is the option (Pimenta et al., 2003a, Tobin, 2002, Hsieh et al., 2003), but an SAS is still preferable to having a pelvic examination (Smith et al., 2001, Verhoeven et al., 2002, Tebb et al., 2004, Serlin et al., 2002, Moens et al., 2003). Despite this, some young women still prefer a clinician collected sample as they have more faith in the result (Serlin et al., 2002). An FCU has the advantage of detecting site specific infection such as urethral chlamydia (Smith et al., 2001), it is gender non-specific, and it is quick to analyse (Watson et al., 2002) but the disadvantages of urine samples are that they are not always easy to transport, particularly through the post, are also more difficult to store and process, and are more likely to have inhibitors (Wiesenfeld et al., 2000, Serlin et al., 2002). Considering the efficacy, transportability and stability of swabs, self administered swabs are often a preferable method, but especially for increasing testing access in remote areas, with clients who are difficult to access, and for large population research studies (Smith et al., 2001, Garrow et al., 2002, Hsieh et al., 2003, Serlin et al., 2002, Knox et al., 2002).

A recently evaluated sampling method for chlamydia testing involves dipping a swab in an FCU (SCUD). This method has a 97% concordance with chlamydia positive
swabs tested with NAAT and circumvents the problem of posting urine samples directly (Costa et al., 2009). Another novel way to send urine through the post is with an anhydrous gel which solidifies the sample before sending it (Bialasiewicz et al., 2009). The ability to test in remote areas, test at home, send tests through the postal service, arrange for drop off tests at designated points, are all hugely advanced by the new testing regimes and make testing higher risk women easier and possible (Morton et al., 1999, Gaydos et al., 2006, Bradshaw et al., 2005).

Generally, self collected vaginal swabs and urine are the preferable choice for chlamydia specimen collection, although if a pelvic examination is required, then it stands to reason that an endocervical swab could be done at the same time. The advantages of accessing testing by the post outweigh any minor increase in sensitivity of having an endocervical swab which requires a consultation with a clinician and usually which specimen used is a pragmatic decision.

1.3.4 Chlamydia serology

Serology testing for detecting acute chlamydia infection has not been widely used because there is little evidence that a positive serology test for chlamydia antibodies represents an acute infection. Positive serology can be due to a previous chlamydial infection and can be correlated with tubal disease (although not exclusively) (Conway et al., 1984). In particular, antibodies to the chlamydial heat shock protein 60 can be used to predict the presence of tubal scarring (Persson, 2002).

1.3.5 Organism load

Quantification of chlamydia load can be determined using a quantitative PCR (qPCR) system targeting the *omp1* gene. The chlamydial load in a positive sample can be quantified by comparing the crossing-threshold of each sample to the crossing-threshold of a standard curve constructed by amplifying different known copy numbers of the *omp1* gene (Stevens et al., 2010). This method can determine the number of copies of chlamydia for clinical samples in both vaginal swabs and urine samples.
There are limited data about any associations with increased organism load. One study reports an association between age or past history of chlamydia infection and organism load (Batteiger et al., 2010, Gomes et al., 2006) but have found no associations between load and clinical presentation (symptoms) or different serovars (Gomes et al., 2006). Horner (2010) hypothesises high infectious load might cause an infection to persist and be diagnosed as a re-infection which might be one reason for high re-infection rates (Horner, 2006). Clearly there is scope for further investigation into the possible influence of organism load on clinical presentation and persistence of an infection.

1.4 Clinical presentations of chlamydia in women

Diseases associated with a chlamydia infection include: acute urethral syndrome, urethritis, bartholinitis, cervicitis, upper genital tract infection including endometritis, salpingo-oophritis, or pelvic inflammatory disease, as well as more systematic illness including reactive arthritis and perihepatitis (Fitz-Hugh-Curtis syndrome) (Peipert, 2003, Jones, 1995, Paavonen et al., 1985, Schachter and Stephens, 2008).

1.4.1 Clinical signs and symptoms

As many as 90% of women and men infected with chlamydia are asymptomatic (Peipert, 2003), but despite the high proportion of asymptomatic chlamydial infection, about a third of women will present with some non specific symptoms when examined, primarily muco-purulent discharge from cervicitis and a hypertrophic endocervix (Stamm, 2008, Peipert, 2003, Jones and Batteiger, 2000). Other non specific symptoms can also be clinical signs of chlamydial infection including dysuria, abnormal vaginal discharge, post-coital bleeding and if associated with upper genital tract infection, abdominal/pelvic discomfort and irregular uterine bleeding (Peipert, 2003, Jones, 1995, Schachter and Stephens, 2008). Chlamydia can also cause epithelial ulceration and scarring in the columnar and transitional epithelium of the endocervix, however these symptoms are not exclusive to chlamydia and they commonly occur with other STIs such as Neisseria gonorrhoea.
and *Mycoplasma genitalium* (Jones and Batteiger, 2000, Peipert, 2003, Stamm, 2008).

### 1.4.2 Upper genital tract infections and chlamydia

#### 1.4.2.1 Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is caused by a primary infection in the lower genital tract which ascends the genital tract along with other bacteria to the endometrium, the fallopian tubes and/or contiguous structures causing inflammation and can cause structural damage (Paavonen et al., 2008, Haggerty et al., 2010). Chlamydia primarily causes lower genital tract infection with subsequent upper genital tract infection caused by organisms including group B *Streptococci, Peptostreptococci, Escherichia coli, Gardnerella vaginalis,* and *Prevotella bivia,* other *Prevotella* species, and rarely *Clostridium* species and *Actinomyces* species (Chendayang, 2005). The generic diagnosis of PID encompasses more specific conditions including endometritis, salpingitis, oophritis, salpingo-oophritis, parametritis, pelvic peritonitis, pyosalpinx, tubo-ovarian abscess, and pelvic perihepatitis. PID is associated with an increased risk of ectopic pregnancy, tubal scarring and related tubal factor infertility (Chendayang, 2005, Risser and Risser, 2007).

Diagnosis of PID is neither sensitive nor specific as there is no conclusive test (Chendayang, 2005). PID diagnosis is based on presenting clinical signs and symptoms, specifically acute pelvic pain as a primary presentation, which is worse with movement, sexual intercourse, and Valsalva manoeuvre with associated adnexal tenderness, however it is also commonly asymptomatic (Chendayang, 2005). PID is likely to be under-diagnosed as clinical diagnosis is dependent on a degree of suspicion from a clinician (Risser and Risser, 2007). The US Centre for Disease Control recommends empirical treatment should be initiated in sexually active young women with a presenting abdominal complaint, if no cause can be identified, and at least one of: cervical motion tenderness, or uterine tenderness, or adnexal tenderness, which can be support a PID diagnosis if any of the following are also present:
• oral temperature >101°F (>38.3°C),
• abnormal cervical or vaginal mucopurulent discharge,
• presence of abundant numbers of white blood cells on saline microscopy of vaginal secretions,
• elevated erythrocyte sedimentation rate,
• elevated C-reactive protein, and
• laboratory documentation of cervical infection with *N. gonorrhoeae* or chlamydia (Workowski and Berman, 2006).

The proportion of PID caused by chlamydia is still largely unknown, partly because the incidence of PID has always been difficult to quantify and is dependent on the background STI prevalence in the population (Haggerty et al., 2010, Risser and Risser, 2007). Estimates for PID incidence following chlamydia infection range between 0% (95% CI: 0-12%) (Morre et al., 2002) and 30% (95% CI: 12-54%) (Østergaard et al., 2000), and up to 27% [OR: 3.4 95% CI: 1.8, 6.3]) of subclinical PID cases (Wiesenfeld et al., 2002). More recently, a PID incidence estimate of 9.5% (95% CI: 4.7%, 18.3%) was found in a UK study of young female University students (Oakeshott et al., 2010b). A review of the literature found the risk of PID increased with repeat infections; four-fold with two infections of chlamydia and 6.4 fold with three or more repeat infections (Hillis et al., 1997).

Hospital admission rates have been used as a measure for PID infection however these do not capture all the cases of PID and do not always correlate with rates of chlamydia. In Australia for example, a divergence between chlamydia notifications and hospital admissions for PID was observed (Chen et al., 2005). However in Sweden, between 1985 and 1994 PID hospital admission rates fell steadily with the introduction of chlamydia screening and the reduction of chlamydia in the population of young women (Kamwendo et al., 1996). It is also quite likely that the reduction in chlamydia was due to HIV prevention strategies which were introduced at the same time (Low and Egger, 2002, Low, 2007).

Two randomised controlled trials (3537 women enrolled) found that the risk of PID in women invited to be screened was about half that of control groups one year after a
single round of register-based screening (summary risk ratio 0.46, 95% confidence intervals 0.27–0.78, $I^2=0\%$) (Østergaard et al., 2000, Scholes et al., 1996). There were biases in the design of both studies which have been described in greater detail in section 1.10.2. A more recent study in the UK (the POPI study) determined that chlamydia incidence was an important cause of PID [attributable risk and attributable risk fraction for the association of chlamydia with PID were 7.9% and 83% respectively] (Low and Hocking, 2010) despite less PID being discovered in the population than expected [PID incidence: 1.6% (95% CI: 1.1, 2.1%)] relative risk 0.17 (95% CI: 0.03, 1.01]) (Oakeshott et al.).

Temporal associations between PID onset and acute chlamydia infection are also difficult to ascertain, particularly considering it is almost impossible to differentiate a primary chlamydia infection from a repeat or chronic infection (Haggerty et al., 2010). Three studies in high-risk populations suggest there might be a rapid onset of PID after an acute chlamydia infection. One study reported 2% of women infected with chlamydia developed PID within two weeks of testing positive (Geisler et al., 2008), Hook et al reported a PID incidence of 3.2% after an acute chlamydia within a median time of 14 days (Hook III et al., 1994), and Bachmann et al reported a PID incidence of 4.5% after a ‘short period’ of time (Bachmann et al., 1999). All three studies were limited by small numbers of PID cases (2 to 3 cases per study).

In asymptomatic populations, a slower progression from chlamydia infection to PID has been demonstrated. One year-long study found no PID cases after an initial chlamydia infection (Morre et al., 2002), while another study found 3.7% of chlamydia cases developed PID within a three month period (Rahm et al., 1986). A short period of time between an acute chlamydia infection and progression to PID raises concerns about the effectiveness of annual testing to prevent serious sequelae.

Overall, given that PID is a serious consequence of an acute chlamydia infection a successful chlamydia control program should reduce PID in the same population, however all research suggests this is difficult to measure as an outcome.
1.4.2.2  Ectopic pregnancy

One of the most serious complications of PID and salpingitis is ectopic pregnancy (Jones and Batteiger, 2000, Bevan et al., 2005). Ectopic pregnancy can have serious consequences. It is the most common cause of maternal mortality in the UK, and accounts for 73% of all maternal first-trimester deaths (Cooper et al., 2002) and 9% of all pregnancy-related mortalities in the US (Paavonen and Eggert-Kruse, 1999). In Australia, one maternal death has resulted from ectopic pregnancy during the two year period from 2003 to 2005 (Sullivan et al., 2007).

There is strong evidence to support an association with PID and ectopic pregnancy, with one study reporting that as many as 9.1% of first pregnancies after an acute episode of PID were ectopic compared with 1.4% in women without PID prior to becoming pregnant (Weström et al., 1992), and another study reports that acute salpingitis increased the risk of ectopic pregnancy sevenfold (Weström et al., 1981). Previous chlamydia infection has been associated with an elevated ectopic pregnancy rate (OR:1.4: 95% CI: 1.0, 2.0) (Bakken et al., 2007) and recurrent chlamydial infections have been demonstrated to increase the risk of ectopic pregnancy; the risk has been estimated to double with two chlamydia infections, and increase 4.5-fold with three or more infections (Hillis et al., 1997). Another study reported the increase in the incidence of ectopic pregnancy has been attributed to the increase in PID caused by chlamydia (Tay et al., 2000), and rates of ectopic pregnancy have been shown to diminish with declining rates of chlamydia infection (Egger et al., 1998). Nonetheless, salpingitis and ectopic pregnancy are difficult to directly attribute to chlamydia, particularly considering salpingitis is often long term, silent and difficult to diagnose (Jones and Batteiger, 2000).

1.4.2.3  Tubal factor infertility (TFI)

Infertility is defined by an inability to conceive a pregnancy after at least one year of trying to become pregnant. One consequence of ectopic pregnancy can include tubal factor infertility caused by tubal scarring. The pathogenesis of tubal scarring caused by chlamydia is not well understood, although one hypothesis is that prolonged or repeated chlamydia infection plays a role in causing chronic inflammation in the
fallopian tubes, leading to a build up of scar tissue and eventually occlusion (Jones and Batteiger, 2000, Land, 2010). A relationship between previous chlamydial infection and tubal factor infertility has been suggested when infertile couples have been found to have had a chlamydial infection (Svenstrup et al., 2007).

Tubal occlusion most likely to be a long term consequence of PID, and is estimated to be a factor in 10 to 30% of cases of infertility (Jones and Batteiger, 2000, Bevan et al., 2005). One study found an association between acute PID and infertility where 16% of women with acute PID subsequently became infertile compared with 2.7% women without PID (Weström et al., 1992). In a more recent review, Land et al determined that the risk of developing tubal factor infertility after PID was 10-20% and the risk of tubal infertility in a chlamydia positive women to be 4.6% (Land, 2010). However there are no prospective studies assessing the relationship between chlamydia infection and TFI and attributing infertility to a previous chlamydial infection is almost impossible to quantify as infertility is often only diagnosed many years after an infection and only in women who have unsuccessfully tried to conceive.

1.4.2.4 Adverse pregnancy outcomes

Chlamydia infection in pregnancy can cause neonatal complications including conjunctivitis and pneumonia in the newborn from an intrauterine infection of the foetus (Beem and Saxon, 1977, Schachter et al., 1979). There is also evidence to suggest that chlamydial infection can also cause early and late onset spontaneous abortion (Baud et al., 2008), stillbirth, prematurity/premature rupture of the membranes (Kovacs et al., 1998), and postpartum endometritis (Mårdh, 2002).

1.4.3 Chlamydia associations with other sexually transmitted infections

Chlamydia can also be associated with increased transmission of other STIs including HIV. The pathological premise is that increased inflammation caused by the chlamydia infection in the urogenital tract caused by an increasing shedding of HIV in the genital tract increasing HIV infectivity and also susceptibility to acquiring HIV (Fleming and Wasserheit, 1999, Chesson and Pinkerton, 2000, Galvin and Cohen,
It is advisable to treat chlamydia cases in high risk communities to reduce the transmission of HIV within the community.

1.5 Treatment of chlamydia

1.5.1 Current recommendations for treatment of chlamydia infection

Chlamydia infection is treated with azithromycin 1 gram orally stat, or doxycycline 100mg orally twice daily for 10 days (Workowski and Berman, 2006). An alternative regime can include erythromycin base 500mg orally four times daily for 7 days, or erythromycin ethylsuccinate 800 mg orally four times daily for 7 days, or ofloxacin 300mg orally twice daily for 7 days, or levofloxacin 500 mg orally twice daily for 7 days (Workowski and Berman, 2006). Doxycycline and azithromycin are equally efficacious 98% and 97% respectively, and doxycycline has the advantage of fewer side effects than azithromycin however azithromycin has the advantage of a one off dose with high efficacy that can be administered at the time of diagnosis (Lau and Qureshi, 2002) and can be used easily for patient delivered partner therapy (Schillinger et al., 2003, Sutcliffe et al., 2009). Recommendations along with immediate treatment include treating current partner/s as well as recent previous partner/s (within 60 days unless the most recent partner was prior to this) and abstain from unprotected sex for 7 days after treatment (Workowski and Berman, 2006). A follow up test is recommended three weeks to three months after treatment is finished as re-infection rates are very high (Whittington et al., 2001, Batteiger et al., 2009, Venereology Society of Victoria and the Australasian College of Sexual Health Physicians, 2002). Azithromycin is the recommended therapy in pregnancy, and an erythromycin base of ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days for infants with chlamydial conjunctivitis or pneumonia which provides an 80% effectiveness and might require a second course (Workowski and Berman, 2006).

If associated PID is suspected, the recommended treatment includes antibiotics effective against chlamydia (azithromycin) and anaerobic organisms common in PID including doxycycline and metronidazole (Workowski and Berman, 2006).
Macrolide resistant chlamydia has been discovered in clinical isolates (Misyurina et al., 2004), however azithromycin resistance is difficult to differentiate between re-infection, non compliance or poor absorption of the drug, or host immune response (Wang et al., 2005). High re-infection or persistent infection was found in women treated with azithromycin regardless of treatment compliance, condom use, partner treatment, or having a steady or new partner suggests a considerable proportion and might be due to treatment failure (Whittington et al., 2001, Schillinger et al., 2003, Batteiger et al., 2009). Treatment with azithromycin is commonly stated as being >95% effective (Lau and Qureshi, 2002), however Horner (2010) suggests that the high re-infection rate might actually be partially due to heterotypic resistance or might be persistent infections rather than re-infections in some cases (Horner, 2006). More surveillance and epidemiological information is required to ascertain if there is any azithromycin resistance developing in the community and what the potential clinical outcomes of azithromycin might indicate.

1.5.2 Partner notification

Treatment of partners is essential to reduce the risk of infection being passed between partners, and is crucial for chlamydia control (Rothenberg and Potterat, 1999). It is not always easy or possible to contact sexual partners and ensure they are treated (Low et al., 2004b), and research reports that partners are only contacted and treated in about 50% of cases for people infected with chlamydia or gonorrhoea (Chacko et al., 2000, Golden et al., 2001, Götz et al., 2005). In Australia, heterosexual women with chlamydia most identified they were likely and able to contact their recent sexual partners although only 46% of cases did so. The main reason given for contacting their partners was because it was considered ‘the right thing to do’ (Bilardi et al., 2010b). Patients were most likely to do so via the phone or face-to-face, however they indicated that they would be keen to utilise web-based methods to pass on information to their partners (Bilardi et al., 2010b, Tomnay et al., 2004).

There are many strategies clinicians can apply to try to maximise the likelihood that partners are treated. There is evidence to suggest that Australian clinicians are
comfortable doing partner notification and that they feel it is part of their responsibility (Bilardi et al., 2009). Most general practitioners (84%) were keen for resources to assist them with partner notification, including websites with information for patients (Tomnay et al., 2004), websites that can send SMS messages anonymously to partners, a website for general practitioners providing guidelines and information about partner notification (Tomnay et al., 2004), patient information sheets accessible through their patient management software, an alert in patient management software that directed them to partner notification resources, educational DVDs, access to government contact tracers and sexual health advice services, and also reminders on pathology forms (Bilardi et al., 2009). Partner notification letters were not as favourable to general practitioners or patients (Tomnay et al., 2004, Tomnay et al., 2005).

Interestingly, 43% of the general practitioners in the Australian study, were providing ‘patient delivered partner therapy’ where patients were provided with medication to give to their sexual partners, even though this is against Australian medical regulations (Bilardi et al., 2009). The effectiveness of this method has been demonstrated by a study in the US where ‘expedited partner therapy’ (similar to patient delivered partner therapy) was shown to be a successful way to treat sexual partners and an effective method for reducing chlamydia re-infection (Golden et al., 2005). In the UK, patient delivered partner therapy is also against UK regulations and so a strategy of ‘accelerated partner therapy’ was evaluated where a partner was provided with medication after either a telephone discussion with a clinician or an evaluation from a pharmacist; this was found to be favourable to both patients and partners (Sutcliffe et al., 2009).

There is scope for improvement in partner notification methods including the introduction of novel approaches to encourage patients and clinicians to contact and ensure sexual partners are treated effectively. This will be essential to the success of any chlamydia control strategy.
1.6 Duration of infection

If left untreated, how long an infection with chlamydia will remain is yet to be conclusively determined (Golden et al., 2000) however it has been established that if left untreated, chlamydia can persist for months or even years (Molano et al., 2005, Fairley et al., 2007, Morre et al., 2002, Stamm, 2008). Chlamydia has been found to spontaneously resolve in a number of cases although this is not easy to quantify as it is ethically challenging to leave diagnosed women untreated. One study reported that in untreated women chlamydia spontaneously resolved in 4% of the women after 1 year, 83% after 2 years, 91% after 3 years and 95% after 4 years (Molano et al., 2005). In The Netherlands, asymptomatic women had a clearance rate of 44.7% per year (Morre et al., 2002). Fairley et al calculated that after 1 year (if no infection lasts longer than 3.5 years) 43% of cases will have resolved or 37% of cases will have resolved if no infection lasts longer than 5 years without any treatment (Fairley et al., 2007).

1.7 Epidemiology of chlamydia in women in Australia

1.7.1 Surveillance and notification of chlamydia in Australia

Chlamydia infection is the most common notifiable bacterial infection in Australia (Department of Health and Ageing, 2010). Legislation explicitly requires notification of genital chlamydia infection to the State or Territory department of health by laboratories and or clinicians depending on the state or territory legislation. In the absence of routine annual testing in Australia, notification data will underestimate the true population based prevalence because of the asymptomatic nature of infection (Hocking and Fairley, 2003).

Chlamydia is significant public health problem among young Australian women in particular with national notification rates having increased from 74 per 100 000 people per year in 1997, to 287 per 100 000 people per year in 2009 (Hocking and Fairley, 2003, Department of Health and Ageing, 2009, O'Rourke et al., 2009) (Figure 1-5). There are more notifications in women than men, with 67% of notifications in females aged 15 to 24 years women, 43% of notifications in males aged 15 to 24
years, and only 15% of females and 34% of males are aged over 30 years old (Department of Health and Ageing, 2009) (Figure 1-6).

One argument for the increasing number of chlamydia notifications is that chlamydia prevalence is increasing proportionally to increasing testing rates – the theory that ‘the more you look for, the more you find’ (Vickers and Osgood, 2010). Mathematical modelling taking into account current sexual behaviour data, increased sensitivity and specificity of chlamydia testing, and considering immunological responses brought about by treatment, has predicted that increased testing has been responsible for increased chlamydia prevalence in Canada (Vickers and Osgood, 2010). In Australia, notification data has suggested that despite increased testing, chlamydia prevalence has been increasing over time. Four years of clinical records from a large sexual health centre including more than 10 000 chlamydia tests were retrospectively reviewed and the results demonstrated that chlamydia positivity (defined as the rate of positive results relative to the number of women tested) increased over 4 years between 2003 and 2007 by an average of 12% per year, demonstrating an independent increase in positive results irrespective of testing rates (O'Rourke et al., 2009).

Generally, in Australia, chlamydia testing rates have been increasing with 725,420 chlamydia tests conducted under Medicare in 2009. More women were tested than men (2.5:1) and 41% tests in women were done in 15 to 24 year olds, among males 31% of tests were done in 15 to 29 year olds. Conversely, testing rates were higher among men over 30 years relative to women over 30 years old (Health Insurance Commission, 2009). Despite the increases in chlamydia testing, the testing rates remain very low with only 12% of 15 and 24 year old women tested in 2009 (Health Insurance Commission, 2009).
Figure 1-5  Chlamydia notifications in Australia by sex (2009) (National Notifiable Diseases Surveillance System, 2010)

![Graph showing the rate per 100,000 for males and females from 1997 to 2009. The graph demonstrates an increase in notifications over time.]

Figure 1-6  Chlamydia notifications by age and sex in Australia (2009) (National Notifiable Diseases Surveillance System, 2010)

![Bar chart showing the rate per 100,000 for males and females across different age groups. The chart indicates a higher rate in younger age groups for both males and females.]

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26
1.7.2 Prevalence of chlamydia

Despite mandatory chlamydia notification, there are limited population based prevalence estimates for chlamydia. The only reported population prevalence estimate is from a population survey of Australian women which determined a prevalence of 3.7% (95% CI: 1.2%, 8.4%) in 18 to 24 year old women and 0.2% (95% CI: 0.0%, 1.1%) in 25 to 35 year old women (Hocking et al., 2006b). A recent systematic review calculated the mean Australian population prevalence for men and women of 4.6% (95% CI: 4.4, 4.8%). Overall mean estimates for female attendees of sexual health clinics was 3.3% (95% CI: 3.0, 3.7%), for adolescents and young adults (both sexes) 5.6% (95% CI: 4.9, 6.4%), for female sex workers (1.6% (95% CI: 1.2, 2.0%) corresponding to 1.4% (95% CI: 0.9, 2.0%), in non-Indigenous women and 8.7% (95% CI: 7.9, 9.7%) in Indigenous women (Vajdic et al., 2005). Clinic based estimates were higher than community based estimates (Vajdic et al., 2005). There have been no large scale population chlamydia prevalence studies to determine population prevalence and chlamydia incidence data for young Australian women.

Table 1-3 details the chlamydia prevalence estimates from numerous Australian studies and surveillance data. Only one of the studies is true population prevalence estimate from women recruited from the Australian population (Hocking et al., 2006b), 16 studies involve women from sexual health services or specialised hospital services and nine results include women from remote and/or Indigenous health services. Community based samples include women from sports clubs and high schools although these were convenience sampled (Kong et al., 2009, Debattista et al., 2002). Only two studies used methods other than NAAT testing (LCR and PCR), one using EIA (Donovan, 2002) and one strand displacement (Jones et al., 2004), and 24 of the 31 results were based on either urine samples exclusively included urine sampling as an option for the women tested, 10 used swabs and five used tampons either exclusively or as an option.

Chlamydia is clearly more prevalent than the Australian notification data reports. However the heterogeneous findings in Table 1-3 suggest a wide range of prevalence
depending on the population tested. The prevalence of chlamydia in women attending a sexual health service ranged from 1.8 to 5.6% although this correlated with an increase in prevalence over time. Notification data suggest young women and Indigenous women have a higher proportion of chlamydia which is consistent with these findings. The prevalence of chlamydia in young women ranged from 2.3% to 27.0% and Indigenous women from 4.9% to 11.1%, and relative to the population prevalence estimate of 0.9% (95% CI: 0.3%, 2.0%), this was much higher (Hocking et al., 2006b).

Limitations to these results include small sample size (Hocking et al., 2006b, Kong et al., 2009), or a sample that is not representative of the overall population of young Australian women including Indigenous women and women from remote and rural Australia (Bowden et al., 1999, Fairley et al., 1997, Miller et al., 1999, Tabrizi et al., 1998, Knox et al., 2002, Lenton et al., 2007, Garrow et al., 2002) women attending sexual health services (Fethers et al., 2000, Donovan, 2002, Fairley et al., 1997, Morton et al., 2002, Williams et al., 2003, Bateson, 2004, Bateson et al., 2006); termination (Garland et al., 2000), adolescent antenatal (Chen et al., 2009, Cheney, 2008, Lenton et al., 2007, Quinlivan et al., 1998) and colposcopy patients (Petersen et al., 2007); disadvantaged youth; or women who have sex with women (Fethers et al., 2000). The results of these studies relative to background population data are important for assessing populations at highest risk of infection.
Table 1-3  Studies estimating the prevalence of genital chlamydia prevalence in women in order of year of testing (Australian data).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design, population and setting</th>
<th>Specimen type</th>
<th>Response rate (%)</th>
<th>Period of study</th>
<th>Median age (age range)</th>
<th>Sample size</th>
<th>Prevalence (%) (95% CI)</th>
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<tbody>
<tr>
<td>Population based</td>
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<tr>
<td>(Hocking et al., 2006b)</td>
<td>Population based study, women recruited consecutively through the Australian telephone directory.</td>
<td>Urine</td>
<td>43</td>
<td>2003 - 2004 (18–24), (25–35)</td>
<td>160</td>
<td>3.1 (1.0, 7.1), 0.2 (0.0, 1.1)</td>
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<tr>
<td>Sexual Health/Family Planning Clinic Attendees</td>
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<tr>
<td>(Fethers et al., 2000)</td>
<td>Retrospective cross sectional study of women who have sex with women [WSW] attending a sexual health service for the first time. 1% indigenous. Retrospective cross sectional study of women who have never had sex with another woman attending a sexual health service for the first time.</td>
<td>Swab 1991-1995 Urine 1996+ Swab 1991-1995 Urine 1996+</td>
<td>59</td>
<td>1991 – 1998 27 (14–56)</td>
<td>830</td>
<td>3.0 (1.8, 4.1)</td>
<td>4.0 (2.8, 5.8)</td>
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<tr>
<td>Donovan, 2002</td>
<td>Consecutive heterosexual patients (excluding sex workers) attending a sexual health clinic for the first time. Consecutive heterosexual patients (excluding sex workers) attending a sexual health clinic for the first time.</td>
<td>Endo-cervical swab Endo-cervical swab</td>
<td>ns ns</td>
<td>1994 26</td>
<td>997</td>
<td>1.8 (1.1, 2.8)</td>
<td>3.5 (2.3, 5.0)</td>
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<tr>
<td>(Fairley et al., 1997)</td>
<td>Sexual health centre/family planning clinic attendees (excluding indigenous women from the data).</td>
<td>Tampon</td>
<td>92</td>
<td>1996 ns</td>
<td>268</td>
<td>4.1 (2.1, 7.2)</td>
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<tr>
<td>(Morton et al., 2002)</td>
<td>Convenience sampling of women attending a sexual health centre (excluding sex workers).</td>
<td>Speculum</td>
<td>ns</td>
<td>1998 ns</td>
<td>3616</td>
<td>2.4 (1.9, 3.6)</td>
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<tr>
<td>(Williams et al., 2003) (1)</td>
<td>Consecutive sampling of women attending an inner city clinic in a family planning setting.</td>
<td>Urine</td>
<td>83</td>
<td>2001 21 (16-38)</td>
<td>373</td>
<td>4.8 (2.9, 7.5)</td>
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<tr>
<td>Authors</td>
<td>Study design, population and setting</td>
<td>Specimen type</td>
<td>Response rate (%)</td>
<td>Period of study</td>
<td>Median age (age range)</td>
<td>Sample size</td>
<td>Prevalence (%) (95% CI)</td>
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<td>Sexual Health/Family Planning Clinic Attendees (continued)</td>
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<tr>
<td>(Williams et al., 2003) (2)</td>
<td>Consecutive sampling of women attending a suburban clinic in a family planning setting.</td>
<td>Urine</td>
<td>75</td>
<td>2001</td>
<td>23 (13-62)</td>
<td>478</td>
<td>1.7 (0.7, 3.3)</td>
</tr>
<tr>
<td>(Bateson, 2004)</td>
<td>Pilot study of consecutive sexually active young women from two family planning clinics.</td>
<td>Urine</td>
<td>40</td>
<td>2003</td>
<td>20 (14-24)</td>
<td>182</td>
<td>3.8 (1.0, 6.6)</td>
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<tr>
<td>(Bateson et al., 2006)</td>
<td>Cross sectional study of consecutive sexually active young women from family planning clinics.</td>
<td>Urine</td>
<td>67</td>
<td>2004</td>
<td>(16-24)</td>
<td>621</td>
<td>5.6 (3.8, 7.4)</td>
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<td>Women attending a specific hospital clinic</td>
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<tr>
<td>(Petersen et al., 2007)</td>
<td>Cross sectional study of women attending a colposcopy clinic in Melbourne.</td>
<td>Endo-cervical swab</td>
<td>99</td>
<td>2005</td>
<td>33</td>
<td>560</td>
<td>2.1 (1.5, 2.7)</td>
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<tr>
<td>(Garland et al., 2000)</td>
<td>Consecutive women attending a hospital termination clinic.</td>
<td>Urine, tampon &amp; swab</td>
<td>100</td>
<td>1996-1997</td>
<td>ns</td>
<td>1175</td>
<td>2.8 (1.9, 3.9)</td>
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<td>Indigenous Australian women</td>
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<tr>
<td>(Bowden et al., 1999)</td>
<td>Consecutive women including women from remote, urban and rural communities from community health centers, family planning clinics and STD clinics.</td>
<td>Tampon</td>
<td>ns</td>
<td>1996</td>
<td>(12-73)</td>
<td>1090</td>
<td>11 (9, 13)</td>
</tr>
<tr>
<td>(Fairley et al., 1997)</td>
<td>Cross sectional survey of community Indigenous women primarily from rural areas, clinic based.</td>
<td>Urine</td>
<td>97</td>
<td>1996</td>
<td>ns</td>
<td>345</td>
<td>7.8 (5.2, 11.2)</td>
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<tr>
<td>(Miller et al., 1999)</td>
<td>Cross sectional survey of community based Indigenous women from Central Australia.</td>
<td>Urine</td>
<td>79</td>
<td>1997</td>
<td>(12-40)</td>
<td>546</td>
<td>7.5 (5.4, 10.0)</td>
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<tr>
<td>Authors</td>
<td>Study design, population and setting</td>
<td>Specimen type</td>
<td>Response rate (%)</td>
<td>Period of study</td>
<td>Median age (age range)</td>
<td>Sample size</td>
<td>Prevalence (%) (95% CI)</td>
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<td><strong>Indigenous Australian women (continued)</strong></td>
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<tr>
<td>(Tabrizi et al., 1998)</td>
<td>Consecutive women from rural and remote areas, attending clinics for sexual health check.</td>
<td>Urine</td>
<td>75%</td>
<td>ns</td>
<td>ns</td>
<td>660</td>
<td>6.1 (4.4, 8.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tampon</td>
<td>100%</td>
<td>ns</td>
<td>ns</td>
<td>880</td>
<td>4.9 (3.3, 6.5)</td>
</tr>
<tr>
<td>(Knox et al., 2002)</td>
<td>Consecutive women from urban and remote areas of Central Australia attending a health clinic. (18% Indigenous).</td>
<td>Urine</td>
<td>ns</td>
<td>1998-1999</td>
<td>ns</td>
<td>292</td>
<td>8.2 (5.3, 12.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tampon</td>
<td>ns</td>
<td>1998-1999</td>
<td>ns</td>
<td>306</td>
<td>11.1 (7.8, 15.2)</td>
</tr>
<tr>
<td>(Miller et al., 2003)</td>
<td>Cross sectional survey of indigenous women people living in rural and remote regions attending medical services.</td>
<td>Urine</td>
<td>ns</td>
<td>1998-2000</td>
<td>ns</td>
<td>1456</td>
<td>9.3 (7.9, 11.0)</td>
</tr>
<tr>
<td>(Garrow et al., 2002)</td>
<td>Consecutive women in remote towns and communities of the Kimberley (26% non-Indigenous) attending medical services.</td>
<td>Vaginal swab or urine test</td>
<td>ns</td>
<td>2000-2001</td>
<td>29</td>
<td>303</td>
<td>9.2 (6.2, 13.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(mean age)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Young Australian women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Chen et al., 2009)</td>
<td>Cross sectional study of 16 to 25 year old pregnant women attending antenatal services in Melbourne.</td>
<td>Urine</td>
<td>88</td>
<td>2006-2007</td>
<td>23 (16-25)</td>
<td>1044</td>
<td>3.2 (1.8, 5.9)</td>
</tr>
<tr>
<td>(Kong et al., 2009)</td>
<td>Convenience sampling of young women at a number of sporting events in rural Victoria.</td>
<td>Urine</td>
<td>&gt;95%</td>
<td>2007</td>
<td>ns</td>
<td>161</td>
<td>5.6 (2.6, 10.3)</td>
</tr>
<tr>
<td>(Cheney, 2008)</td>
<td>Consecutive pregnant women younger than 20 years old attending a young parents’ clinic.</td>
<td>Urine</td>
<td>58</td>
<td>2003-2006</td>
<td>19 (14-20)</td>
<td>212</td>
<td>13.7</td>
</tr>
<tr>
<td>(Lenton et al., 2007)</td>
<td>Cross sectional study of pregnant women attending a remote are antenatal health service</td>
<td>Urine</td>
<td>52</td>
<td>2004-2006</td>
<td>22</td>
<td>218</td>
<td>2.7 (1.0, 5.9)</td>
</tr>
<tr>
<td>(Quinlivan et al., 1998)</td>
<td>Cross-sectional sample of pregnant women attending an adolescent pregnancy clinic (33% Indigenous).</td>
<td>Endo-cervical swab</td>
<td>92</td>
<td>1997</td>
<td>(13-17)</td>
<td>921</td>
<td>27.0 (18.4, 37.4)</td>
</tr>
<tr>
<td>Authors</td>
<td>Study design, population and setting</td>
<td>Specimen type</td>
<td>Response rate (%)</td>
<td>Period of study</td>
<td>Median age (age range)</td>
<td>Sample size</td>
<td>Prevalence (%) (95% CI)</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Young Australian women (continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Debattista et al., 2002)</td>
<td>Volunteer sampling of students from high schools in rural and urban areas.</td>
<td>Urine</td>
<td>30-50</td>
<td>1998-2001</td>
<td>(15-18)</td>
<td>516</td>
<td>2.3 (1.1, 4.1)</td>
</tr>
<tr>
<td>(Debattista et al., 2002)</td>
<td>Consecutive pathology records of disadvantaged youth some in detention (≥47% Indigenous).</td>
<td>Urine</td>
<td>ns</td>
<td>1998-2001</td>
<td>ns</td>
<td>249</td>
<td>19.7 (14.9, 25.1)</td>
</tr>
<tr>
<td>(Heal et al., 2002)</td>
<td>Cross sectional sample of youth (4% Indigenous) from GP clinics in Mackay Queensland.</td>
<td>Urine</td>
<td>68</td>
<td>2001</td>
<td>21 (mean age) (18-24)</td>
<td>381</td>
<td>5.0 (2.8, 7.4)</td>
</tr>
<tr>
<td>(Jones et al., 2004)</td>
<td>Convenience sampling of youths attending a youth health clinic in Geelong Victoria.</td>
<td>Urine f</td>
<td>100</td>
<td>2002-2003</td>
<td>(12-25)</td>
<td>154</td>
<td>5.8 (2.7, 10.8)</td>
</tr>
<tr>
<td>(Bowden et al., 2005)</td>
<td>Convenience sampling of youths two high schools in the ACT.</td>
<td>Vaginal swab or urine</td>
<td>31</td>
<td></td>
<td>17 (15-20)</td>
<td>469</td>
<td>0.7 (0.09, 2.6)</td>
</tr>
</tbody>
</table>

*f*EIA testing done for all swabs for testing done prior to 1994; *Data not stated; *Study accompanied by an intervention; *urine sample; *tampon sample; *strand displacement testing used.
1.8 Epidemiology of chlamydia internationally in women

1.8.1 Surveillance and notification of chlamydia internationally

The European community has established a Centre for Disease Control aimed at analysing surveillance data and monitoring any infectious diseases threats within the European community, and the centre has recently launched guidelines for chlamydia control in Europe (Van de Laar and Fontaine, 2009, European Centre for Disease Prevention and Control, 2009). The primary aim of the guidelines is to reduce the proportion of countries without any, or very little organised chlamydia surveillance or control activity (at least 45% of EU and EAA/AFTA countries) and the secondary aim is to increase evidence based research into effective chlamydia control and surveillance methods (Van de Laar and Fontaine, 2009). A review of European surveillance data in 2007 show very heterogeneous prevalence estimates and disparate surveillance methods across the 23 countries in Europe included in the review. Countries vary between mandatory and voluntary notification, comprehensive versus sentinel surveillance, case-based versus aggregated data, and also who is responsible for reporting cases (laboratories, physicians, hospitals, other, or any/all of these). All countries except Austria and Spain have national coverage (European Centre for Disease Prevention and Control, 2009).

Notification rates in Scandinavian countries are generally higher because of opportunistic screening, increased contact tracing and mandatory notification (European Centre for Disease Prevention and Control, 2009). General practitioners are generally involved in screening in the Netherlands and Belgium whereas in Germany STI patients are more likely to be seen in hospital-based STI clinics than private practice as with in the UK in genito-urinary medicine clinics despite a number of general practitioners diagnosing chlamydia in women (van den Broek et al., 2010). In the Netherlands for example, no case-registration exists for chlamydia and surveillance relies on STI and HIV-treatment centres to obtain data from the presumably high-risk populations and the bulk of infections (van den Broek et al., 2010). Whilst this might detect trends and emergent infections the majority of young people in the Netherlands when surveyed said they would go to their general
practitioner if they suspected they had an STI (van den Broek et al., 2010). In Australia, the majority of chlamydia diagnoses are made by general practitioners but the testing rate is still very low.

### 1.8.2 Prevalence of chlamydia internationally

Several chlamydia prevalence surveys have been conducted internationally (Table 1-4). The prevalence varies between countries and within countries depending on the sampling frame and response rates of the studies involved. One limitation of these studies is the conjecture that women who are more likely to test positive for chlamydia might also be more likely to refuse to participate in a population based sexual health study (Miller, 2008). All results demonstrate a consistently high prevalence of chlamydia particularly in young women (range: 3.0% to 7.7%). Generally chlamydia appeared to be more prevalent in young women internationally than in Australian (3.1%), except for one estimate from the UK (3.0%) for women in the same age group (Fenton et al., 2001b). This U.K estimate was inconsistent with other UK studies reporting a higher prevalence between 5.7% and 7.7% and data from the UK chlamydia screening pilot project which reports a prevalence of 8.5%. UK data did vary depending on the health care setting (range: 3.4% - 17.6%) (Pimenta et al., 2003a).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Sampling frame</th>
<th>Specimen type</th>
<th>Median age (age range)</th>
<th>Sample size</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Fenton et al., 2001b)</td>
<td>United Kingdom</td>
<td>Postcode address lists</td>
<td>Urine</td>
<td>18-44</td>
<td>2055</td>
<td>1.5 (1.1, 2.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18-24</td>
<td>379</td>
<td>3.0 (1.7, 5.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-34</td>
<td>872</td>
<td>1.7 (1.0, 2.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35-44</td>
<td>804</td>
<td>0.6 (0.3, 1.4)</td>
</tr>
<tr>
<td>(Andersen et al., 2002)</td>
<td>Denmark</td>
<td>County health service</td>
<td>Vaginal flush</td>
<td>21-23</td>
<td>2506</td>
<td>7.7 (6.7, 8.8)</td>
</tr>
<tr>
<td>(Low et al., 2004a)</td>
<td>United Kingdom</td>
<td>GP registers</td>
<td>Vulval swabs and urine</td>
<td>16-25</td>
<td>309</td>
<td>7.2 (4.8, 10.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26-39</td>
<td>130</td>
<td>0.8 (0.1, 5.2)</td>
</tr>
<tr>
<td>(Datta et al., 2007)</td>
<td>United States</td>
<td>NHANESa study</td>
<td>Urine</td>
<td>14-19</td>
<td>1649</td>
<td>4.6 (3.7, 5.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20-29</td>
<td>1000</td>
<td>1.9 (1.0, 3.4)</td>
</tr>
<tr>
<td>(Bohm et al., 2009)</td>
<td>Germany</td>
<td>Gynaecology patients (asymptomatic and symptomatic)</td>
<td>Urine and endocervical swabs</td>
<td>13-50</td>
<td>135 799</td>
<td>5.0 (4.9, 5.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;26</td>
<td>83 575</td>
<td>6.6 (6.4, 6.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26-35</td>
<td>39 239</td>
<td>2.5 (2.3, 2.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;35</td>
<td>12 985</td>
<td>1.4 (1.2, 1.6)</td>
</tr>
<tr>
<td>(Mossong et al., 2009)</td>
<td>Luxembourg</td>
<td>Family planning clinics; Compulsory health checks at secondary schools &amp; occupational health checks;</td>
<td>Urine</td>
<td>15-25</td>
<td>1327</td>
<td>5.8 (5.0, 6.7)</td>
</tr>
<tr>
<td>(Oakeshott et al., 2010b)</td>
<td>United Kingdom</td>
<td>University students</td>
<td>Vaginal swabs</td>
<td>16-27</td>
<td>2 519</td>
<td>5.7 (4.8, 6.7)</td>
</tr>
<tr>
<td>(Imai et al., 2010)</td>
<td>Japan</td>
<td>Tertiary student register</td>
<td>Urine</td>
<td>18-36</td>
<td>4 003</td>
<td>9.5</td>
</tr>
</tbody>
</table>

aNational Health and Nutrition Examination Survey.
1.8.2.1  **Risk factors for chlamydia**

The main risk factors associated with a chlamydia infection have been identified as: young age, unprotected sex, increased numbers of sex partners (recent and lifetime partners) and recent partner change (Table 1-5). Women are at an increased risk of acquiring an infection with unprotected sexual contact with an infected partner as the concordance of infection between sexual partners is between 45% (Rogers et al., 2008) and 75% (Markos, 2005) and male to female and female to male transmission frequencies are equal (Quinn et al., 1996) (Table 1-5).

In Australia, Indigenous women have a higher overall prevalence with some studies reporting as high as 11% in 1999 (Bowden et al., 1999, Bowden, 2005). A systematic review found that the mean prevalence chlamydia rate in Indigenous Australian women was 8.7% (95% CI: 7.9, 9.7%) compared with 1.4% (95% CI: 0.9, 2.0%) for non-Indigenous women (Vajdic et al., 2005, Fairley et al., 1997). Indigenous people accounted for 41% of chlamydia notifications, with Indigenous to non Indigenous age standardised rate ratios of 16 (95% CI: 14, 17) (Wright et al., 2005). This is a major public health concern for this community in Australia (NCHECR, 2004).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Study/ sampling frame (age in years)</th>
<th>OR (95% CI) or P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Young Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Valkengoed et al., 2000)</td>
<td>The Netherlands</td>
<td>General practice register (≤ 25)</td>
<td>1.9 (1.1, 3.2)</td>
</tr>
<tr>
<td>(Fenton et al., 2001b)</td>
<td>United Kingdom</td>
<td>General population (18-24)</td>
<td>3.0 (1.7, 5.0)</td>
</tr>
<tr>
<td>(Heal et al., 2002)</td>
<td>Australia</td>
<td>General practice (&lt;20)</td>
<td>P &lt; 0.1</td>
</tr>
<tr>
<td>(Verhoeven et al., 2003a)</td>
<td>Belgium</td>
<td>General practice clinics (18-22)</td>
<td>4.1 (1.4, 11.8)</td>
</tr>
<tr>
<td>(Adams et al., 2004)</td>
<td>United Kingdom</td>
<td>Systematic review (20-24)</td>
<td>4.0 (5.0, 8.0)</td>
</tr>
<tr>
<td>(Hocking et al., 2006b)</td>
<td>Australia</td>
<td>General population (18-24)</td>
<td>16.0 (1.8, 758.1)</td>
</tr>
<tr>
<td>(Datta et al., 2007)</td>
<td>USA</td>
<td>General population (14-19)</td>
<td>4.7 (2.1, 10.5)</td>
</tr>
<tr>
<td>(Imai et al., 2010)</td>
<td>Japan</td>
<td>Tertiary students (18) (19) (20)</td>
<td>2.0 (1.4, 2.8) 2.1 (1.6, 2.8) 1.5 (1.0, 2.0)</td>
</tr>
<tr>
<td><strong>2. Numbers of sexual partners (lifetime)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Datta et al., 2007)</td>
<td>USA</td>
<td>General population (1) (2) (3-5) (6+)</td>
<td>1.2 (0.4, 3.3) 2.6 (1.1, 6.6) 5.4 (2.1, 13.9) 6.3 (2.1, 18.7)</td>
</tr>
<tr>
<td>(Imai et al., 2010)</td>
<td>Japan</td>
<td>Tertiary students (4+)</td>
<td>3.2 (2.4, 4.1)</td>
</tr>
<tr>
<td><strong>3. Numbers of sexual partners (last 12 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Heal et al., 2002)</td>
<td>Australia</td>
<td>General practice (2+)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>(Paukku et al., 2003)</td>
<td>Finland</td>
<td>University health clinic (3-5) (6+)</td>
<td>6.8 (1.7, 20.0) 6.3 (1.6, 20.0)</td>
</tr>
<tr>
<td>(Verhoeven, 2003 #1095)</td>
<td>Belgium</td>
<td>General practice clinics (2) (3-5) (6+)</td>
<td>6.0 (2.3, 16.0) 8.8 (3.0, 26.1) 9.7 (2.8, 34.3)</td>
</tr>
<tr>
<td>(LaMontagne et al., 2004b)</td>
<td>USA</td>
<td>Family planning clinics (2+)</td>
<td>1.5 (1.4, 1.6)</td>
</tr>
<tr>
<td>(Mossong et al., 2009)</td>
<td>Luxembourg</td>
<td>Secondary schools (3+) Occupational health service (3+)</td>
<td>7.6 (2.9, 20.0) 2.6 (1.3, 4.9)</td>
</tr>
</tbody>
</table>
### 4. Unprotected sexual intercourse

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Sampling frame</th>
<th>OR (95% CI) or P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Fenton et al., 2001b)</td>
<td>United Kingdom</td>
<td>National population survey</td>
<td>4.2 (1.2, 14.7)</td>
</tr>
<tr>
<td>(Gaydos et al., 2003)</td>
<td>USA</td>
<td>2+ partners without condoms</td>
<td>1.3 (1.1, 1.4)</td>
</tr>
<tr>
<td>(Imai et al., 2010)</td>
<td>Japan</td>
<td>Tertiary students</td>
<td>1.3 (1.1, 1.4)</td>
</tr>
</tbody>
</table>

### 5. Recent partner change

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Sampling frame</th>
<th>OR (95% CI) or P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Valkengoed et al., 2000)</td>
<td>The Netherlands</td>
<td>General practice register</td>
<td>3.1 (1.7, 5.9)</td>
</tr>
<tr>
<td>(Heal et al., 2002)</td>
<td>Australia</td>
<td>General practice</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>(Gaydos et al., 2003)</td>
<td>USA</td>
<td>Family planning clinics</td>
<td>1.2 (1.0, 1.3)</td>
</tr>
<tr>
<td>(LaMontagne et al., 2004b)</td>
<td>USA</td>
<td>Family planning clinics</td>
<td>1.2 (1.0, 1.3)</td>
</tr>
</tbody>
</table>

### 6. Indigenous status (Australian population)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Sampling frame</th>
<th>OR (95% CI) or P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Fairley et al., 1997)</td>
<td>Australia</td>
<td>Indigenous communities Far North Queensland &amp; Torres Strait Islands</td>
<td>P = 0.05</td>
</tr>
<tr>
<td>(Wright et al., 2005)</td>
<td>Australia</td>
<td>Western Australian Notifiable Infectious Diseases Database</td>
<td>rate ratio: 16 (95% CI, 14,17)</td>
</tr>
</tbody>
</table>

#### 1.8.3 Chlamydia incidence

Currently there are no incidence data for women chlamydia in Australia. In Europe, surveillance data provide chlamydia estimates which range from the lower levels of 0.5 per 100 000 people (Romania) and 6.9 per 100 000 people (Hungary) to higher levels of 588 per 100 000 people (Iceland), 517 per 100 000 people (Sweden), 488 per 100 000 people (Norway) and 474 per 100 000 people (Denmark). The overall European total incidence rate based on surveillance data is estimated at 122.60 per 100 000 people (European Centre for Disease Prevention and Control, 2009). These chlamydia estimates do not represent true population data as they are dependent on the rates of testing in each country, whether or not notification is mandatory and accuracy of surveillance data for each country. The large variation between countries suggests surveillance methods are inconsistent and most likely underestimated. Countries with introduced policies about screening including surveillance have higher incidence figures.
Young people (15 to 24 years old) had the highest notification rate accounting for two-thirds of all cases (rate 367 per 100,000), Denmark, Norway, Finland, Iceland and the UK recording the highest age-specific rates (European Centre for Disease Prevention and Control, 2009) (Figure 1-7). Differences between men and women also vary with an overall male to female ratio of 1:1.2 although again this varied between countries. In the Netherlands and the UK women and men have similar chlamydia notification rates however, in other Northern European countries and the US; women have a much higher notification rate than men.

Figure 1-7  Distribution of chlamydia cases by age and gender in EU and EEA/EFTA countries, 2006 (n=187,804.) (European Centre for Disease Prevention and Control, 2009)
In the US, chlamydia is a notifiable disease and is recorded by the Centre Disease Control (CDC); the CDC recommends annual screening of all sexually active women younger than 26 years of age. Chlamydia notification in the US was 401 per 100 000 (people) in 2008 ranging from 160 per 100 000 in New Hampshire to 728 per 100 000 in Mississippi (Division of STD Prevention, 2009). This is comparable with the European surveillance data.

The highest age specific rates in the US was among 15 to 19 year olds (3275.8 per 100 000 females) and 20 to 24 years of age (3179.9 per 100 000 females), and chlamydia was three times higher in females than males. Chlamydia notifications were also reported to be eight times higher in black Americans than whites, five times higher in American Indian/Alaskan natives and three times higher in Hispanics than white Americans (Division of STD Prevention, 2009).

Population based research reports incidence rates between 3 and 34 per 100 women years (Burstein et al., 1998, Batteiger et al., 2009, Rietmeijer et al., 2002, Richey et al., 1999). Recent results of a cohort study in the United Kingdom report an incidence of 4.9 (95% CI: 2.7, 8.8) per 100 women years among 16 to 24 year old women from general practitioner clinics, 10.6 (95% CI: 7.4, 15.2) from genitourinary medicine clinics and 6.4 (95% CI: 4.2, 9.8) for women from family planning clinics (LaMontagne et al., 2007).

Overall predictors for chlamydia incidence were younger age (Geisler et al., 2004, van den Broek et al., 2010, LaMontagne et al., 2007, Rietmeijer et al., 2002), black race (Rietmeijer et al., 2002), a history of chlamydia infection (Geisler et al., 2004, LaMontagne et al., 2007, Rietmeijer et al., 2002), a history of other STIs (Batteiger et al., 2009), inconsistent condom use (Rietmeijer et al., 2002), increased number of recent sexual partners (Geisler et al., 2004, Batteiger et al., 2009), and acquisition of new sexual partner/s (Rietmeijer et al., 2002) (unless they used a condom which was protective against chlamydia) (LaMontagne et al., 2007).
1.8.4 Chlamydia re-infection

Immunity for chlamydia is only short term after treatment and therefore treatment for chlamydia will not prevent further infection. If partners are not treated effectively, then the possibility of a re-infection of chlamydia is very likely. Repeat infection for chlamydia is common with a peak re-infection rate estimated in 19% to 20% of cases at 8 to 10 months after the initial infection (Hosenfeld et al., 2009). Worryingly, repeated infections are more likely to cause the more serious sequelae of an acute episode of chlamydia including PID or salpingitis (Hillis et al., 1997) and therefore it is important to include partner treatment as part of chlamydia clinical management.

If a patient presents with another chlamydia infection, it is not always easy to differentiate a persistent infection from a re-infection. It has to be established if the prescribed antibiotics were taken and absorbed, current partners were treated and there was no unprotected sex until both partners had been treated, and if there had been any unprotected sex with other partners in the interim. It can be difficult to determine treatment failure and the exact level of chlamydial antibiotic resistance is unknown (Wang et al., 2005). Genotyping can help identify re-infections particularly if this can be identified in both sexual partners. If a follow up infection is the same genotype as the previous infection, the repeat infection is possibly due to a re-infection from the same partner, an infection of the same genotype from another sexual partner or treatment failure (Batteiger et al., 2009).

Population based studies have reported re-infection rates between 4 to 51 per 100 women years (Oh et al., 1996, Veldhuijzen et al., 2005, Xu et al., 2000, Schillinger et al., 2003) with a median of 13.9% (Hosenfeld et al., 2009). In the United Kingdom, a prospective cohort of 16 to 24 year old women had a re-infection rate of 29.9 (95% CI: 19.7, 45.4) per 100 person years in women recruited from general practice clinics, 22.3 (95% CI: 15.6, 31.8) per 100 person years from family practice clinics and 21.1 (95% CI: 14.3, 30.9) per 100 person years from GUM clinics (LaMontagne et al., 2007). Re-infection was determined by the first positive test after a confirmed negative test.
Other studies of specific groups have also reported re-infection rates ranging from 1.7% for a cohort of women from sexual health centres study in the US (Peterman et al., 2006), 7% in a multi-centred cohort study after 4 months (Whittington et al., 2001), 26.3% in female adolescents from school based clinics (Gaydos et al., 2008) to 34% in US army recruits although the latter were a ‘high risk’ group and retesting occurred after 30 days only (Barnett and Brundage, 2001).

In a recent US longitudinal study Batteiger et al found that out of 268 repeat infections, 84.2% were defined as definite or probable re-infections, 13.7% were due to probable treatment failure, and 2.2% were persistent infections without treatment (Batteiger et al., 2009).

Predictors of re-infection include younger age (Xu et al., 2000, Gaydos et al., 2008, Peterman et al., 2006), non-white women compared with white women in the US (Xu et al., 2000, Peterman et al., 2006) and the U.K. (LaMontagne et al., 2007), having a previous infection with chlamydia or having had a previous infection with another STI (Oh et al., 1996, Peterman et al., 2006, LaMontagne et al., 2007, Kjaer et al., 2000), increased numbers of sexual partners (Peterman et al., 2006, LaMontagne et al., 2007), rapid acquisition of new sexual partners (LaMontagne et al., 2007), and incomplete partner treatment (LaMontagne et al., 2007).

As with incidence data there are no re-infection data for the Australian female population, despite a previous infection being one of the highest risks for infection. Considering the greatest risk for adverse sequelae from chlamydia occurs with repeated infections, partner treatment, repeat testing and follow up is particularly pertinent in chlamydia control.

1.8.4.1 Determining an algorithm for identifying re-infection

To determine if a repeat infection is in fact a re-infection as opposed to a persistent infection or new infection, all other possibilities need to be ruled out. Batteiger et al designed an algorithm for determining re-infection with chlamydia (Figure 1-8), including behavioural factors such as coitus without condoms between infected partners, treatment adherence and absorption, possible treatment failure, and
confirmation with genotyping. A repeat was considered a new infection if the initial and subsequent infections had a different genotype (Batteiger et al., 2009). In addition to this, genotypes of the infected partners would also assist in the identification of persistent infections.

![Algorithm to differentiate chlamydia re-infection and persistent infection adapted from Batteiger et al (2009)](image)

Figure 1-8 Algorithm to differentiate chlamydia re-infection and persistent infection adapted from Batteiger et al (2009) (Batteiger et al., 2009)
1.9 Chlamydia control

The persistence and spread of any STI is dependent on the reproductive rate ($R_0$) of the infection within a community. The $R_0$ represents the number of secondary infections that are the direct result of primary infection introduced into a community that is naive to the infection at a specific point in time ($R_0=0$). The $R_0$ is dependent on the probability of transmission of an infection ($\beta$), the rate of partner change ($c$) and the duration of the infection ($D$) and is defined as $R_0 = \beta cD$ (Anderson, 1999). If $R_0$ is greater than one then the infection will spread within a community until it reaches a steady state, and the aim of chlamydia (and other infectious diseases) control is to create a community where the $R_0$ is less than one so that the infection will eventually die out (Anderson, 1999).

Understanding the factors associated with the $R_0$ provides a good basis for strategies to control the infection. Reducing the transmissibility of chlamydia between individuals ($\beta$) can be achieved by increasing the awareness of the protective effect of condoms and making condoms readily available particularly to high risk groups. For example, condom use has been demonstrated to significantly reduce PID in a population by up to 30 to 60% (Ness et al., 2004). Reducing partner change ($c$) is also difficult to achieve and recent sexual behaviour research in Australia and internationally suggest young people are having more sexual partners and more concurrent sexual partners than before (Smith et al., 2009, Johnson et al., 2001).

The final variable in determining the $R_0$ in a population is the duration of infection ($D$). The average duration of infection is a powerful predictor of the prevalence of an infection in a population and is directly related to the availability and effectiveness of treatment. For chlamydia this yet to be conclusively determined (Golden et al., 2000) however it has been established that if left untreated, chlamydia can persist for months or even years (Fairley et al., 2007, Morre et al., 2002, Stamm, 2008, Molano et al., 2005). The duration of an infection can be reduced by prompt treatment, partner treatment, active case finding and increased access to healthcare services and screening can reduce the duration of infection of chlamydia.
1.10 Chlamydia screening

Chlamydia is an ideal candidate for screening as it is a common, curable and easily treated infection that is often asymptomatic, however, at this stage there is no one ‘gold standard’ screening program that has been demonstrated to reduce chlamydia prevalence or associated morbidity. The most commonly recommended approach is screening sexually active young people under 25 years, however there is an absence of evidence to support an organised screening program in this population (Low and Egger, 2002, Low, 2007). For a chlamydia screening program to be effective it must be cost effective, must achieve sufficient participation rates at frequent enough intervals to interrupt disease transmission, and the natural history should be well understood (Low, 2007, Low and Egger, 2002). The current level of screening required to have an effect on chlamydia prevalence is unknown, although mathematical modelling suggests the screening rate in Australia should be in least 30% of the population to effect a change (Regan et al., 2008). Quality randomised trials of multiple rounds of screening with biological outcome measures are still needed to determine the balance of benefits and harms of chlamydia screening.

1.10.1 Screening effectiveness

Unlike Australia, many countries have implemented chlamydia testing policies. In Sweden, a screening policy was introduced in the 1980s (Low, 2004). Although there is no co-ordinated national screening program in Sweden, it is compulsory for clinicians to provide free testing, treatment and contact tracing to any patient with suspected chlamydia, and mandatory for clinicians to report all positive diagnoses. The Swedish screening policy recommends testing all sexually active women aged between 15 and 29 years seeking contraception and abortion, and testing all male sexual contacts or men who are symptomatic (Ripa, 1990, Herrmann and Egger, 1995) however considering opportunistic screening is targeted through health care settings, primarily young women and not men are tested. In the initial period (between 1985 and 1993) after opportunistic screening was introduced, chlamydia screening rates increased and chlamydia positivity decreased by nearly 70% in women and 61% in men and the policy was considered a success. In an analysis of
the data since the mid-1990s, it can be shown that chlamydia positivity subsequently increased, suggesting long term opportunistic screening was not effective (Herrmann and Egger, 1995). There are a number of theories as to the lack of long term reduction of prevalence of chlamydia in Sweden. One is that men were not included sufficiently despite mandatory partner notification, another is that the initial reduction in prevalence was due to changes in sexual behaviour as a direct result of a concurrently run HIV prevention campaign and not due to the introduced chlamydia screening policy (Low and Egger, 2002, Low, 2007). These results have been reflected in other countries with and without screening programs who also report an increase in population prevalence during the same time period (Low and Egger, 2002)

Denmark has had a similar experience: a chlamydia screening policy was introduced only to report a similar trend of decreasing chlamydia positivity followed by an increase in cases which occurred over the same time period as Sweden (Low, 2007, Hocking et al., 2008b).

In 1988, parts of the United States introduced opportunistic screening, principally targeting young women attending STI and family planning clinics (Hillis et al., 1995). Screening was introduced federally by 1995 under the national Infertility Prevention Program which provided chlamydia screening for all women under 25 years old who were sexually active. In an effort to reduce chlamydia incidence and re-infection, the US Centre for Disease Control (US CDC) also endorsed behavioural education, partner treatment including expedited partner therapy, and follow up testing three months after a treatment for a positive result (US CDC, 2010). Between 1988 and 1993 chlamydia positivity fell from 11% to 5%, and there is some evidence to demonstrate that positivity is either stabilising or decreasing over the last few years, in response to increased testing (US CDC, 2010, Satterwhite et al., 2010). In 2008, US testing data available through the Health Plan Employer Data and Information Set (HEDIS) demonstrated an increase in testing rates for 16 to 26 year old female enrollees, by between 43% and 55% (National Committee for Quality Assurance, 2009). The changes in the US also appeared favourable, however chlamydia positivity in 15 to 24 year old women increased in six of the ten regions decreasing in
only two regions, with the other two regions remaining static (Low, 2007, Hocking et al., 2008b).

In the United Kingdom a chlamydia screening pilot was funded by the Department of Health in the Wirral and Portsmouth areas, targeting women attending general practitioners, GUM clinics, family planning clinics, adolescent health clinics, and women’s health services. In 1999 and 2000, 76% and 84% of women were tested as part of the pilot, screening a total of 16,930 women in total (Pimenta et al., 2003b). During 2002, the U.K. National Chlamydia Screening Programme was phased in, offering opportunity for chlamydia screening programs to be implemented. In 2005 to 2006 the effective screening rate was less than 5% in more than half the programme areas although overall, by 2009-2010 testing had increased to 22.1% of 15 to 24 year olds (UK Health Protection Agency, 2006, UK Health Protection Agency, 2010) which was still well below the pilot testing rate.

1.10.2 Outcome measures for a screening program

Successful outcomes of a screening program are difficult to establish: measures must include proportion of screening uptake as well as changes in morbidity attributable to chlamydia infection. Objective endpoints, such as ectopic pregnancy or tubal infertility are very difficult to diagnose as they require invasive procedures, are often delayed in relation to chlamydia infection and are relatively rare. PID is the most commonly used biological outcome because it is the most frequent acute complication of lower genital tract (section 1.4.2.1), and is strongly associated with impaired fertility (Paavonen et al., 2008). PID is a difficult outcome to measure as clinical diagnosis of PID is known to be insensitive, non-specific and subjective (Simms et al., 2003b) and often misclassified, making the effect size difficult to quantify. Also, since clinicians usually cannot be blinded to the screening allocation in trials, symptoms reported in follow up consultations should be recorded in a standard way, with the final outcome assessment made by an independent blinded committee. Nonetheless, PID prevalence has been demonstrated to be effectively reduced by chlamydia screening. Two randomised controlled trials found that the risk of PID in women invited to be screened was about half that of control groups
one year after a single round of register-based screening (summary risk ratio 0.46, 95% confidence intervals 0.27–0.78, I²=0%) (Low et al., 2009, Scholes et al., 1996, Østergaard et al., 2000), although there was bias in the design of both studies. In the earlier published study (Scholes et al., 1996) the authors used the register of a health maintenance organisation in the USA to identify, invite, and follow up their target population. Women randomised to the screening group only were telephoned to increase the number with a risk assessment and allow screening appointments to be made. These practices changed the planned ratio in intervention and control groups from 1:2 to 1:1.6 (total 2607). Sixty four per cent of women in the intervention group and an unknown proportion in the control group were screened for chlamydia. Østergaard et al. conducted a cluster randomised trial in 17 high schools in Aarhus County, Denmark (8909 students) (Østergaard et al., 2000). Sexually active female and male students responding to the invitation were asked to collect urine and/or vaginal specimens at home, or told that they could be tested at a local health clinic. Response rates were higher in those assigned to the intervention (32% of those randomised) than control group (24%). Participants in the intervention group were given additional information about the importance of partner notification if diagnosed with chlamydia. The limitations of these results were that the ascertainment of PID was not blinded and loss to follow up one year later was nearly 50%.

A third, more recent study in the UK (the POPI study) was conducted to determine if PID incidence was reduced with the introduction of population screening. The results of the POPI study suggest either chlamydia causes less PID than originally thought, or there is less PID than originally estimated as the PID incidence was low [PID incidence: 1.6% (95% CI: 1.1, 2.1%)] relative risk 0.17 (95% CI: 0.03, 1.01)] (Oakeshott et al.) Results demonstrated that the chlamydia is an important cause of PID as the attributable risk and attributable risk fraction for the association of chlamydia with PID were 7.9% and 83% respectively. The POPI trial also found that most PID was associated with incident infection, highlighting the need for more community based incidence data.
Mathematical models provide the only source of information about how chlamydia screening would prevent PID in the long term. In these models, the reduction in PID depends on reducing transmission at a population level by yearly repeated screening, treatment and partner notification to reduce the risk of exposure to chlamydia, and not to an individual effect of interruption of ascending infection (Turner et al., 2006a, Welt et al., 2000).

A reduction in chlamydia transmission, attributable to screening, would provide good primary evidence of effectiveness. Comparing chlamydia test positivity after a single screening round biases the result in favour of the screened group, which includes incident infections, whilst infections in the control group include prevalent infections that might have been present before the trial started. Ideally, the effect of chlamydia screening on chlamydia transmission would be determined in a population in whom prevalent infections had been detected and treated, for example following a prevalence study with high participation, follow up, treatment, and partner notification rates. The chlamydia screening intervention would then be implemented in randomly assigned areas over two or more screening intervals. The final comparison would be made between screened and unscreened communities in a follow up prevalence survey.

1.10.3 Implications for chlamydia screening programs

Published trials about opportunistic chlamydia screening provide indirect short-term evidence of inadequate quality. Even where opportunistic screening services are coordinated nationally with defined service standards, coverage of regular screening and outcomes of opportunistic screening are difficult to measure because health service data about screening uptake are not routinely linked to data about chlamydia-associated complications and neither data source is linked to population records. Current data from the best-performing region in the National Chlamydia Screening Program in England show that, in contrast to predicted uptake of 50% (Pimenta et al., 2003a), only 2.5% of 16-24 year olds were screened in the past year (White, 2007), and chlamydia positivity rates remain at 10-11% (Low, 2007). A current Chlamydia Screening Implementation project in the Netherlands will show
whether or not the uptake of a register-based approach with repeated yearly screening invitations (Sheldon, 2007) can achieve the results observed by Scholes et al. (Scholes et al., 1996), and Østergaard et al. (Østergaard et al., 2000).

1.10.4 Barriers to screening

For a chlamydia screening program to be successful, barriers that inhibit screening must be identified and addressed (Wiesenfeld et al., 2000, Joffe, 1999). Clinicians as well as the participants being targeted for screening can experience both pragmatic and psychosocial obstacles to chlamydia testing.

There have been many qualitative studies identifying barriers to screening however the quality of the studies varied considerably. Some of the qualitative studies discussed have very small number of participants and participant selection was often non-random (Christianson et al., 2003, Henning et al., 2007) and most of the studies are from outside Australia. For example one study which used a qualitative approach reports on a small cross-sectional study interviewing only four women with positive chlamydia tests (France et al., 2001). As well as this, some of the studies involving general practitioners had very low participation rates as well (Temple-Smith et al., 2009). Despite these limitations, there is a striking consistency in the reported results of the studies.

1.10.4.1 Barriers to chlamydia testing: clinicians

The majority of chlamydia testing is done in Australia by general practitioners, and they have been surveyed to determine their knowledge about chlamydia testing and screening. Generally, clinicians have demonstrated a lack of knowledge of the benefits of testing for screening and treating chlamydia (Cook et al., 2001, Temple-Smith et al., 2009, McNulty et al., 2004). They perceive there is a lack of evidence for the benefits of chlamydia testing and want to see evidence that chlamydia screening works (McNulty et al., 2004, Ma and Clark, 2005). General practitioners also lack clinical knowledge about chlamydia including when and how to take specimens for an accurate chlamydia diagnosis (Temple-Smith et al., 2008, Temple-Smith et al., 2009, Hocking et al., 2008a, McNulty et al., 2004). For chlamydia screening to be
successful in general practice, gaps in knowledge will be needed to be identified and educational tools will have to be developed, implemented and evaluated.

General practitioners are concerned about the extra time required to do a test particularly since they feel their workload expectations are constantly increasing (Duncan et al., 2001). They are concerned about the extra demands of having to give a positive chlamydia result during a consultation, particularly if a sexual history and partner notification are required (McNulty et al., 2004, Hocking et al., 2008a, Merritt et al., 2007, Ma and Clark, 2005, Temple-Smith et al., 2009). General practitioners worry that a chlamydia test might result in extra testing including testing for other STIs and therefore more time taken which can be difficult in the context of a medical consultation for an unrelated condition and might (Cook et al., 2001). This is on top of feeling unsupported with partner notification (Temple-Smith et al., 2009, Hocking et al., 2008a) relevant health promotion material (Khan et al., 2008).

Clinicians also report that they lack the skills and ability to be able to query and discuss sexual health issues with young patients, particularly in an unrelated medical consultation (McNulty et al., 2004, Cook et al., 2001, Tebb et al., 2004). In one study of physicians, only one third admitted that would adhere to the recommended chlamydia protocols and test an asymptomatic sexually active young woman aged 19 years (Cook et al., 2001), missing opportunities for testing patients likely to be at risk. One of the main reasons for not testing people is that the clinician does not want to embarrass the patient by suggesting they have a test, (Temple-Smith et al., 2008) or are concerned that discussing chlamydia in a consultation unrelated to sexual health might upset patients (McNulty et al., 2004, Temple-Smith et al., 2009, Merritt et al., 2007, Temple-Smith et al., 2008, Ma and Clark, 2005).

1.10.4.2 Barriers to chlamydia testing: Young women

Young women also present a number of obstacles preventing them from seeking testing, accepting testing and/or being comfortable having testing. A number of common themes have been reported in the literature including inaccurate beliefs and lack of knowledge about chlamydia. Qualitative research reports that people are
less likely to accept chlamydia screening if they have not heard of chlamydia, or if they think that chlamydia is a "minor" infection or an uncommon infection. They are also less likely to agree to have a test if they believe chlamydia is very hard to cure, if they think the tests are not accurate and if they think "you would know if you had it" i.e. that there would be symptoms. Also, falsely, a woman is less likely to think that her current sexual partner (and hence herself) is at risk of chlamydia if her partner is "known" (the definition of "known" varies considerably, as sometimes partners are only "known" for a few hours) (Blake et al., 2003, Christianson et al., 2003, Ford et al., 2004a, Henning et al., Santer et al., 2003). This ties in with another significant theme – denial – when an individual does not want to acknowledge sexual activity, thinking themselves at low risk of having chlamydia, which then includes thinking their partner is at low risk of having chlamydia (Santer et al., 2003).

Stigma was also identified as a reason for not having a chlamydia test (France et al., 2001, Christianson et al., 2003, Ford et al., 2004a, Henning et al., 2007, Mills et al., 2006, Pavlin et al., 2008, Piercy, 2006). In many studies women and men reported feeling put off chlamydia screening by the moral connotations of a chlamydia diagnosis. Women in particular did not like to be asked about their sexual history and have indicated that they would lie if asked about how many previous sexual partners they had. They reported feeling shame, guilt, self-blame, embarrassment, anger, low self-esteem, shock, worry, unhappiness and surprise on being diagnosed with chlamydia (Piercy, 2006, France et al., 2001). A diagnosis of chlamydia is seen as having a strong stigma attached to it. Some women believe that to use condoms shows distrust of your partner. Interestingly, one study found that men are less likely to use condoms following a chlamydia diagnosis than women (Kangas et al., 2006).

Themes surrounding fear and anxiety about being tested and testing positive were common. Women and men reported feeling fearful about infertility and future reproductive health, were anxious about partner notification and worried about the negative effect of a chlamydia diagnosis on their personal relationships (France et al., 2001, Duncan et al., 2001, Blake et al., 2003, Ford et al., 2004a, Kangas et al., 2006, Mills et al., 2006, Pavlin et al., 2008). There was also anxiety surrounding confidentiality and privacy being breached (Dixon-Woods et al., 2001, Blake et al.,
These included concerns about the confidentiality of attending a clinic and of results, wanting to keep STI screening private, not wanting anyone to know and thinking general practice is not confidential or private enough for chlamydia testing.

There were also pragmatic concerns. The time and cost involved in having a chlamydia test can put young women and men off testing. Having to physically go to a clinic as well as discomfort with sample collection (especially pelvic examinations and physician-collected swabs) were also barriers to accepting chlamydia screening (Dixon-Woods et al., 2001, Henning et al., 2007, Chacko et al., 2008).

1.10.4.3 Increasing acceptability

Young women identified a number of factors that would increase the acceptability of chlamydia screening and make a positive diagnosis easier to deal with.

Firstly, it was important to have accurate knowledge about chlamydia (Blake et al., 2003, Darroch et al., 2003, Santer et al., 2003, Piercy, 2006, Henning et al., 2007, Heritage and Jones, 2008). People would be more likely to accept screening for chlamydia is if they think that chlamydia is a serious condition, if it is known that chlamydia is common, if there is awareness that a person who has chlamydia may have no symptoms, if they understand that tests are important as well as the testing process, and if they are aware of the long-term effects of chlamydia infection in particular the possibility of infertility. Young people want better access to information about chlamydia via health leaflets, doctors, schools, magazines, billboards and TV ads and some indicated that they feel that humour is an important tool in conveying this information. One study strongly emphasized the need to focus on the positive aspects of choosing to have chlamydia tests (such as exhibiting responsible self-caring behaviour) rather than focusing on the "negatives" of a chlamydia diagnosis (Blake et al., 2003).

Chlamydia testing was also considered to be more acceptable if it was considered personally relevant (Pimenta et al., 2003a, Dixon-Woods et al., 2001, Ford et al., 2004a, Mills et al., 2006, Henning et al., 2007). This was particularly the case if it was
offered during a sexual health consultation and if it was offered in the context of ‘routine health maintenance’.

Another significant theme identified was a desire for "choice" in how chlamydia screening is offered. Women want to have a range of testing options including urine tests, self-administered swabs, pelvic exams and clinician-collected swabs. While home-testing options, self-testing options, outreach health professionals and mobile health vans were acceptable, women in some studies were less open to outreach testing than men because they found being offered chlamydia testing in a more public environment intimidating (Lorimer et al., 2009). Women feel it is important that they are "in control" of chlamydia tests and results. They want to be able to choose to participate in chlamydia screening, to be actively offered screening and to be able to refuse screening.

Also, testing needs to be easy, preferably free and quick; PAP tests are also thought to be a good time to offer a chlamydia test (Pimenta et al., 2003a, Dixon-Woods et al., 2001, Fenton et al., 2001a).

Finally, themes relating to the support needed when dealing with a diagnosis of chlamydia were common. Women more so than men, want support for partner notification, for dealing with a positive chlamydia diagnosis and fear of its possible future effect on reproductive health. In comparison to men, women are more likely to want to talk more about their positive diagnosis with someone. Women feel chlamydia needs to be normalised and destigmatised (Duncan et al., 2001, Blake et al., 2003, Christianson et al., 2003, Kangas et al., 2006, Piercy, 2006, Chacko et al., 2008).

For a screening program to be successful, it has to implement NAAT testing techniques; be accessible to high prevalence populations - young women particularly; include information that will reduce the stigma of having an STI making people more comfortable with a positive diagnosis; as well as being cost effective. Current screening programs demonstrate the satisfactoriness of chlamydia screening (Pimenta et al., 2003b) especially when the testing techniques are less invasive,
appropriate information is given to young women, adequate support is available should the test be positive, proper contact tracing has occurred and future testing assured (Pimenta et al., 2003b). Clinicians require adequate education about testing for chlamydia, how to introduce sexual health questioning within the context of a consultation with a young woman, support and information for contact tracing, and management and financial support for screening to work in the context of the general practice.

1.10.5 Cost effectiveness

A systematic review published in 2006 of the available evidence published prior to August 2004, found that there was still uncertainty about the cost-effectiveness of opportunistic chlamydia screening in general practice (Roberts et al., 2006). More recent literature reports that there still remains considerable uncertainty about the cost-effectiveness of population-based chlamydia screening. While some studies suggest that chlamydia screening could be cost-neutral or cost effective, others found that it was not cost-effective. Although the quality of the studies has improved since the systematic review by Roberts in 2004 (Roberts et al., 2006), the uncertainty around the risk of progression to chlamydia associated complications, still threatens the validity of the results of these evaluations. This highlights the need for further evidence around the natural history of chlamydia infection and the importance of further well designed randomised controlled trials evaluating the impact of chlamydia screening on chlamydia transmission and the burden of chlamydia infection in the population.

Papers found either that screening became cost-neutral after a period of time (Andersen et al., 2006), or was cost-neutral for screening every two or more years (de Vries and van Bergen, 2008), or was cost saving when the prevalence of chlamydia among women was at least 5.1% and at least 12.1% among men (Novak et al., 2004). Only one study found that proactive register based screening for chlamydia was not cost-effective using screening participation data based from empirical studies and conservative estimates for the risk of PID (Roberts et al., 2007). This evaluation used more realistic empirical data of actual screening participation
rates. The progression of chlamydia to PID is not entirely understood, and several studies were sensitive to the assumptions made about progression to PID (Adams et al., 2007, Andersen et al., 2006, de Vries and van Bergen, 2008, Roberts et al., 2007, de Vries et al., 2006). Also, the study by Roberts found that when high uptake of screening was assumed and high incidence of PID, the incremental cost effectiveness ratios fell dramatically (Roberts et al., 2007).

There were two Australian based studies, both of which used static decision analytic models (Walleser et al., 2006, Ward et al., 2006). The study by Ward and colleagues evaluated a one off screen for chlamydia for women up to age 34 and reported that a one off screen would become cost neutral at a prevalence of at least 5.7% in the population. The data used in this model were out of date, with over estimation of the proportion of symptomatic infections and risk of progression to PID (van Valkengoed et al., 2004). While the study by Walleser (Walleser et al., 2006) found that opportunistically screening women under 25 years is a potentially worthwhile undertaking, the analysis also found that the uncertainties around the natural history of chlamydia and the effectiveness of screening highlighted the need for further primary data collection in these areas.

There has been considerable debate in the literature about the validity of natural history data used to parameterise cost-effectiveness analyses of chlamydia screening. A study published by van Valkengoed and colleagues in 2004 (van Valkengoed et al., 2004) aimed to evaluate the assumptions about the probability of complications after an asymptomatic chlamydia infection. It identified published cost-effectiveness studies and evaluated these for the evidence of the quoted probabilities. It found that studies often quote high rates of complications following chlamydia infection and that these are frequently based on data from high risk populations and case control studies. Van Valkengoed argued that an over-estimation of current complication rates is likely and that this may be leading to an over-estimation of the cost-effectiveness of chlamydia screening programs. As a follow up to this study, Hu and colleagues (Hu et al., 2004) explored how alternative assumptions about the natural history of chlamydia can affect the estimated cost-effectiveness of chlamydia screening. They found that different natural history
assumptions affect cost-effectiveness outcomes. Assumptions about the combined risk of persistent and repeat infections have the greatest impact on the composition of optimal screening strategies, whereas assumptions about the risk of PID most greatly influenced the magnitude of incremental cost-effectiveness ratios (Hu et al., 2004).

It is still unclear whether men should be actively targeted for screening. The systematic review by Gift and colleagues concluded that the decision to screen men for chlamydia ultimately depends on many factors including local prevalence of infection among men as well as women (Gift et al., 2008).

At this stage, without any clear understanding of the risk of complications following chlamydia infection, it is difficult to draw any firm conclusions about the cost effectiveness of population-based chlamydia screening. This highlights the need for further evidence around the natural history of chlamydia infection and the importance of well designed randomised controlled trials evaluating the impact of chlamydia screening on chlamydia transmission and the burden of chlamydia infection in the population.

1.10.6 Screening strategies and interventions to increase screening

Strategies that have been identified to increase chlamydia testing include linking chlamydia screening to Pap testing, increasing clinicians’ knowledge of chlamydia screening protocol, improving clinicians’ communication skills and ability to discuss sexual history taking, possibly including more than one intervention to increase the effect (Ginige et al., 2007). The Australian chlamydia screening pilot (ACCEPt) that is currently being trialled is using a multifaceted approach including an intervention in general practice that will include computer alerts to remind general practitioners to test a patient for chlamydia, financial incentives for tests in the target population, engaging clinic staff and identifying a ‘practice champion’ to promote and assist monitoring of chlamydia testing, providing specific educational material and regular feedback to clinicians on their testing rates and where possible, incorporating practice nurses into chlamydia testing and management within the clinic (Hocking et
al., 2009). The aim of the pilot is to produce world-first evidence to demonstrate if a chlamydia screening strategy increases testing to a level that results in the reduction of chlamydia and some of the chlamydia sequelae in the population.

1.10.6.1 The use of computer alerts in preventive health strategies

One specific intervention that has been trialled previously in primary care is the use of on-screen computer reminders to increase preventive health activity by clinicians. Studies have investigated the effect of computerised reminders on prompting clinicians to perform particular activities such as blood pressure assessment (McDowell et al., 1989b), cervical screening (McDowell et al., 1989a), vaccination rates of patients with particular vaccines (Dexter et al., 2001, Rosser et al., 1992), and increase correct and appropriate prescribing of specific medications (Koide et al., 2000). Each of these studies reported a significant increase in the preventive care activity. The randomised controlled trial by Dexter et al. (Dexter et al., 2001), reported a 35% higher pneumococcal vaccination rate and 50% higher influenza vaccination rate of patients attending general practitioners receiving a computerised reminder compared with patients attending general practitioners in the control group. In Veteran Affairs clinics in the US a clinical alert program increased HIV testing rates by 100% compared with no change in control clinics (Goetz et al., 2008). Further to this, qualitative research involving interviews with health care providers in the U.K. have also reported that computer pop ups or reminders can help with increasing chlamydia testing in general practice (McNulty et al., 2008, McNulty et al., 2004); however, these are based on general practitioners’ views in small qualitative studies.

A Cochrane review of computer alerts in clinical practice found small to moderate improvements in testing when on-screen computer reminders were implemented [interquartile range (IQR: 0.4 to 16.3) median increase in test ordering (3.8%)] was found overall (Shojania et al., 2009). However there was considerable variation in results with a trial of a reminder for Pap test screening reporting a non-significant result of 0.6% (Frank et al., 2004) and another trial exploring the impact of a diabetes testing prompt reporting a significant increase of 16.3% (Kenealy et al., 2005).
One of the studies in this thesis was a randomised controlled trial which aimed to determine if using a computer reminder in general practice increased chlamydia testing. In Australia, 90% of general practitioners use computers in their practices (Australian Bureau of Statistics, 2002), and an ‘on-screen reminder’ programmed into clinical software is potentially an easy and inexpensive option to increase testing. There has not been any research determining what the effect an alert would have on chlamydia testing in general practice but the positive effect for other preventive health strategies suggests it might be useful as part of an intervention for increasing chlamydia screening.

1.10.6.2 Incentive payments

Incentive payments have also been successfully utilised to increased clinicians preventive activities, however, a Cochrane review published in 1999 found a statistically significant increase in only one of the two studies in the review which targeted immunisation rates (Giuffrida et al., 1999). Despite this, Australian evidence shows that financial incentives for general practitioners can impact on their prescribing and testing practices including monetary incentives available for general practitioners including a bulk billing incentive and incentives to increase childhood immunization rates (Medicare Australia, 2009).

Also, more specifically, incentive payments have been used successfully as part of the chlamydia screening pilots conducted in the United Kingdom. General practitioners were reimbursed up to £20 per eligible person screened, with screening acceptance rates within general practitioner clinics of up to 81% (Pimenta et al., 2003a, Pimenta et al., 2003b). However, once the chlamydia screening program was rolled out across the country, incentive payments were removed and screening participation rates within general practitioner clinics fell to below 10% (Health, 2004). Incentive payments were offered to general practitioners to enrol patients for chlamydia screening in Amsterdam with 94% acceptance (Hoek et al., 1999). Finding an appropriate and sustainable amount for an incentive payment is the key to an incentive payment being effective.
Several cross-sectional surveys of qualitative interviews with general practitioners in both the United Kingdom and Australia have reported that general practitioners believe that chlamydia testing rates would increase with incentive payments to general practitioners or the clinics (McNulty et al., 2008, Hocking et al., 2008a, Ma and Clark, 2005, Merritt et al., 2007, Perkins et al., 2003). Although, without randomised controlled trial evidence, it is not possible to predict how well general practitioners would respond to an incentive payment to increase chlamydia screening rates.

1.10.6.3 **Utilising a ‘practice champion’ to encourage chlamydia testing**

A “practice champion” is an identified clinician within a general practice who takes responsibility to “drive” the screening process and help to facilitate chlamydia screening within that clinic. Interviews with the chlamydia coordinators in the National Chlamydia Screening Program in the United Kingdom found that having someone within the clinic in this role of practice champion, or even an external coordinator who handled the treatment, follow up and partner notification, would make screening more acceptable to general practice (McNulty et al., 2008).

1.10.6.4 **Providing specific educational material and regular feedback to clinicians on their testing rates**

Surveys or interviews with general practitioners, other health care providers and clinic staff have suggested that guidance and education are needed for both health care providers and the general population (Hocking et al., 2008a, Ma and Clark, 2005, Merritt et al., 2007, McNulty et al., 2004). It has been suggested that providing general practitioners with tactics for introducing chlamydia screening during a consultation would facilitate testing (Merritt et al., 2007, McNulty et al., 2004). An 18 month intervention conducted in New South Wales, Australia that was designed to improve chlamydia testing in general practice included providing general practitioners with tactics for introducing chlamydia testing during a general consultation such as the question, “We are offering a chlamydia test to all sexually active 15 to 25 year olds; would you like a test?”. The intervention was developed by participating general practitioners targeting both young men and women aged under
25 years and included an information sheet for general practitioners, a partner notification letter, information sheet for patients and waiting room posters. However this was an uncontrolled intervention study which found only a modest impact on chlamydia testing rates (Merritt et al., 2007).

Feedback to general practitioners about their chlamydia testing rates has also been suggested as a possible way of increase testing rates. Interviews with health care providers have reported that providing them with ongoing feedback on their chlamydia testing rates would help motivate them to test for chlamydia (McNulty et al., 2008) (Merritt et al., 2007). If an intervention included incentive payments, feedback about the amount of incentive payments earned might also motivate more testing.

1.10.6.5 Utilising practice nurses for chlamydia testing and management

Surveys of Australian general practitioners’ chlamydia testing management practices have found that female general practitioners have a greater knowledge of chlamydia and its appropriate clinical management and conduct a greater number of tests (Khan et al., 2006, Hocking et al., 2006a). Unsurprisingly, findings from the National Chlamydia Screening Programme in the United Kingdom show that older male general practitioners are less comfortable with sexual health work, including chlamydia testing (Perkins et al., 2003). When interviewed, practice nurses perceive that young women are more comfortable with practice nurses conducting chlamydia testing rather than the general practitioner. These findings suggest that female practice nurses may be more appropriately placed to manage chlamydia testing, follow up and management in general practice (Perkins et al., 2003). Despite this, there would need to be consideration as to how to implement using practice nurses for chlamydia testing and management as it would need to include patients who were attending the general practitioners for an unrelated health consultation.

General practitioners report that screening needs to be made part of everyday practice, so that it becomes normalised and will be easy to raise in non-sexual health related consultations (McNulty et al., 2008, Hocking et al., 2008a), a finding also
supported by interviews with young women (Pavlin et al., 2008). Surveys and interviews with health care providers suggest that general practitioners would feel more comfortable offering chlamydia tests if there were national screening guidelines or screening program (Hocking et al., 2008a, Ma and Clark, 2005).

1.10.6.6 Other options for screening

As well as opportunistic screening, other options might also be considered as an adjunct to a screening program to maximise coverage of the population. Interventions such as testing young people in school clinics (Østergaard et al., 2000), sending test kits that can be returned through the post (Hocking et al., 2006b, Macleod et al., 1999, Valkengoed et al., 2002), advertised drop off points for testing (Martin et al., 2009, Morton et al., 1999), or screening in youth based sports clubs (Kong et al., 2009), have been utilised successfully in research studies in Australia, although all these interventions have limitations. Testing in schools does not capture young people once they leave school, sending kits through the post has a poor uptake by young people, and sports clubs are not sustainable long term.

1.11 Conclusions

Chlamydia is a prevalent infection causing significant morbidity in sexually active young people although the burden of disease in young women is still unknown in Australia. More research is warranted into the natural history of chlamydia including understanding the burden of PID and infertility directly attributable to chlamydia. At this stage there is no successful, consolidated screening program and chlamydia appears to be increasing in the populations at risk. The literature suggests that there is a need for further research into the effectiveness of an opportunistic screening program involving a multi-faceted intervention with the view to implement a cost-effective screening program which reduces the burden of disease associate with chlamydia infection. This thesis tests the use of one specific intervention designed to increase testing in young women, and provides the first population based incidence and re-infection data for young women in Australia which will be crucial in the design and measuring the effectiveness of a chlamydia screening program.
CHAPTER 2.

CLINICAL ASPECTS AND EPIDEMIOLOGY OF MYCOPLASMA GENITALIUM INFECTION IN YOUNG WOMEN.

2.1 Introduction

*Mycoplasma genitalium* is another sexually transmissible infection which can also cause significant morbidity in young women. Less is known about the public health implications of *M. genitalium*, particularly in Australia, because unlike *C. trachomatis*, *M. genitalium* is not notifiable and there are no population data available for Australian women.

This chapter describes the biology of *M. genitalium*, the clinical presentation of a woman with *M. genitalium*, the diagnostic methods for *M. genitalium*, the epidemiology of *M. genitalium*, and current recommendations for testing for *M. genitalium* in Australia.

2.2 Terminology

In this PhD, all discussions about Mycoplasma will only include *Mycoplasma genitalium* in women which will be referred to as *M. genitalium* unless otherwise indicated.

2.3 Biology of Mycoplasmas

2.3.1 Characteristics of Mycoplasmas

Mycoplasmas are very small (150 to 250 nm) prokaryotes that lack a cell wall but have both DNA and RNA which differentiates them from viruses (Fraser et al., 1995). *M. genitalium* was originally isolated from the urethral tract of two men with non-
gonococcal urethritis (Tully et al., 1981) and has since been shown to exist in parasitic association with ciliated epithelial cells in the genital and respiratory tracts (Jensen et al., 1993). *M. genitalium* is the smallest prokaryote capable of self-replication, and it was the first micro-organism to have its genome consisting of 580,074 base pairs fully sequenced (Fraser et al., 1995).

*M. genitalium* is a fastidious anaerobic organism with some unique attributes that allow it to be a successful pathogen despite its size (Baum SG, 2000), including its ability to encode a flask-shaped complex organelle enabling colonisation and invasion of human host cells (Totten et al., 2008) (Figure 2-1). The organism is able to translocate cytoplasmic enzymes to its membrane surfaces in the organelle so that it is able to adhere to extracellular matrix molecules such as mucin and fibronectin (Blaylock et al., 2004). Mycoplasmas then are able to parasitise sterols and a wide range of biosynthetic precursors such as amino acids, nucleotides and fatty acids evolving into an interplay with human cells and that leads to a persistence and replication in vivo over many months (Blaylock et al., 2004, Baseman et al., 2004).
Figure 2-1  Typical *Mycoplasma genitalium* bacteria growing in a cell culture. The arrows point to the specialised tip-shaped organelles which have adhered to the cells.
2.3.2 Taxonomy

Mycoplasmas are categorised within the family Mycoplasmataceae, order Mycoplasmatales and class Mollicutes (mollis soft; cutis skin); the family Mycoplasmataceae contains two genera that are pathogenic to humans: Mycoplasma and Ureaplasma. The genus Mycoplasma contains over 100 species including the species *M. genitalium* and *M. hominis* which are found in the human genital tract (Baum SG, 2000).

2.3.3 Serovars: distribution and clinical presentations

Although heterogeneity of *M. genitalium* serotypes has been shown using RFLP methods (Jensen et al., 1991), this method cannot be done directly from clinical specimens and therefore has limitations. The investigation of genotypes using PCR technology has found a number of differing serotypes in the *M. genitalium* genetic structure. One study found at least four variants of *M. genitalium* (Ma and Martin, 2004) and another study identified 56 different sequence types and one mixed sequence (Hjorth et al., 2006). It appears plausible from further investigation, that *M. genitalium* has the ability to generate unlimited variants from its genome, which would allow the organism to adapt to various environments and/or to evade host defences by antigenic variation (Ma et al., 2007). Genotyping and further development of genetic differentiation between genetic strains may assist in clarifying differing clinical presentations and antibiotic resistance in the various genetic strains of *M. genitalium* (Totten et al., 2008).

2.4 Diagnosis of *M. genitalium*

*M. genitalium* is a fastidious organism, and therefore it has been difficult to use culture to diagnose the infection; serology has not been widely used either because of cross-reactivity with other Mycoplasmas (Taylor-Robinson, 1983). As with chlamydia, the advent of a diagnostic polymerase chain reaction (PCR) test (Jensen et al., 1991, Palmer et al., 1991) (section 2.4.1), has made detection more reliable and applicable to testing larger populations, and as a direct result since the mid 1990s more research into *M. genitalium* infection has been accomplished (Tosh et
al., 2007). Also, importantly, sequence-based typing systems have demonstrated *M. genitalium* is sexually transmissible between partners (Hjorth et al., 2006), with concordance rate of infection for female partners of infected men ranging from 46 to 63% (Anagrius and Lore, 2002, Anagrius et al., 2005, Falk et al., 2004, Keane et al., 2000).

### 2.4.1 Polymerase chain reaction (PCR) diagnosis of *M. genitalium*

In 1991, Jensen et al developed a PCR test based on the MgPa-1/MgPa-3 primer set located in the conserved regions of the *mgpB* gene which can be detected at very low levels, making testing for diagnostic purposes in clinical samples possible (Jensen et al., 1991, Jensen et al., 2003). *M. genitalium* strains isolated from clinical samples showed a degree of diversity in the main gene of the MgPa gene sequence (Jensen et al., 1996) which led to the development of a PCR amplification test based on the rRNA gene sequences (Jensen et al., 2003), specifically relying on the detection of the 16S rRNA sequence specific to *M. genitalium* (Bjornelius et al., 2000, Jensen et al., 2003, Yoshida et al., 2002). Both tests have been used for clinical diagnosis of *M. genitalium* clinically and in *M. genitalium* research.

In a comparative study by Edberg et al to determine the differences between MgPa gene PCR and 16S rRNA gene PCR, the results reported real-time MgPa gene PCR detected 97.4% of *M. genitalium* in true-positive samples, conventional 16S rRNA gene PCR detected 80.3% and real-time 16S rRNA gene PCR detected 68.4% (Edberg et al., 2008). Contrary to this, in 2009, a sample of 830 stored vaginal swab samples were tested for *M. genitalium* with both the 16S rRNA gene PCR and the real-time MgPa gene PCR. The 16S rRNA gene PCR was found to have a concordance of 98.9% (sensitivity 95.0% and specificity 99.1%) when compared with real-time MgPa gene PCR, suggesting it is as valuable an assay to use for *M. genitalium* diagnosis in clinical samples as the MgPa gene PCR assay (Twin et al., 2011).

Although true sensitivity and specificity of any of the PCR assays in women are unknown, one study demonstrated a high specificity of PCR tests 99.6% relative to
infected patients who tested positive with two different assays (Wroblewski et al., 2006). There is no 'gold standard' test as yet for *M. genitalium*.

### 2.4.2 *M. genitalium* sampling methods

*M. genitalium* can be detected from a vaginal swab, endocervical swab or a first catch urine sample (FCU). Wroblewski et al (2006) estimated the relative sensitivities for the detection of *M. genitalium* is 91% for vaginal specimens, 53% for cervical specimens and 65% for FCU specimens using PCR compared with transcription-mediated amplification test (TMA) (Wroblewski et al., 2006), although Moi et al (2009) found a higher sensitivity in cervical swabs than FCU (86% versus 62% respectively) (Moi et al., 2009). The high sensitivity of self administered vaginal swabs makes home based testing for *M. genitalium* possible and increases accessibility and population based research options.

### 2.5 Clinical presentations of *M. genitalium* in women

*M. genitalium* is commonly asymptomatic in infected women. This is supported by a number of studies which have found no association with infection and any genital symptoms (Andersen et al., 2007, Huppert et al., 2008, Tosh et al., 2007). In some cases, women infected with *M. genitalium* can present with genito-urinary symptoms including vaginal discharge and dysuria (Korte et al., 2006, Anagrius et al., 2005, Pepin et al., 2005, Moi et al., 2009), and related upper genital tract infection symptoms (Uno et al., 1997, Cohen et al., 2002). Overall, the research suggests that *M. genitalium* presents similarly to chlamydia but appears to cause milder symptoms than gonococcal infections in women (Short, 2008, Moi et al., 2009).

#### 2.5.1 Clinical signs and symptoms: Lower genital tract infection

In women, *M. genitalium* has been established as a cause of urethritis in women (Uno et al., 1997, Falk et al., 2005, Anagrius et al., 2005) and cervicitis (Gaydos et al., 2009, Moi et al., 2009, Pepin et al., 2005). Cervicitis is a particularly important diagnosis as it increases the risk of developing an upper genital tract infection. The extent of *M. genitalium* related cervicitis has been studied in Japanese women.
attending obstetric and gynaecological clinics in Japan in 1997, where 5 (7.8%) of women with cervicitis were infected with *M. genitalium* (Uno et al., 1997). In a cross sectional study in 2003, 24 (11%) of 215 women with cervicitis had *M. genitalium* (Manhart et al., 2003) and in two studies of women recruited from STD clinics in Sweden, one study found 10.2% of women with cervicitis tested positive for *M. genitalium* (Falk et al., 2005), and in the other study population showed 13.3% tested positive for *M. genitalium* (Anagrius et al., 2005). Pepin et al (2005) reported a weak association with symptoms of cervicitis in West African female sex workers based on symptoms of cervical discharge, cervical pus, easily induced bleeding and inflammatory cervix \( p \leq 0.05 \) for each of the four signs which was similar to findings for chlamydia (Pepin et al., 2005). All these studies demonstrated a significantly higher proportion of women with cervicitis had *M. genitalium* than women without *M. genitalium*, however one study of a consecutive cohort of women with vaginal discharge at an STD clinic in Paris found a high prevalence of *M. genitalium* [38% (95% CI, 31–46%)] but found no association with *M. genitalium* infection and cervicitis (Casin et al., 2002) (Table 2-1).

The limitations to these studies include the variability in the diagnostic criteria for cervicitis which is based on clinical symptoms and/or the presence of inflammatory markers (Table 2-1).

### 2.5.2 Upper genital tract infections and *M. genitalium*

#### 2.5.2.1 Pelvic inflammatory disease (PID)

The aetiology and natural history of pelvic inflammatory disease (PID) is not well understood, and is difficult to definitively diagnose as it can be asymptomatic and requires a clinical diagnosis [refer to Chapter 1, section 1.4.2.1]. *N. gonorrhoea* and chlamydia are known causes of PID, however there is a large proportion non-gonococcal, non-chlamydial PID where the primary pathogen is unknown (Haggerty, 2008). Since the 1980s there has been some evidence leading to a suspected association with *M. genitalium* infection and PID using serology to identify antibodies. Using serology, women with pelvic inflammatory disease were found to
have a higher titre of *M. genitalium* antibodies and have no antibodies to chlamydia or *M. hominis* (Møller BR et al., 1984). However, serology for Mycoplasma is less accurate as it can demonstrate a cross reactivity with other organisms giving a false positive. The pathogenesis of *M. genitalium* to upper genital tract infection is plausible considering it causes lower genital tract infection, the organisms can attach to vectors such as spermatozoa and travel to the upper genital tract (Svenstrup et al., 2003) and animals have been shown to develop lower genital tract infection and salpingitis after inoculation with *M. genitalium* (Taylor-Robinson et al., 1987).

There is more recent evidence to support the association of *M. genitalium* with PID using more accurate diagnostic techniques such as PCR. One study reported 7 of 50 women (14%) diagnosed with PID tested positive for *M. genitalium* and negative for chlamydia and *N. gonorrhoea* (Haggerty et al., 2006), and another study reported a prevalence of *M. genitalium* was 13% in cervical specimens compared with 0% in the control group in a case controlled study of women with clinically suspected PID in the UK (Simms et al., 2003a). A recent review of the literature also stated there is a strong evidence that *M. genitalium* is associated with PID considering all the evidence associating *M. genitalium* with acute endometritis and adnexitis, independent of gonococcal and chlamydial infection (Haggerty, 2008).

The proportion of PID attributable to *M. genitalium* is unclear, particularly as there are limited and inconsistent PID data and few *M. genitalium* studies. Predictors for *M. genitalium* associated PID have been reported as younger age (under 25 years)[AOR: 2.7 (95% CI: 1.5, 4.7)], douching two or more times per month [AOR: 2.0 (95% CI 1.2, 3.4)], and smoking [AOR:2.0 (95% CI 1.3, 3.3)] (Short et al., 2009). A recent study specifically designed to determine the attributable risk of *M. genitalium* with PID found that *M. genitalium* was unlikely to be a major contributor to PID infection in young women in the UK[risk ratio: 2.35 (95% CI: 0.74, 7.46)(p=0.14)]. This study involved a large population of women followed up over at least one year, and the clinical records of any of the patients diagnosed with PID were reviewed by two physicians who did not know the bacteriological results (Oakeshott et al., 2010a).
2.5.2.2 Tubal factor infertility (TFI)

Early serological evidence found antibodies to *M. genitalium* in women who had been infertile for two years (Moller et al., 1985). There has been some evidence to support *M. genitalium* associated salpingitis and *M. genitalium* has been detected in the fallopian tube tissue of a woman with acute salpingitis (Cohen et al., 2005). Clausen et al (2001) found that 22% of women with tubal factor infertility tested positive for *M. genitalium*, whereas women with normal fallopian tubes only test positive for *M. genitalium* in 6.3% of cases (Clausen et al., 2001). Svenstrup et al followed this up in 2007 and determined *M. genitalium* was detected in 17% of women with tubal factor infertility compared with 4% of women with normal tubes [OR: 4.5 (95% CI 1.2, 15.6)] (Svenstrup et al., 2007). As with chlamydia, fallopian tube damage is hypothesised to be caused by *M. genitalium* damaging ciliated human fallopian tubes causing scarring and occlusion (Baczynska et al., 2007).

2.5.2.3 Endometritis

There is also evidence to support *M. genitalium* as a cause of endometritis, in a study of 115 women who presented to an STD clinic in Nairobi with persistent acute pelvic pain for no more than 14 days. Of the 58 women who had histologically confirmed endometritis, 9 (16%) tested positive for *M. genitalium* in either their cervix, endometrium or both, compared with only one woman (2%) who tested positive for *M. genitalium* out of the 57 women without endometritis (p=0.02) (Cohen et al., 2002). In another study, 9 (16%) of women with histologically confirmed endometritis tested positive for *M. genitalium* compared with 1 (2%) of women without *M. genitalium* [p=0.02] (Cohen et al., 2002).

2.5.2.4 Adverse pregnancy outcomes

Results have been conflicting about the potential role *M. genitalium* has played in causing adverse pregnancy outcome. Edwards et al found an association between *M. genitalium* infection and preterm labour [OR 3.5 (95% CI: 1.4, 8.6)] (Edwards et al., 2006), while other studies have found no relationship between pregnancy
complications and *M. genitalium* infection. In Japan, women were tested for Mycoplasmas, Ureaplasmas, chlamydia and gonorrhoea, and although adverse pregnancy outcomes were associated with infection with *Ureaplasma parvum* there was no association with *M. genitalium* and adverse pregnancy outcome (Kataoka et al., 2006). Oakeshott et al examined 1216 pregnant women and found that only one of the women infected with *M. genitalium* had a miscarriage and none of the infected women followed up had preterm labours (Oakeshott et al., 2004). This was comparable to another study of women in Guinea-Bissau (Labbe et al., 2002). In a more recent study done by Short et al in pregnant women presenting at the emergency department of a hospital in the US, no association was found with spontaneous abortion during pregnancy [AOR:0.9 (95% CI 0.2, 3.8)] (Short et al., 2010).
Table 2-1  Results of studies assessing reproductive tract disease in women and *Mycoplasma genitalium*.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. (%) detected/total patients with disease</th>
<th>No. (%) detected/total patients without disease</th>
<th>OR (95% CI) or P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervicitis</strong></td>
<td></td>
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<tr>
<td>(Uno et al., 1997)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/64 (7.8%)</td>
<td>0/80</td>
<td>0.01</td>
</tr>
<tr>
<td>(Casin et al., 2002)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42/99 (42)</td>
<td>23/71 (32)</td>
<td>0.19</td>
</tr>
<tr>
<td>(Manhart et al., 2003)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24/215 (11)</td>
<td>26/504 (5)</td>
<td>0.004</td>
</tr>
<tr>
<td>(Pepin et al., 2005)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>34/172 (16.5)</td>
<td>28/363 (7.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>(Falk et al., 2005)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>12/118 (10.2)</td>
<td>13/336 (4.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>(Anagrius et al., 2005)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>4/20 (13.3)</td>
<td>6/227 (2.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>(Gaydos et al., 2009)</td>
<td>38/133 (28.6)</td>
<td>24/191 (12.7)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Acute endometritis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(Cohen et al., 2002)</td>
<td>9/58 (16)</td>
<td>1/57 (2)</td>
<td>0.02</td>
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<tr>
<td><strong>Pelvic inflammatory disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Simms et al., 2003a)</td>
<td>6/45 (13)</td>
<td>0/37</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Tubal factor infertility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Clausen et al., 2001)</td>
<td>29/132 (22)</td>
<td>11/176 (6.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>(Svenstrup et al., 2007)</td>
<td>5/30 (17)</td>
<td>7/164 (4.2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Cervicitis defined by:

- <sup>a</sup>Purulent or mucopurulent cervical discharge or ≥20 PMNs/HPF (Uno et al., 1997)
- <sup>b</sup>≥20 PMNs/HPF (Casin et al., 2002)
- <sup>c</sup>Mucopurulent cervicitis (visible mucopus or >30 PMNs/HPF in cervical mucus (Manhart et al., 2003)
- <sup>d</sup>Many indicators of cervicitis measured; shown is the association of mucopurulent discharge [yellow cervical exudates (“swab test”)](Pepin et al., 2005)
- <sup>e</sup>More PMNs than epithelial cells in wet smear of lateral fornix and lateral vaginal wall (Falk et al., 2005)
- <sup>f</sup>≥30 PMNs/HPF (Anagrius et al., 2005)
- <sup>i</sup>Cervical discharge or friability (Gaydos et al., 2009)

[Totten et al., 2008]
2.5.3 *M. genitalium* associations with other sexually transmitted infections

A systematic review and meta-analysis of 19 articles by Mavedzenge determined that in 12 studies there was a statistically significant association between *M. genitalium* and HIV infection. There was significant heterogeneity between the different study results but overall, the results demonstrated a statistically significant two-fold increased odds of HIV among *M. genitalium*-infected populations (including both men and women) with a summary odds ratio of [OR: 2.01 (95% CI: 1.4, 2.8)]. The association was stronger in sub-group analyses among studies in sub-Saharan Africa [OR: 2.6 (95% CI: 2.2, 3.1)] and studies with healthy control populations [OR: 2.6 (95% CI: 2.1, 3.2)]. There was no statistical evidence of publication bias. The strong evidence suggests testing and treatment of *M. genitalium* positive individuals in high-risk populations be investigated as a potential HIV prevention strategy (Mavedzenge, 2009).

2.5.4 Organism load and clinical presentation

There is limited information about any clinical effect increased organism load of *M. genitalium* might have; one study reported increased bacterial load for *M. genitalium* in an first catch urine (FCU) sample did not significantly correlate with urethritis or cervicitis (Hogdahl and Kihlstrom, 2007). Further research is warranted into the impact the quantity of infectious load may have on the persistence of an infection, how well an infection responds to antimicrobial therapy and if load influences the transmission dynamics, particularly in relation to other sexually transmitted organisms such as chlamydia.

2.6 Treatment of *M. genitalium*

2.6.1 Current recommendations for treatment of *M. genitalium* infection

The recommended treatment for *M. genitalium* is 1g azithromycin stat (Mena et al., 2009). An important part of *M. genitalium* treatment is treatment of the patient’s current and recent sexual partners with azithromycin, and having no unprotected sex with an untreated partner for 7 days. A ‘test of cure’ is recommended one month
after treatment to determine the infection has not persisted; particularly considering *M. genitalium* can be azithromycin resistant. If *M. genitalium* persists, it is important to determine if the treatment has not been adhered to or not absorbed, or if it is a re-infection from an untreated partner or from a new partner. If the infection is determined to be an azithromycin resistant infection, the recommended treatment is 400mg/day of moxifloxacin for 10 days (Hamasuna et al., 2005, Bradshaw et al., 2006b, Bradshaw et al., 2008).

### 2.6.2 Antibiotic resistance

*M. genitalium* has been found to be resistant to many antibiotics including quinolones and tetracyclines, except for moxifloxacin which appears to be effective against all the strains examined thus far (Hamasuna et al., 2005, Falk et al., 2003, Bradshaw et al., 2006b, Bradshaw et al., 2008, Jensen et al., 2008). The current recommended treatment of azithromycin (1 g) has only an 85% efficacy at best for uncomplicated *M. genitalium* infections in both men and women (Bradshaw et al., 2006b, Bradshaw et al., 2008, Mena et al., 2002, Bjornelius et al., 2008, Jensen et al., 2008), and other macrolide resistant strains of *M. genitalium* have been identified which are resistant to erythromycin and clarithromycin (Jensen et al., 2008). There is also concern that azithromycin resistance is increasing and moxifloxacin resistance might be developing (Jensen JS, 2009).

Resistance appears to be dependent on background use of azithromycin. In countries where azithromycin is used as a first line treatment for non-gonococcal urethritis (NGU) macrolide resistance is very high. Greenland for example uses azithromycin for NGU and one study has shown 100% (95% CI: 71.7, 100) of *M. genitalium* cases were resistant to azithromycin, whereas in Sweden doxycycline is used for NGU and the same study found 1.6% (5% CI: 0.4, 4.4%) *M. genitalium* macrolide resistance (Jensen JS, 2009). Some clinicians are now suggesting that treatment for *M. genitalium* should include an extended course of azithromycin of 500mg stat followed by 250mg daily for 4 days (Hay and Ugwumadu, 2009). Future resistance to azithromycin appears to be inevitable and less expensive medication other than moxifloxacin will have to be explored to treat *M. genitalium*. 
2.7 Epidemiology of *M. genitalium* in women internationally

2.7.1 Prevalence

There are few population data for *M. genitalium* prevalence and predictors of infection. There have been three main research prevalence findings for women, one in the US, one in the UK and one in Denmark. In the US, a large sample of sexually active 18 to 27 year old women had a low prevalence of 0.8% (95% CI: 0.4, 1.6) (Manhart et al., 2007). Another study of 21 to 23 year old Danish women involved in a large population based study found a higher prevalence of 2.3% (95% CI: 1.3-3.2) (Andersen et al., 2007). More recently a study of sexually-active female University students in the UK had a prevalence of 3.3% (95% CI: 2.6-4.1) (Oakeshott et al., 2010a). Women recruited from STD clinics have tended to have a higher prevalence of *M. genitalium* (from 4.0% to 7.0%) than the background population data suggest (Manhart et al., 2003, Anagrius et al., 2005, Falk et al., 2005, Moi et al., 2009, Hogdahl and Kihlstrom, 2007). Generally, *M. genitalium* prevalence has been found to be consistently lower than chlamydia (Andersen et al., 2007, Hay et al., 2009) (Table 2-2).

In Australia, *M. genitalium* prevalence was reported as 4.1% (95% CI: 1.8, 6.3) in a pregnancy termination service termination after 9 months of testing, which was similar to the prevalence of chlamydia at the same clinic [5.2% (95% CI: 2.3, 8.0). Women with M. genitalium had a slightly higher mean age (24.1 years old) compared with the women who tested positive for chlamydia (21.9 years old) (Marceglia et al., 2010). Otherwise there are no *M. genitalium* data for women in Australia.
Table 2-2  Studies estimating the prevalence of genital *Mycoplasma genitalium* prevalence in women in order of year of testing (Australian data).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design, population and setting</th>
<th>Specimen type</th>
<th>Response rate (%)</th>
<th>Period of study</th>
<th>Median age (age range)</th>
<th>Sample size</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Manhart et al., 2003)</td>
<td>Randomly sampled first time attendees at an STD clinic in the US.</td>
<td>Stored cervical secretions</td>
<td>ns</td>
<td>1984-1986</td>
<td>(16-45)</td>
<td>719</td>
<td>7.0</td>
</tr>
<tr>
<td>(Oakeshott et al., 2004)</td>
<td>Pregnant women recruited from general practices in the first 10 weeks of gestation, in the UK.</td>
<td>Stored urine samples</td>
<td>88</td>
<td>1998-2000</td>
<td>31</td>
<td>915</td>
<td>0.7 (0.1, 1.2)</td>
</tr>
<tr>
<td>(Manhart et al., 2007)</td>
<td>Sub sample of a random sample of adolescents in the US.</td>
<td>Urine</td>
<td>76</td>
<td>2001-2002</td>
<td>(18-27)</td>
<td>1714</td>
<td>0.8 (0.4, 1.6)</td>
</tr>
<tr>
<td>(Oakeshott et al., 2010a)</td>
<td>Convenience sampling of University students (female) in the UK.</td>
<td>Self collected vaginal swabs</td>
<td>ns</td>
<td>2004-2006</td>
<td>21 (15–27)</td>
<td>2378</td>
<td>3.3 (2.6, 4.1)</td>
</tr>
<tr>
<td>(Moi et al., 2009)</td>
<td>Cross sectional study of women with lower genital tract infection attending an STD clinic in Norway.</td>
<td>Urine and/or endocervical swabs</td>
<td>ns</td>
<td>2005-2007</td>
<td>ns</td>
<td>7646</td>
<td>4.0</td>
</tr>
</tbody>
</table>

aData not stated
2.7.1.1 Risk factors for young women

Conflicting risk factors were identified in the few population based *M. genitalium* studies that have been done. Manhart et al in 2007 conducted sexual health research through schools in the US, including testing for *M. genitalium*. The risks associated with *M. genitalium* infection included ‘ever having lived with a sexual partner’ [prevalence ratio [PR]: 11.2; (95% CI: 3.2, 39.5)], being Black American as opposed to white American [PR: 7.2; 95% CI: 2.9, 17.9]], and using a condom during the last vaginal intercourse [PR: 3.9 (95% CI: 1.3, 11.5)]. Prevalence also increased by 10% with each additional vaginal intercourse partner during the past year [PR: 1.1 per partner (95% CI: 1.0, 1.2)]; and there was no association with inconsistent condom use. Limitations of this study included the high proportion of missing data, particularly information about numbers of sexual partners, and a limitation for this literature review is that these data included both young men and women (Manhart et al., 2007).

The POPI study done in the UK reported a prevalence estimate of 3.3% (95% CI: 2.6, 4.1) and risk factors for infection included having two or more sexual partner in the previous 12 months, co-morbidity with Bacterial vaginosis, black ethnicity and women who smoked. Co-morbidity with Bacterial vaginosis [adjusted risk ratio: 2.54 (95% CI: 1.61, 4.01)] and multiple partners [adjusted risk ratio: 2.23 (95% CI: 1.39, 3.58)] were independent risk factors for *M. genitalium* infection (Oakeshott et al., 2010a).

Andersen et al in Denmark used frozen vaginal pipette samples from a chlamydia screening programme and found different risks associated with *M. genitalium* infection. Increasing numbers of sexual partners were associated with *M. genitalium*: women with 4 to 5 partners in the last year were even more likely to contract *M. genitalium* [OR: 19.8 (95% CI: 5.0, 78.6)] and women with more lifetime partners had a stronger association with *M. genitalium* [>10 lifetime partners OR: 7.3 (95% CI: 2.0, 26.3)]. Having a partner with urogenital symptoms was also significantly associated with the infection [OR: 2.5 (95% CI: 1.1, 6.2)], but being in a steady relationship for more than a year significantly reduced the risk of the infection compared to those
being in a steady relationship for less than six months [OR: 0.1 (95% CI: 0.0, 0.5)]. The use of condoms was not associated with \textit{M. genitalium} infection (Andersen et al., 2007). The tests were conducted on samples that had been stored for seven years and there is evidence to suggest that this reduces the sensitivity of the tests, thereby reducing the prevalence in the sample tested (Carlsen and Jensen, 2010).

Manhart et al studies stored cervical samples from first time attendees of an STD clinic in Seattle, USA and \textit{M. genitalium} was detected in 7.0% (50/719) of the women. \textit{M. genitalium} infection was associated with younger age, decreasing by 10% for each year of age [OR 0.9 (95% CI 0.8, 1.0)]. \textit{M. genitalium} was also associated with having more than two new partners in the 30 days prior to testing [OR: 3.3 (95% CI 1.2, 9.5)], smoking [OR: 2.7 (95% CI 1.3, 5.7)], being in the proliferative phase of their menstrual cycle [OR: 2.6 (95% CI 1.3, 4.9)], frequent douching [OR 2.5 (95% CI 1.1, 5.6)], and history of spontaneous miscarriage [OR 2.4 (95% CI 1.0, 5.8)] (Manhart et al., 2003). Again the samples were stored over a long period of time, and this sample is from an STI clinic where women are more likely to be diagnosed with an STI, thus overestimating the \textit{M. genitalium} prevalence.

2.7.2 Incidence and re-infection of \textit{M. genitalium}

The POPI study in the UK has just been completed and provides the first published the first \textit{M. genitalium} incidence estimates in women. The incidence of \textit{M. genitalium} in women was 1.26% (95% CI: 0.63, 2.24) and the estimate of annual incidence was 0.91% (95% CI: 0.46, 1.63). Predictors of incident \textit{M. genitalium} in this study were co-morbidity with Bacterial vaginosis, black ethnicity and having two or more partners in the previous 12 months (Oakeshott et al., 2010a).

2.8 \textit{M. genitalium} testing in Australia

In Australia, \textit{M. genitalium} testing is not widely available and it is not a notifiable infection. \textit{M. genitalium} testing in Australia has been limited to sexual health centres in Melbourne and Sydney which have adopted in house PCR assays (Lowe, 2009). Nonetheless, these services tend to only test symptomatic patients (urethritis, cervicitis, pelvic inflammatory disease and proctitis) and known sexual contacts of
people with \textit{M. genitalium} only, and do not do routine screening of asymptomatic individuals. More recently, testing has begun more routinely in a hospital termination clinic in Melbourne (Marceglia et al., 2010).

2.9 Conclusions

\textit{M. genitalium} is an emerging sexually transmissible infection internationally and has been demonstrated to cause upper genital tract infection. There are no population data available for women in Australia and the burden of disease caused by \textit{M. genitalium}, including upper genital tract infection, is unknown. Concerningly, \textit{M. genitalium} appears to be increasingly becoming azithromycin resistant in countries where macrolides are used for non-gonococcal urethritis, and there have been reported cases of moxyfloxacin resistance \textit{M. genitalium} as well. Considering azithromycin is commonly used in Australia, it is important to understand the proportion of infections that are azithromycin resistant as well as factors that might contribute to treatment failure in the female population.

This thesis aims to investigate the epidemiology of \textit{M. genitalium}, providing the first prevalence and incidence estimates for \textit{M. genitalium} in Australian women. Understanding the burden of disease associated with \textit{M. genitalium} will contribute to the discussion about the development of a commercially available test, and explore the degree of antibiotic resistance in Australian women.
CHAPTER 3.

PROGRAM OF RESEARCH

3.1 Rationale

As highlighted by this literature review, *Chlamydia trachomatis* is a serious public health problem in young women in Australia and the true burden of infection and related sequelae are unknown. Considering chlamydia is often asymptomatic and testing rates for chlamydia remain low, the notification data for chlamydia are likely to underestimate the extent of chlamydia in the population. Further, there are few population based prevalence estimates and no incidence data for women. Internationally re-infection rates for chlamydia are very high which is concerning considering repeated infections are more likely to cause upper genital tract infections such as PID. The re-infection rates for chlamydia in Australia are also unknown will be essential for developing clinical guidelines, in particular retesting guidelines and partner management for women who test positive. Re-infection rates and incidence data will be important data for the development of chlamydia control strategies.

The Australian Government is piloting a chlamydia screening program to determine the most effective ways to increase opportunistic chlamydia testing in general practice. Understanding the prevalence, incidence and re-infection rates of chlamydia in the population will be crucial to the design of the pilot and to measure the effectiveness of the pilot. The majority of testing for chlamydia in Australia is undertaken in general practice, however although there are still considerable barriers to testing, both practical and psychosocial, there is scope for novel approaches to assist general practitioners to increase testing rates. Given that internationally chlamydia screening programs have not been demonstrated to effectively reduce the prevalence of chlamydia, Australia now has a unique opportunity to develop a screening program specific for its population.
*M. genitalium* is another STI which is also explored in this thesis. There has been less research on this emerging STI, although *M. genitalium* has been associated with serious upper genital tract infections, including PID and tubal factor infertility. International reports suggest *M. genitalium* is less prevalent than chlamydia however there are very little incidence data for *M. genitalium* in women. In Australia *M. genitalium* is not routinely tested for and is not notifiable and to date there have been no population based estimates for *M. genitalium* in young women. *M. genitalium*, like chlamydia is commonly asymptomatic, and as a consequence the burden of disease attributable to *M. genitalium* in young Australian women is currently unknown.

### 3.2 Aims of the thesis

The aims of this thesis were:

1. To further understand the epidemiology of chlamydia in young Australian women.
2. To explore a novel intervention to increase chlamydia testing in general practice.
3. To identify the acceptability of testing and psychosocial barriers to testing by young women.
4. To understand the epidemiology of *M. genitalium* in young Australian women and provide the first information about the burden of disease attributable to *M. genitalium*.

### 3.3 Overview of thesis

This thesis describes the results of two studies: The first of which was a randomised controlled trial which aimed to determine the effectiveness of a computer alert in general practitioner’s patient software system which was designed to prompt general practitioners to test young women for *Chlamydia trachomatis*. The outcome was the difference in testing rates over a 12 month period between clinics with the alert and clinics without the alert. This study is described in full in Chapter 4 (the ‘C-Alert’ study).
The second study in the thesis was a longitudinal study in a cohort of young Australian women to determine prevalence, incidence and re-infection estimates for genital chlamydia known as the Chlamydia Incidence and Re-infection Study or the ‘CIRIS’ study. This study included a sub-study which aimed to determine prevalence, incidence re-infection estimates for *M. genitalium* in the same cohort. The methods for the CIRIS study are described in Chapter 5, the prevalence estimates and a comparison between the two infections at baseline are described in Chapter 6, predictors for incident infection and treatment failure for genital *C. trachomatis* are described in Chapter 7, and the incidence and re-infection estimates for *M. genitalium* and predictors of incident infection and re-infection are described in Chapter 8. Chapter 9 describes the results of the psychosocial implications of testing, and Chapter 10 describes the incidence of induced abortion in the cohort which was an incidental finding of the CIRIS study.
CHAPTER 4.

THE C-ALERT STUDY: ‘COMPUTER REMINDERS FOR CHLAMYDIA SCREENING IN GENERAL PRACTICE: A RANDOMISED CONTROLLED TRIAL.’


4.1 Introduction

4.1.1 Background

Genital Chlamydia trachomatis is the most common notifiable sexually transmitted infection (Australian Bureau of Statistics, 2003) in Australia with more than 62,000 notifications in 2009 and has been increasing steadily over the last ten years according to National Notification data (National Notifiable Diseases Surveillance System, 2010). The rise in notifications is of concern because chlamydia infection can cause significant morbidity, particularly for women. Lower genital tract infection can cause secondary pelvic inflammatory disease and up to two-thirds of cases of tubal infertility and one-third of cases of ectopic pregnancy may be directly attributable to chlamydia infection (Peipert, 2003).

Since up to 80% of chlamydial infections are asymptomatic (Peipert, 2003), screening will be the only effective way to detect the majority of cases. Non-invasive testing (first pass urine specimens or self collected vaginal swabs) is very acceptable to both women and general practitioners and both sampling methods are very sensitive and specific for chlamydia testing using nucleic acid amplification tests (Schachter,
Treatment is highly effective, and the use of a single dose antibiotic treatment now make widespread screening feasible (Peipert, 2003, Lau and Qureshi, 2002). Screening programs for chlamydia are being adopted in many parts of the developed world including the United Kingdom which has implemented a chlamydia screening program targeting women and men aged 16 to 24 years (LaMontagne et al., 2004a). The most effective screening methods are yet to be determined and a randomised controlled trial is currently underway in Australia to determine the effectiveness, feasibility and acceptability of a chlamydia screening program in young people (Hocking et al., 2009).

Australia does not currently have a national chlamydia screening program (Hocking et al., 2008b), however annual chlamydia screening is recommended by the relevant Australian medical professional bodies for sexually active women under 25 years (RACGP, 2009, Royal Australasian College of Physicians, 2010). Currently, Australia tests about 12% of women aged 15 to 24 years for chlamydia each year (Health Insurance Commission, 2008), and even though there is no empirically determined optimal testing rate for chlamydia (Kretzschmar et al., 2009), this is a small number considering over 80% of women in this age group visit a general practitioner each year for their own health (Health Insurance Commission, 2008). Therefore interventions aimed at facilitating chlamydia testing by general practitioners are an obvious way to increase chlamydia testing rates in Australia (Hocking et al., 2008b, Ginige et al., 2007).

One potentially inexpensive method for encouraging general practitioners to test women is the use of an ‘on-screen reminder’ programmed into clinical software. A recent Cochrane review analysed the results of studies on the effectiveness of computer alerts in preventive care action and found computer reminders achieved small to moderate improvements. A median increase in test ordering of 3.8% was found overall (Shojania et al., 2009). However there was considerable variation in results with a trial of a reminder for Pap test screening reporting a non-significant result of 0.6% (Frank et al., 2004) and another trial exploring the impact of a diabetes testing prompt reporting a significant increase of 16.3% (Kenealy et al., 2005). There
were no studies exploring the impact of an on-screen computer alert on chlamydia testing rates in general practice.

4.1.2 Aims

The aim of this study was to determine if a prompt programmed into general practitioner’s patient management software which reminded general practitioners to discuss chlamydia testing with young women, would be an effective method for increasing chlamydia testing rates. The prompt was designed to be incorporated with other evidence-based interventions as part of a chlamydia screening program in Australia.

4.2 Methods

The design of this study was a cluster randomised controlled trial which was set in general practices in Melbourne (population ~4 million), the capital city of the State of Victoria, Australia between 20th February 2006 and 9th October 2007. The intervention period was 12 months, and data were also collected for each clinic for the 12 months prior to the intervention period.

4.2.1 Participants

General practice clinics were eligible if: they were located within the metropolitan area of Melbourne, the clinic had at least one full time equivalent doctor working in the practice, women aged 16 to 24 years old constituted at least 10% of the practice population, and they used the ‘Medical Director’ (MD) computerised patient record system (Health Communications Network, 2005). A practice was ineligible if the clinic did not have MD, the clinic had insufficient numbers of female patients in the target age group, the clinic was outside metropolitan Melbourne, or for other reasons (for example the clinic was closing very soon, the clinic’s phone was disconnected, or there was no response after repeated phone call attempts).
4.2.2 Intervention

A computer alert was programmed by the developers of the Medical Director software: The Health Communications’ Network (Health Communications Network, 2005). The alert was programmed to ‘pop up’ whenever a patient record of a woman aged 16 to 24 years was opened, and advised the general practitioner to consider offering chlamydia testing in accordance with the Royal Australian College of General Practitioner’s (RACGP) recommendation (RACGP, 2005). The RACGP is the professional organisation for general practitioners in Australia and the recommends that all sexually active women under the age of 25 years should be tested for chlamydia. When the alert popped up, the general practitioner had two choices to close it, they had to press either “OK” or tick the box “Please do not prompt me again for this patient” (Figure 4-1). The control group had no alert, and all general practitioners within a practice were in the same arm of the trial.
Figure 4-1 A screenshot of the alert as it appeared when the patient record is opened.
4.2.3 Trial outcome

There were two time periods in the study. The first time period in the trial was 12 months prior to the trial commencing (pre-trial period) and the second time period was the 12 months during the trial period (trial period). The primary outcome measured was the change in the proportion of 16 to 24 year old women tested by participating general practitioners between the two time periods.

4.2.4 Sample size

At the time the trial began, approximately 4% of 15 to 24 year old Australian women were being tested by general practitioners for chlamydia (Medicare Australia, 2004). We hypothesized that the rate of individual women tested by the end of the trial would reach 10% in the intervention group and 6% in the control group. Assuming an intracluster correlation of 0.08 for a cluster size of 100 (which assumes a design effect of 9), a total of 64 clinics (32 in each group) would be required to give 80% power to detect the hypothesized difference with a type I error of 5%.

4.2.5 Randomisation

Clinics were randomised using a randomised block design with block size of four to ensure equal numbers in each arm of the trial.

4.2.6 Implementation

General practices were selected from the Melbourne business telephone directory (Yellow Pages) ‘general practitioner’ section (Telstra Corporation Ltd., 2005) and advertised in Divisions of General Practices in targeted areas in Melbourne (Appendix A). A research assistant contacted all the clinics initially by telephone to determine their eligibility, beginning with those in geographical areas with the highest population proportion of 16 to 24 year old women. Eligible and interested general practitioners were sent a letter of introduction (Appendix B) and then visited by a research assistant to further explain the study. The general practitioner then signed a consent form (Appendix C) and a request to allow the release of de-
identified data from their pathology provider (Appendix D), after reading a plain language statement which outlined the study in detail (Appendix E) (Figure 4-2).

A statistician placed each randomisation sequence number and the corresponding allocation into a sealed, completely opaque envelope given to the research assistant at the time of her visit to each clinic. Neither the research assistant nor the doctors were aware of the assigned group until the envelope was opened at the clinic and a mobile phone text message was sent to the study statistician who verified that the sequence number and allocation matched the details on a central database. At the time of recruitment the alert was installed onto the computers of the consenting doctors within the intervention clinics and the process for collecting the data was explained to the clinic staff. The general practitioners were eligible for professional development points with the RACGP for their involvement in the study and every clinic received $150 to reimburse them for the costs incurred from being in the study.

Doctors in both the intervention and control groups received a chlamydia educational package (Figure 4-3) (Appendix F). The pack included treatment guidelines (Appendix G), partner notification information (Venereology Society of Victoria and the Australasian College of Sexual Health Physicians, 2002), RACGP guidelines for chlamydia testing (Appendix I) (RACGP, 2005 Physicians, 2002 #1039), educational information for general practitioners about chlamydia (Appendix J) and a toll-free 1800 phone number to speak to a sexual health practitioner if they required clinical advice. The researchers developed an educational DVD for the general practitioners which included demonstrations showing how general practitioners could broach the subject of chlamydia testing in the general practice setting (Appendix K).
Figure 4-2  Flowchart showing the recruitment and data collection sequence.
Figure 4-3   The GP education pack including a DVD.
4.2.7 Data collection

Chlamydia testing and consultation data were obtained for the two time periods for each general practitioner – the pre-trial period and the trial period. The total number of consultations with women aged 16 to 24 years, the total number of unique consultations with women aged 16 to 24 years, the total number of tests conducted for 16 to 24 year old women, the total number of women who had at least one test and the total number of women who had at least one positive chlamydia test were obtained for each doctor for each study period. Testing rates and positivity rates were calculated for each clinic. Consultation data were obtained from the Health Insurance Commission, the Australian Government body responsible for funding general practitioner consultations. Chlamydia testing data were obtained from the pathology laboratories servicing the doctors. Both data sets included the general practitioner provider (identification) number, enabling the two datasets to be linked by general practitioner and clinic.

General practitioner completed a questionnaire collecting demographic data, general practitioners’ knowledge of chlamydia, and testing and management practices (Appendix L). These questionnaires were completed at the beginning of the study. At the end of the study, each general practitioner was sent a report which included their testing rates, the overall testing rates along with a report of the findings from the trial. They were also required to complete a self-audit questionnaire to gain the RACGP professional development points.

4.2.8 Statistical analyses

For each study group the prevalence of 16 to 24 year old women tested at least once for chlamydia was estimated using the observed proportion calculated separately for two 12 month periods. The numerator of the observed proportion was the number of women who had at least one test during the time period and the denominator was the number of women who had at least one consultation during the time period. We also calculated the chlamydia positivity for each time period which was defined as the proportion of those tested at least once with at least one positive test.
Confidence intervals for all proportions and a p-value for the comparison of the estimated proportions between study groups were calculated separately for each 12 month period. All the analyses were adjusted for clustering by general practitioner and clinic. An ‘intention to treat’ analysis was used for this trial, so data from individual general practitioners or clinics for whom the computer alert malfunctioned or was discontinued for any other reason were analysed as part of the intervention group.

A mixed effects logistic regression model with a three level hierarchy (patients, individual general practitioner and general practitioner clinics) was fitted to the data that included results from both study groups and both time periods. The model included random intercepts for individual general practitioner and general practitioner clinic to capture heterogeneity in the prevalence of testing at both the individual practitioner and clinic level. The impact of the intervention on the proportion of women tested was explored by fitting an interaction between time period and intervention group. This term quantifies whether the change in testing proportion between pre-trial and trial period was greater in the intervention group than in the control group. The model also included fixed regression effects for the age of the patient (a binary variable for ages 16 to 19 and 20 to 24), and the sex of the general practitioner. The data structure was assumed to be completely nested (patients within general practitioners within general practitioner clinics), so we did not estimate explicitly the proportion of the correlation between observations from the same general practitioner that would result from patients with repeat consultations or from general practitioners working at more than one general practitioner clinic within the study period. Consultations and test results from patients and general practitioners were, however, correctly attributed to individual general practitioners and general practitioner clinics respectively but without tracking the identity of the patient or general practitioner. All analyses were performed using ‘Stata 10.2’ (Stata Corporation, 2007).

Ethics committee approval was granted from the University of Melbourne Human Research Ethics Committee (HREC ethics number 050429).
The study was registered on the Australian Clinical Trials Register, registration number ACTRN012605000411640.

4.3 Results

4.3.1 Participants

The first clinic was recruited in February 2006 with follow up of all clinics completed in October 2007, the clinics were recruited from many suburbs in Melbourne (Appendix M). Of the 708 clinics contacted, 385 were ineligible, 255 declined to participate and 68 were recruited into the study (Figure 4-4). Most clinics were ineligible because they saw inadequate numbers of women in the target population (33%), or they did not use Medical Director (29%). Other clinics were ineligible if they were found not to be a general practice clinic on contact (12%), they were located outside of metropolitan Melbourne (8%), or for other reasons (the clinic was closing in a week’s time, their phone was disconnected, or there was no response after repeated phone call attempts) (18%).

There were 34 clinics (114 general practitioners) in the intervention group and 34 clinics (111 general practitioners) in the control group. Two general practitioners withdrew from different clinics in the control group and two general practitioners and their clinics withdrew from the intervention group before the end of the trial period.
A clinic was ineligible if: the clinic did not have MD, the clinic had <10% female patients 16-24 years old in the practice population, the clinic was outside metropolitan Melbourne, or for other reasons (the clinic was closing in a week’s time, their phone was disconnected, or there was no response after repeated phone call attempts).

Figure 4-4  Flowchart overview of included clinics and GPs.
4.3.2 Baseline characteristics

The baseline characteristics of the clinics and participating general practitioners were similar between both groups (Table 4-1).

Table 4-1 The characteristics of study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  a (% )</td>
<td>95%CI b</td>
</tr>
<tr>
<td><strong>Number of GPs</strong> (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (≤3 GPs)</td>
<td>25 (22)</td>
<td></td>
</tr>
<tr>
<td>Medium (3-5 GPs)</td>
<td>53 (47)</td>
<td></td>
</tr>
<tr>
<td>Large (&gt;5 GPs)</td>
<td>34 (30)</td>
<td></td>
</tr>
<tr>
<td><strong>Size of Practice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (40) (32, 49)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67 (59) (48, 69)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 years</td>
<td>47 (41) (31, 52)</td>
<td></td>
</tr>
<tr>
<td>45-54 years</td>
<td>42 (38) (29, 47)</td>
<td></td>
</tr>
<tr>
<td>&gt;54 years</td>
<td>24 (21) (14, 31)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of hours practiced/week</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 hours</td>
<td>17 (16) (9, 25)</td>
<td></td>
</tr>
<tr>
<td>20-34 hours</td>
<td>38 (35) (26, 45)</td>
<td></td>
</tr>
<tr>
<td>35-49 hours</td>
<td>39 (36) (27, 46)</td>
<td></td>
</tr>
<tr>
<td>&gt;49 hours</td>
<td>15 (14) (8, 22)</td>
<td></td>
</tr>
<tr>
<td><strong>Years in general practice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;11 years</td>
<td>33 (33) (22, 45)</td>
<td></td>
</tr>
<tr>
<td>11-20 years</td>
<td>31 (31) (22, 41)</td>
<td></td>
</tr>
<tr>
<td>&gt;20 years</td>
<td>37 (37) (27, 47)</td>
<td></td>
</tr>
<tr>
<td><strong>Postgraduate qualifications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41 (37) (28, 47)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>71 (63) (53, 72)</td>
<td></td>
</tr>
<tr>
<td><strong>Interest in sexually transmitted diseases</strong> d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less interested</td>
<td>2 (2) (1, 7)</td>
<td></td>
</tr>
<tr>
<td>More interested</td>
<td>99 (98) (93, 99)</td>
<td></td>
</tr>
</tbody>
</table>

aN=number, bCI= confidence interval, cGP= general practitioner, d‘Interest in sexually transmitted infections’: This is based on the self-reported response to: “How much interest do you have in the management of sexually transmitted infections?” yes: ‘very interested’ or ‘moderately interested’; no: ‘not very interested’.
4.3.3 General practitioners’ knowledge, management of and attitude to chlamydia screening

The self-completed questionnaire asked general practitioners about their knowledge of chlamydia using vignettes, open ended questions as well as graduated Likert scales. Three vignettes described potential patients which the clinician was doctor was required to answer how likely they would have been to test them for chlamydia. The proportion of general practitioners who would test a pregnant young woman with history of sexual activity from 16 years old for chlamydia was 77.1%; when asked about a 40 year old woman on the oral contraceptive pill, 6.3% indicated they would recommend a chlamydia test; and 100% of general practitioners recommended testing a 24 year old woman with deep dyspareunia. Of the three case vignettes, 71.4% (95% CI: 64.4, 77.6) answered all three correctly (Peipert, 2003). When general practitioners were asked about whom they screen in general practice, 93.8% indicated they would probably screen a young woman for chlamydia who was sexually active and had a vaginal discharge. However, if the same patient had no symptoms and was having a consultation for a non-sexually related complaint, only 16.6% of doctors would screen her for chlamydia.

When asked about specimens, the majority of general practitioners (>90%) indicated that they would collect a urine specimen and/or cervical swab for diagnosing chlamydia in women, and many chose to collect both in the same patient. About 5% indicated they would use a Pap smear for a chlamydia test in women, and about 3% indicated they would take a specimen of blood for a diagnosis.

General practitioners were also asked about treatment. Azithromycin was the main antibiotic of choice by most general practitioners to treat chlamydia in non pregnant women (77.9%), and doxycycline was the next most popular choice (22.6%). In a pregnant patient, only 18.9% still chose azithromycin; many general practitioners switched to using erythromycin (21%) and roxithromycin (3.4%) and some persisted with doxycycline (3%) but 34.5% of general practitioners that answered the question didn’t know what to prescribe. If a patient tested positive, 72% of general practitioners recommended retesting in an average of 7.1 weeks time. Most general
practitioners recommended testing and treating the partners of positive patients (97%), but only about 30% recommended presumptively treating partners of infected patients.

When general practitioners were asked their opinions about screening in general, most agreed that testing should be recommended for sexually active women under 25 years, or for all women with at least two sexual partners in the last year. Most general practitioners (85.9%) considered chlamydia screening would increase their consultation time with patients; on average by 5.8 minutes per patient. If the patient tested positive, the average number of consultations required for adequate care of that patient was estimated at 2.6 consults per patient, and average time taken was estimated at 49.1 minutes. More than 90% of general practitioners agreed that screening should be done by general practitioners and was not just the responsibility of sexual health clinics.

4.3.4 Testing proportions

During the 12 month pre-trial period, similar proportions of women were tested in the intervention and control clinics: 8.3% (95% CI: 6.8, 9.8) in the intervention group, and 8.8% (95% CI: 6.8, 10.7) in the control group (P=0.76 difference in proportions tested). During the trial period, both groups increased their testing during the trial period from 8.3% (95% CI: 6.8, 9.8) to 12.2% (95% CI: 9.1, 15.3) (p<0.01) in the intervention group, and from 8.8% (95% CI: 6.8, 10.7) to 10.6% (95% CI: 8.5, 12.7) (p<0.01) in the control group.

The interaction between the estimated effect of time period and intervention group shows that general practitioners in the intervention group had a 27% greater increase in chlamydia testing rates compared with the control group [adjusted odds ratio (AOR):1.27 (95%CI: 1.11, 1.45)] over the period of the trial (Figure 4-4). Testing in the intervention group increased by 3.9% and in the control group by 1.8%, a net increase in testing of 2.1%. Based on this net increase, the number of patient consultations that would, on average, result in one additional chlamydia test is 1/0.021 = 50. The intracluster correlation coefficient was 0.05.
Table 4-2  Adjusted odds ratios for the effect of the intervention on the proportion tested.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AOR(^a) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP gender</td>
<td></td>
</tr>
<tr>
<td>Male GPs</td>
<td>1.0</td>
</tr>
<tr>
<td>Female GPs</td>
<td>3.9 (3.1, 5.0)</td>
</tr>
<tr>
<td>Patient age group</td>
<td></td>
</tr>
<tr>
<td>16 to 19 years old</td>
<td>1.0</td>
</tr>
<tr>
<td>20 to 24 years old</td>
<td>1.6 (1.5, 1.8)</td>
</tr>
<tr>
<td>Study Group</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.0</td>
</tr>
<tr>
<td>Intervention</td>
<td>1.1 (0.8, 1.5)</td>
</tr>
<tr>
<td>Time period</td>
<td></td>
</tr>
<tr>
<td>Pre-trial period</td>
<td>1.0</td>
</tr>
<tr>
<td>During trial period</td>
<td>1.4 (1.2, 1.5)</td>
</tr>
<tr>
<td>Interaction term(^b)</td>
<td></td>
</tr>
<tr>
<td>Trial period</td>
<td>1.3 (1.1, 1.4)</td>
</tr>
</tbody>
</table>

\(^a\)AOR= Adjusted Odds Ratio, adjusted for clustering at the GP & clinic level.
\(^b\)Interaction between the time period and the intervention group.
4.3.5 Proportion positive for chlamydia

The positivity for chlamydia did not change during the time periods for the intervention [change = -1.0% (95% CI: -2.9, 0.9), p=0.53] or control groups [change = -0.6% (95% CI: -2.5, 1.3), p=0.31] (Table 4-3).

Table 4-3 Chlamydia test numbers, percentages of tests per individuals tested and positivity rates in both trial groups, for pre- trial and post- trial periods.

<table>
<thead>
<tr>
<th>Pre-trial period</th>
<th>During the trial period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
</tr>
<tr>
<td>Women consulted N</td>
<td>Women tested N (%)</td>
</tr>
<tr>
<td>12 719</td>
<td>1030 (8.8)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
</tr>
<tr>
<td>11 514</td>
<td>956 (8.3)</td>
</tr>
</tbody>
</table>

N = numbers of women
4.3.6 Technical problems

There were some technical difficulties with the alert. After considerable efforts, the alert failed to load in three clinics due to software incompatibilities, and in some clinics the alert was accidentally uninstalled following software upgrades; the alert was reinstalled as soon as practicable. Overall, the alert did not operate for approximately 14.8% of practice time in the intervention clinics.

4.4 Discussion

4.4.1 Principle findings

We demonstrated that a computer alert in a general practice patient management system increased general practitioner chlamydia testing in young women by 27%. Although there was a slight decrease in chlamydia positivity in the intervention group, this did not reach statistical significance, suggesting that there was unlikely to have been much of a change in the chlamydia risk profile of women being tested. These data are the first to demonstrate the effectiveness of a computerised alert for the purpose of increasing chlamydia testing in a primary health care setting.

We found that chlamydia testing also increased in the control group. This was not an unexpected finding considering that chlamydia testing rates have been increasing steadily during the last five years in Australia and was probably consistent with background increases in testing (Hocking et al., 2008b).

4.4.2 General practitioner knowledge

Most of this sample of doctors demonstrated correct knowledge, practice and management of chlamydia in young women. A high proportion of the general practitioners used the correct specimen selection, appropriate treatment (except during pregnancy) followed up a positive patient appropriately, but fell short in the area of asymptomatic screening and recognising risk factors for chlamydia infection.

Considering effective chlamydia screening by general practitioners will be dependent on doctors having adequate information about whom to screen, correct specimen
methods, and how to treat and follow up an infection effectively and gaps in knowledge will need to be addressed (Verhoeven et al., 2003b). These results suggest that the education of general practitioners should focus on how to screen asymptomatic patients, the identification of risk factors associated with chlamydia infection, and how to treat an infection adequately especially in pregnancy. Male general practitioners consistently demonstrated a lack of knowledge about chlamydia risk factors and were much less likely to screen an asymptomatic female patient. The sample male general practitioners also had less interest in STI management and if this was demonstrated to be the case in the general Australian general practitioner population, it might always prove to be a hurdle in equalling the education standards for STI management. Also further research is required to ascertain why there is such an inconsistency between testing rates for chlamydia, what general practitioners appear to be willing to do with respect to opportunistic screening, and how to turn the theory of screening into practice.

4.4.3 Limitations of the trial

There are limitations that should be considered when interpreting these data. The study sample had an over-representation of female general practitioners (59% compared with 35.4% in the underlying Victorian population of general practitioners) (Australian Institute of Health and Welfare, 2003), and most of the general practitioners in the study sample indicated on the questionnaire that they were very likely to be interested in sexually transmissible infections. Therefore the results of our study may not be generalisable to the entire population of Victorian general practitioners.

Another factor that potentially affected the generalisability of the results was the high ineligibility rate. Many clinics were not included because they had too few female patients in the age group or the clinic did not use Medical Director. However, this was a pragmatic trial and it was understood that not all medical clinics would be eligible. It was important to include clinics with enough young female patients to ensure the study had sufficient statistical power, and budgetary limitations only allowed for the development of the intervention for one medical software system. It
is encouraging to note however, that 90% of general practitioners now use computers in their practice (Australian Bureau of Statistics, 2002), which favours future implementation of computerised medical record alerts in Australia.

Also, it was possible that any one woman may be represented more than once in the study if she had a consultation and/or test in more than one study clinic during the pre trial and/or trial periods. Fortunately, this was unlikely because clinics were spread over a wide geographical area. The nature of our data collection precluded being able to identify unique women, although we were able to analyse data for individuals.

One last limitation was the intervention itself. It appeared on the basis of age and gender regardless of whether or not the patient was sexually active, and it did not always load effectively or remain on the system for the full period of the study. These factors however, would have most likely resulted in an underestimate of the intervention on testing particularly in younger women.

4.4.4 Strengths of the trial

There were a number of strengths of this study: the sample was a good representation of geographical locations of general practice clinics across Melbourne (Appendix M). The trial had equivalent demographic representations in the intervention and control groups and the general practitioner retention was very high with a response rate for obtaining the test rate data and questionnaire data at 98%. Another potential strength in the design of this study is that there is a lack of other medical computer alerts for this age group in general practice so ‘alert fatigue’ is less likely (Demakis et al., 2000).

4.4.5 Comparisons with other research outcomes

In the Cochrane review by Shojania et al (2009), studies done to determine the effects of computer alerts on clinician preventative care were analysed, and the benefit of a point-of-care, on-screen reminder on clinician process adherence demonstrated an overall benefit of 3.8% for test ordering (Shojania et al., 2009). The
absolute increase in test ordering demonstrated in our study was 2.1% which was slightly lower than the median for the review, however it is within the interquartile range for test ordering reported in this review (IQR: 0.4 to 16.3) (Shojania et al., 2009). Further research into the different methods of computer on-screen alerts is recommended to also help to determine how to maximise the effect of a prompt in clinical practice.

4.4.6 Potential implications for this research

This research has a number of implications for chlamydia screening in general practice. The success of the use of a computer alert to increase the test rates of chlamydia would suggest that general practitioner’s patients would benefit by using computer alerts to prompt for testing for chlamydia. Given that discussing chlamydia can be difficult, in particular in a consultation unrelated to sexual health (McNulty et al., 2004) the prompt may be used as a visual aid to introduce the topic of chlamydia testing with young women in the consulting rooms. While in our sample, the alert increased the proportion tested by 27%, we still found a very low testing rate. Mathematical models of chlamydia transmission have suggested that we need to get testing rates up to over 30% to have any impact on chlamydia prevalence, suggesting that other interventions will be needed to get testing to high enough levels to have an impact on prevalence (Turner et al., 2006b) (Regan et al., 2008). However, it is important to note, that there still remains no definitive chlamydia testing rate that has been demonstrated to reduce chlamydia in the population (Kretzschmar et al., 2009). Other studies have shown that complex interventions including multiple components such as the appointment of a ‘clinic chlamydia champion’ to encourage testing, providing regular feedback on testing performance and educational packages, can be very effective at increasing chlamydia testing rates (Shafer et al., 2002). A computer alert could be included as part of such an intervention package.

4.5 Conclusion

The study provides evidence of the impact of alerts in general practice and specifically on the potential for increasing chlamydia testing rates. These results add to the current existing literature on health outcomes and the use of alerts in primary
care, and suggest there might be a possibility for a more extensive use of alerts for other sexually transmissible infections. Overall, the results of this study suggest that alerts alone may not be sufficient to get chlamydia testing levels up sufficiently high enough to have an impact on chlamydia prevalence but that they could be included as part of a more complex intervention.
CHAPTER 5.

METHODS USED FOR THE CHLAMYDIA INCIDENCE AND RE-INFECTION RATES (CIRIS) STUDY.


5.1 Introduction

This chapter describes the methods used for the CIRIS study (the Chlamydia Incidence and Re-infection Study) which is a longitudinal study of a cohort of young Australian women. Chapter 5 is an introduction to Chapters 6, 7, 8, 9 and 10 which report the results of the study.

5.2 Background

5.2.1 Study background

Genital Chlamydia trachomatis ('chlamydia') infection is a significant public health problem among young Australian women, with notification rates increasing from 74 per 100 000 people per year in 1997, to 287 per 100 000 people per year in 2009 (Department of Health and Ageing, 2009). Prevalence estimates among young Australian women range from 3% to 5% in community-based samples (Hocking et al., 2006b, Kong et al., 2009), but these estimates are based on small sample sizes with
limited precision and there are no incidence data for chlamydia in young women. In light of Australia’s future national chlamydia testing pilot program (Hocking et al., 2008b), there is an urgent need for reliable chlamydia prevalence and incidence estimates that can be used to both inform the design of the pilot and monitor its performance.

*M. genitalium* is another important sexually transmitted pathogen that is associated with lower genital tract infection (Jensen et al., 1993), upper genital tract infection (Lusk et al., 2010, Cohen et al., 2002, Clausen et al., 2001) and an increased risk of HIV transmission (Mavedzenge, 2009, Lusk et al., 2010). Generally, *M. genitalium* prevalence has been found to be consistently lower than chlamydia in the same population (Andersen et al., 2007, Manhart et al., 2007, Hay et al., 2009). In Australia, *M. genitalium* testing is not widely available and there are no population data available for women. Understanding the burden of disease attributable to *M. genitalium* will inform future *M. genitalium* policy, contribute to the debate about the development of an available commercial assay and provide important information about treatment failure.

### 5.2.2 Methods background

The CIRIS study was a 12 month longitudinal study of young Australian women aged 16 to 25 years. This study recruited women from primary care clinics and aimed to measure the prevalence, incidence and re-infection rates of genital chlamydia infection and *M. genitalium*.

Cohort studies are one of the most important study designs in modern epidemiology. While they can be complex to organise and expensive to conduct, they have a considerable advantage over case control studies in that they avoid several important sources of bias which might be introduced by the subjects when they know their disease status, by the researchers when he or she knows whether a subject is a case or control, and in the selection of the controls (Doll, 2001). However, the validity of a cohort study’s results can be severely compromised if
participation is low there is substantial bias, or if there is significant loss to follow up of study participants, particularly if this loss to follow up is related to their exposure.

Representative samples of young people can be particularly difficult to recruit and retain in a longitudinal study, in part because of the difficulty in identifying an appropriate sampling frame and also because young people change address frequently (Lee et al., 2005). Other published longitudinal studies of young women have been limited by high loss to follow up, low participation rates and retention bias (LaMontagne et al., 2007, Whittington et al., 2001, Fortenberry et al., 1999, Lee et al., 2005).

5.2.3 Aims

The aims of the CIRIS study were primarily to further understand the epidemiology of chlamydia in young Australian women and provide population-based prevalence data and the first incidence data in young Australian women.

The secondary aim of the CIRIS study was to determine the epidemiology of *M. genitalium* in young Australian women and provide the first prevalence and incidence estimates for *M. genitalium* in young Australian women.

The aim of this chapter is to detail the methods that were used in the CIRIS study in detail. This chapter describes the methods used to recruit a representative sample of women into the study, and the methods used to retain the cohort of women in the study. This chapter also describes the characteristics of the sample of women who were recruited and retained in the study and explores factors associated with loss to follow up, in order to validate the methods used for this study.

5.3 Methods

5.3.1 Participants

CIRIS was a prospective cohort study of 16 to 25 year old women recruited through primary health care clinics, including general practice clinics and family planning/sexual health clinics. Women were eligible for the study if they had ever
been sexually active, were not knowingly pregnant at the time (although they were
not tested for pregnancy at the time of recruitment), were competent with English
as a written language and were able to be followed up using the Australian postal
system during the following 12 month period and could provide a postal address to
send packages to or arrange to pick up follow up packs from their clinic.

5.3.2 Sampling frame and recruitment method

The sampling frame for this study was primary care clinics in the states of Victoria,
New South Wales and the Australian Capital Territory, in Australia. Between May
2007 and August 2008, eligible female patients were recruited from 29 separate
general practice and family planning/sexual health clinics in rural and urban areas in
south eastern Australia, where 60% of the population of Australia live (Australian
Bureau of Statistics, 2006). To facilitate obtaining a reasonably representative
sample, clinics were chosen as recruitment sites on the basis of the socio-
demographic profile of their local area based on the Australian census data from

The research assistant collated all the general practices from the Telstra Yellow
Pages within the areas that had been chosen (Telstra Corporation Ltd., 2005). The
clinics within each area were randomly ordered and phoned sequentially to
determine their eligibility and interest in the study. Metropolitan clinics were eligible
if they had consultations with at least 150 16 to 25 year old women per fortnight,
and had a private area for recruiting. Regional and rural clinics were chosen
opportunistically for logistical reasons, but were only included if they had a private
space for recruiting purposes. The clinics were visited and the study was explained in
full to all administrative and clinical staff; if the clinic had specific human research
ethics requirements that had not already been granted, an application for ethics was
completed and the study commenced only after ethics was granted for the clinic.

A team of research assistants were trained and were based in each clinic for up to six
weeks, depending on the individual clinic. Over the six weeks, the research assistant
approached all 16 to 25 year old women who presented for a consultation,
irrespective of the reason for their presentation, to invite them to participate in the study. All research assistants were female and were chosen to fit in with the type of clinic they were recruiting from: for example younger research assistants recruited in youth clinics and mature aged research assistants recruited from general practice (Figure 5-1 Some of the research assistants who recruited for the study Figure 5-1). To ensure minimal disruption to the clinic clients and staff, all research assistants were trained and supervised closely, and the CIRIS research team liaised frequently with clinic personnel. Confidentiality and discretion were maintained by discussing the study with patients in a private space within the clinic, and information provided to the research team was not disclosed to their clinician unless requested by the participant. Research assistants also signed a confidentiality agreement which was given to the clinic (Appendix N). Research assistants were independently employed by the University of Melbourne to minimise any impact on the clinic and to separate the relationship between the study and the participant’s usual clinical care.
Figure 5-1 Some of the research assistants who recruited for the study.
Once recruited, all participants received a study pack with a copy of their consent form (Appendix O), including a ‘Revocation of Consent form should they decide to withdraw (Appendix P), the plain language statement (Appendix Q), information about the study, and information on chlamydia and other sexually transmissible infections (Appendix R, Appendix S and Appendix T). In addition, all participants were given condoms and lubricant and an individual business card with their study number on it and contact details for the study (Figure 5-2).

![Business card with details for the study participant with their unique ID code on the back of the card.](image-url)
5.3.3 Questionnaire data

At the time of recruitment (referred to as ‘baseline’), the participants completed a questionnaire which collected demographic information, sexual behaviour data (number of opposite and same sex partners and condom use), recent antibiotic and contraceptive use data, and the presence of any genital symptoms (Appendix U). Questionnaires were sent out at each three month follow up requesting information relevant to the previous three months including numbers of new sexual partners, contraceptive use, details about recent general practitioner visits, STI testing, antibiotic use, and any pregnancies, including miscarriage or termination of pregnancy (Appendix V). Importantly, at every follow up stage, the questionnaires were different if woman tested positive at the previous test (Appendix W). The positive questionnaires asked about treatment, partner notification, further testing, symptoms and also the same questions that the ‘negative’ women were asked.

At the end of the study, a final psychosocial questionnaire was also sent to the women asking questions about their experience of being involved in the study, how they felt about having a chlamydia test, and the type of specimen they preferred, how they thought they might feel and react if they had tested positive and whether or not they would change their sexual behaviour as a result of being in the study amongst other questions (Appendix X). Women who had tested positive at any stage during the study were asked a series of similar questions, but instead of asking how they thought they might feel or react, they were asked how they did feel or react when they did test positive (Appendix Y).
5.3.4 General practitioner education pack

All the general practitioners in the study were provided with an information pack which included:

- Introduction to CIRIS study letter (Appendix Z)
- CIRIS study synopsis
- Chief investigator contact list
- Copy of consent and consent revocation forms (Appendix O and P)
- Copy of participant information form (Appendix Q)
- CIRIS study time interval chart (Appendix AA)
- “Guidelines for preventive activities in General Practice” – RACGP (Appendix I).
- “No barriers to chlamydia testing in sexually active young women” MJA, 183(10)548-549.
- Sexual health clinic contact list (specific to local area)
- Sexual health web links page
- Chlamydia trachomatis DVD (Appendix K)
- General Practitioner information CD (Appendix BB)
- STI notification form (Appendix CC)
- Partner letters for Chlamydia trachomatis and Mycoplasma genitalium (Appendix DD and Appendix EE)
- Treatment guideline sheets for Chlamydia trachomatis and Mycoplasma genitalium (Appendix FF and Appendix GG)
- Patient fact sheets for Chlamydia trachomatis and Mycoplasma genitalium (Appendix R and Appendix S)
- “National Management Guidelines for Sexually Transmissible Infections” (Venereology Society of Victoria and the Australasian College of Sexual Health Physicians, 2002) (Appendix G)
- Brochures about general STI information (Appendix J and Appendix T).
Figure 5-3  Instructions for how to take a self collected vaginal swab.

(Appendix HH)
5.3.5 Follow up

All participants were asked to self-collect a vaginal swab (at baseline, six and 12 months for chlamydia testing and anyone who tested positive for chlamydia at baseline or at six months, was also required to return a swab three months later as a test for re-infection (Appendix AA). Women were tested for *M. genitalium* at baseline and 12 months and followed up if they tested positive.

Table 5-1 Schedule for the swabs, slides and questionnaires collected throughout 12 months of the study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>swab</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>slide</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>questionnaire</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+/- either sent or not sent - if a participant tested positive at baseline, they received a swab at 3 months and the same was for positive at 6 months. All women received a swab and slide at baseline, 6 months and 12 months, and a questionnaire at every stage.

Participants were also asked to complete a sexual behaviour questionnaire every three months regardless of whether or not they collected a swab (Appendix V and Appendix W). All follow up was done through the standard Australian postal service, and follow up packs were designed to be nondescript, simple to use and free (Figure 5-4 and Figure 5-5).
Figure 5-4  The follow up package.

Figure 5-5  Contents of a follow up kit.
A prompt was sent via SMS (mobile phone text message) or email a week prior to sending out the follow up kit (depending on the participant’s preference) (Figure 5-6) (Appendix II) to alert the participants to expect a delivery, and this was also a cue for them to update their contact details if necessary. Similarly, a reminder was sent if the follow up pack had not been returned within two weeks (Appendix JJ). If there was still no response after a further two weeks, research staff made up to ten telephone calls at different times of the day and different days of the week. For continuity, the same staff followed up the participants throughout the study. Also, the participants were able to contact study staff at any stage by calling a free-call telephone number or emailing the CIRIS email address. A website was designed with detailed information about the study and participants could also notify any changes in their contact details via the website (Figure 5-7). Participants were excluded from further follow up if their telephone number was disconnected/continually unanswered, emails ‘bounced back’, or their follow up parcels were ‘returned to sender’.
Figure 5-6  Examples of an SMS and an email prompt.

- **SMS Example:**
  - **Message:** CIRIS reminder: soon you will receive follow up info in post. If contact details changed pls reply.

- **Email Example:**
  - **From:** CIRIS Research
  - **To:** anon@anon.com.au
  - **Subject:** Reminder from CIRIS
  
  Hi

  Soon you will receive follow up information in the post for the CIRIS project. If your contact details have changed could you please let us know either by SMS on 0417 539 739 or email ciris@mshc.org.au.

  Thank you for your assistance with this important research.

  Regards,

  Jenny Walker
  And the CIRIS team
CIRIS: A longitudinal study of chlamydia incidence and re-infection among young Australian women

Chlamydia trachomatis infection is the most commonly notified sexually transmissible infection (STI) in Australia, with over 40,000 infections notified in 2005. Infection with chlamydia can have considerable complications, particularly for women – it is a leading cause of pelvic inflammatory disease and tubal infertility. Up to 85% of people with infection do not have any symptoms, so are unaware they have chlamydia, yet chlamydia is easy to diagnose with self-collected specimens and simple to treat with single dose antibiotics. Over 85% of infections diagnosed in women are among those aged 15 to 24 years.

The Commonwealth Department of Health and Ageing recently announced funding for a chlamydia screening pilot program. Several questions must be asked regarding the development of this screening program including who to screen and the optimal screening frequency – for example should it be annual or every two years.

The School of Population Health, University of Melbourne in collaboration with Family Planning Victoria, Royal Women’s Hospital, National Centre for HIV Epidemiology and Clinical Research, Canberra Sexual Health Centre, Sydney Sexual Health Centre and Southern Cross University, has secured funding from the Commonwealth Department of Health and Ageing to investigate the optimal screening interval for chlamydia among young Australian women. This longitudinal study with a 12 month follow up period will estimate the incidence and re-infection rate of chlamydia among young Australian women. A representative sample of 1,400 Australian women aged 16 to 25 years will be recruited from general practices, sexual health centres and family planning clinics, both rural and urban, in Victoria, New South Wales and the ACT. Women will be followed up over a 12 month period and will be regularly tested for chlamydia using self-collected vaginal swabs mailed through standard mail.

Further information about this study can be contacted at cira@mshe.org.au or 1800 082 820.
5.3.6 Incentives

Incentives were provided in the form of gift vouchers redeemable at a number of large retail outlets; at three months, a AUD$10 voucher, AUD$20 at six and nine months and AUD$50 at 12 months and the participants indicated on their questionnaire which type of voucher they wanted (Figure 5-8).

![Figure 5-8](image-url) Tick box on follow up questionnaire for participants to indicate their preferred voucher.
Small gifts (eg tampons, confectionery, cosmetics) were included in all follow up kits (Figure 5-9).

Figure 5-9  Some of the samples included in follow up kits for the participants.
5.3.7 Generalisability and bias

To assess the generalisability of the study sample, the demographics and sexual behaviour profiles reported at baseline were compared with the background population of women in Australia in the same age group.

To determine any selection bias, women who declined to participate were compared with women who had agreed to participate although this was limited to their age of the women and the clinic they attended women because women who declined to be part of the study had not consented to allow the use of their information in the study. The participation proportion was calculated by determining the number of women who were recruited relative to the number of eligible female patients attending that service. The research assistants were provided with daily log sheets (Appendix KK) to account for all women who attended the clinic within the age group on that day and where possible, the age and reason for refusal was collected for all non-participators. These log sheets were collated by the research team.

To identify any loss to follow up bias, the women who completed the study were compared with the women who were lost to follow up. The comparison included a comparison of the demographics and sexual behaviour information and chlamydia test results of the participants the time of their final response. Reasons for women withdrawing or not completing the study were recorded and were included in the results, however these were not always forthcoming and it was not appropriate to follow these women up to find out why they failed to continue.

5.3.8 Sample size

Assuming a design effect of 2, a sample size of 860 was required to obtain a chlamydia incidence of 4.5% per year (±2.0), as chlamydia incidence was the primary aim of the CIRIS study. We assumed a 20% loss to follow up and aimed to reach a sample of 1100 women.
5.3.9 Statistical analysis

For the purposes of this analysis, participants were regarded as ‘lost to follow up’ if they did not provide a swab and complete a questionnaire for the final stage of the study. All data were analyzed using STATA version 11.1 (Stata Corporation, 2009). All analyses were adjusted for clustering at the individual clinic level. Hazard ratios and adjusted hazard ratios and robust standard errors were calculated using Cox regression methods to explore associations between women who remained in the study and participants who were lost to follow up. Each individual’s observation period was represented in the dataset thus allowing variables such as number of new sex partners to be recorded separately for each time period. Age was categorized as 16 to 20 years versus 21 to 25 years for some of the analyses.

5.3.10 Ethics

Ethics approval to conduct this study was obtained from ten Human Research Ethics Committees throughout Australia including: The University of Melbourne Health Sciences Human Ethics Sub-Committee, Bayside Health Service District Human Research Ethics Committee, ACT Health and Community Care Human Research Ethics Committee, Family Planning Victoria Ethics Committee, North Coast Area Health Service Human Research Ethics Committee, South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committee, The University of Newcastle Human Research Ethics Committee, University of NSW Human Research Ethics Committee, The University of Ballarat Human Research Ethics Committee, and the Family Planning NSW Ethics Committee.

5.4 Results

5.4.1 Participants

The study was discussed with 2835 consecutive 16 to 25 year old female patients from 29 clinics by the research assistants in each clinic. Of these women, 1137 were ineligible for participation; 297 (26%) had never had vaginal sex with a man, 341 (30%) were travelling or otherwise unable to receive mail, 47 (4%) were not
competent to consent or were not literate in English, 114 (10%) were pregnant at
the time of recruitment, and 338 (30%) for other reasons. Of the 1698 eligible
women, 582 (34%) declined to be in the study, 452 (78%) who declined were ‘not
interested’, 105 (18%) stated they had ‘no time’, and 19 (3%) of women declined for
other reasons.

Of the 1698 eligible women, 1116 consented to the study, giving a participation rate
of 66% (Figure 5-10). Women who were recruited into the study were also invited to
be involved in a sub-study where they were tested for *M. genitalium* and Bacterial
vaginosis; 1110 women were recruited into the sub-study as well as the primary
chlamydia study [the results of the Bacterial vaginosis analysis are not included in
this thesis]. There was no difference in participation by age of women (21 to 25 years
compared with 16 to 20 years) (OR: 1.1, 95% CI: 0.8, 1.5).
The median age of the women recruited into the study was 21 years and 738 (66%) were recruited from general practitioner clinics and 378 (34%) were recruited from sexual health or family planning clinics. Participants were more likely to be Australian born and more well-educated in comparison with the underlying Australian population of the same age (Table 5-2) (Australian Bureau of Statistics, 2006). Participants were also more sexually active on average in comparison with a representative sample of Australian women reported in the 2001 national sexual behavior study (Table 5-2) (Smith et al., 2003).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Study sample (95% CI)</th>
<th>Australian population of 16 to 25 year old women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COB</strong>&lt;sup&gt;a&lt;/sup&gt; (Australian Bureau of Statistics, 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Australian born</td>
<td>11.5 (9.6, 13.5)</td>
<td>21.6</td>
</tr>
<tr>
<td>Australian born</td>
<td>88.5 (86.5, 90.4)</td>
<td>78.4</td>
</tr>
<tr>
<td><strong>Indigenous status</strong> (Australian Bureau of Statistics, 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not indigenous</td>
<td>97.7 (96.6, 98.5)</td>
<td>97.9</td>
</tr>
<tr>
<td>Indigenous</td>
<td>2.3 (1.5, 3.4)</td>
<td>2.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Education</strong> (Australian Bureau of Statistics, 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ year 12</td>
<td>56.1 (53.1, 59.1)</td>
<td>79.1</td>
</tr>
<tr>
<td>Tertiary</td>
<td>43.9 (40.9, 46.9)</td>
<td>20.9</td>
</tr>
<tr>
<td><strong>Employment</strong> (Australian Bureau of Statistics, 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed/Not working</td>
<td>38.5 (35.6, 41.5)</td>
<td>40.4</td>
</tr>
<tr>
<td>Employed</td>
<td>61.5 (58.5, 64.4)</td>
<td>59.6</td>
</tr>
<tr>
<td><strong>No. sexual partners last 12 months</strong> (Smith et al., 2003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 2</td>
<td>67.3 (64.3, 70.1)</td>
<td>95</td>
</tr>
<tr>
<td>3 – 4</td>
<td>19.6 (17.3, 22.2)</td>
<td>6.5</td>
</tr>
<tr>
<td>5+</td>
<td>13.1 (11.1, 15.3)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Country of birth; <sup>b</sup> 95% confidence interval; <sup>c</sup> South Eastern Australia
5.4.2 Retention

Of the 1116 participants who commenced the study, 877 (79%) completed the final stage of the study at 12 months. The largest loss to follow up was during the first three months with 94 (8%) failing to return after their initial contact. A total of 928 (83%) participants completed the three month follow up, 889 (80%) sent back their six month follow up, 853 (76%) returned the nine month follow up, and 877 (79%) returned the 12 month follow up (Figure 5-11). Not all participants who completed the 12 month follow up returned all study material, 392 (35%) participants skipped at least one of the three month follow ups. Only 31 participants (2.7%) withdrew from the study, with most providing no reason for withdrawal.

Figure 5-11 Proportion of women who completed follow up at each stage of the study.
Follow up was continued for 15 months to allow individuals 3 months to finally respond to the final stage of the study. All subjects who remained in the study till the end were censored at the time that they returned their final questionnaire and swab, and Figure 5-12 below shows the Kaplan-Meier survival curve for loss to follow up over time.

Figure 5-12  Time under observation until loss to follow up.

Participants who completed the final stage of the study were compared with those participants who were lost to follow up to assess if there was any retention bias. The crude and adjusted hazard ratios for factors associated with loss to follow up are shown in Table 5-3. Loss to follow up in the study was associated with being recruited from a sexual health or family planning clinic relative to a general practice [adjusted hazard ratio (AHR): 1.6 (95% CI: 1.0, 2.7)]. Loss to follow up was less likely to be associated with a past history of having chlamydia [AHR: 0.8 (95% CI: 0.5, 1.0)] or having a higher educational level [AHR: 0.7 (95% CI: 0.5, 1.0)], but no other associations were found for any other demographic or behavioural data (Table 5-3).
The median number of new sexual partners for women retained in the study was 1.2, and for women lost to follow up was 1.7 however this difference did not reach statistical significance (p=0.4) (Table 5-3).

Table 5-3  Unadjusted and adjusted hazard ratios for women retained in the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total number of women (n)</th>
<th>Number (%) lost to follow up</th>
<th>Hazard Ratios (95% CI)a</th>
<th>Adjusted Hazard Ratiosb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPc</td>
<td>738</td>
<td>140 (19.0)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>SHSd</td>
<td>378</td>
<td>99 (26.2)</td>
<td>1.5 (0.9, 2.4)</td>
<td>1.6 (1.0, 2.7)</td>
</tr>
<tr>
<td>Clinic location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>455</td>
<td>88 (19.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Metro</td>
<td>661</td>
<td>151 (22.8)</td>
<td>1.2 (0.7, 2.2)</td>
<td>1.4 (0.8, 2.4)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 21 years old</td>
<td>452</td>
<td>100 (22.1)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt; 20 years old</td>
<td>664</td>
<td>139 (20.9)</td>
<td>0.9 (0.6, 1.3)</td>
<td>1.0 (0.7, 1.3)</td>
</tr>
<tr>
<td>Education level achieved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to year 12</td>
<td>609</td>
<td>140 (23.0)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Tertiary</td>
<td>477</td>
<td>85 (17.8)</td>
<td>0.7 (0.5, 1.0)</td>
<td>0.7 (0.5, 1.0)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed/Not working</td>
<td>418</td>
<td>81 (19.4)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Employed</td>
<td>668</td>
<td>143 (21.4)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.1 (0.9, 1.5)</td>
</tr>
<tr>
<td>Tested positive for chlamydia prior to study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>965</td>
<td>202 (20.9)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>114</td>
<td>20 (17.5)</td>
<td>0.8 (0.6, 1.0)</td>
<td>0.8 (0.5, 1.0)</td>
</tr>
<tr>
<td>Number of new sexual partners during the studye</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 2 partners</td>
<td>706</td>
<td>173 (24.5)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt; 2 partners</td>
<td>410</td>
<td>66 (16.1)</td>
<td>0.8 (0.6, 1.0)</td>
<td>0.8 (0.5, 1.2)</td>
</tr>
</tbody>
</table>

a 95% confidence interval.
b Adjusted Hazard Ratios = adjusted for type of clinic recruited from, location of recruitment site, age, education level reached, employment status, numbers of new sexual partners at each stage, if tested positive prior to the study.
c General practice clinic.
d Sexual health service/Family Planning clinic.
e Cumulative number of new partners throughout the study.
During the follow up period, 392 (35%) participants changed their postal address. Of these, 287 participants changed their address once, 87 changed their address twice, 16 changed their address three times and two changed address four times. It was not recorded how often email or telephone numbers changed, however this was commonly done.

5.5 Discussion

5.5.1 Key results

This study was successful in retaining a high proportion (nearly 80%) of participants with minimal attrition bias. Considering the study required participants to complete questionnaires about sensitive subject matter and provide self-collected genital samples through the post, we would suggest that the methods we used were successful and might be replicated in other similar studies to achieve community based results. The results of the study are discussed in Chapters 6, 7, 8, 9 and 10.

5.5.2 Limitations

There were limitations to the study. Australian-born women were overrepresented, which was not unexpected, considering that women with insufficient English skills were excluded from the study for logistical reasons. Participants also tended to be more well-educated compared with the background population of the same age (Australian Bureau of Statistics, 2006), a common finding in similar studies (Hocking et al., 2006b, Smith et al., 2003, Traeen et al., 2002). Further, women participating in this study were more sexually active on average compared with the national sexual behavior study, The ‘Australian Study of Health and Relationships’ (Smith et al., 2003), however, this study was conducted in 2001 and more recent data suggest young women are becoming more sexually active (Smith et al., 2009).

5.5.3 Strengths

The study had a number of strengths. Firstly we achieved a high retention rate of nearly 80% and a high participation rate of 66%. Secondly, a high proportion of women were recruited from general practice (66%), thus providing a more
community based sample, particularly given that nearly 90% of women in this age group attend a general practitioner for their own health each year (Hocking et al., 2008b). Further, our cohort had a strong representation from younger women, with nearly 50% of participants being aged less than 20 years, an age group frequently under-represented in sexual health studies (Hocking et al., 2006b, Smith et al., 2003).

5.5.4 Interpretations

To estimate population prevalence and incidence, it was important that the sample was recruited using robust population sampling methods; given this, the recruitment rate of 66% was relatively high particularly considering a recent UK chlamydia incidence study, reported a recruitment rate of 26% for women recruited from primary care clinics (LaMontagne et al., 2007). The Australian Longitudinal Women’s Health Study, a cohort of women that aimed to measure women’s health indicators reported a recruitment rate of 42% using postal questionnaires (Lee et al., 2005). We had also an almost 80% retention of women over 12 months, which compares very well with the retention rate of 61% in the UK study over 18 months (LaMontagne et al., 2007). The recently published cohort of women in Norway reported an excellent 12 month retention rate of 93% at 12 months, but this study relied on face to face meetings, which was not practical nor cost effective in the Australian context, given the vast distances between study participants (Skjeldestad et al., 2009). Neither the UK nor the Norwegian study however, explored any potential role of retention bias.

We used face to face contact for recruitment as telephone-based and mail-based recruitment have been less effective for recruiting women into other similar studies in Australia (Lee et al., 2005, Hocking et al., 2006b). Our follow up was conducted via mail, which has been demonstrated to be an acceptable method for follow up chlamydia testing and is more practical given that some participants live in rural and isolated areas (Østergaard et al., 1998). However, the high retention of participants in other longitudinal studies where follow up was conducted in person either by using consultations or home visits (Skjeldestad et al., 2009, Batteiger et al., 2009) suggests this might be more a more effective method for retaining people in
longitudinal studies, but this is expensive to implement and was not logistically practical in our case.

Overall, women who remained in the study were more well-educated, a very common finding in similar types of research (Hocking et al., 2006b, Smith et al., 2003, Traeen et al., 2002). Retention bias has been reported in other sexual health cohort studies, where loss to follow up was highest in women from low socio-economic backgrounds (Fortenberry et al., 1999), women recruited from sexual health centres as opposed to general practice clinics, and women who were more sexually active (Whittington et al., 2001).

5.5.5 Suggested methods

We would suggest that it is likely that women chose to remain in our study for a number of reasons. The participants had easy access to study staff via email or a free-call telephone number; there was regular communication with the participants; wherever possible, each participant was contacted by the same research assistant and this engendered familiarity and trust. All research assistants employed on the study were thoroughly trained and fully informed, and the research team liaised closely with clinics addressing any queries or concerns quickly. Recruiting in privacy, ensuring confidentiality, supplying appropriate information and managing positive results efficiently, respectfuIlly and at no cost also increased trust. Further, incentive payments and the small gifts encouraged good will among participants. Research assistants who were independent of the clinical relationship were used to recruit the women. This method was intentionally used to minimize any influence the clinical situation had on participation and to reduce the impact on the clinicians who are already very busy and may not want to discuss sexual activity unless it is considered relevant to the consultation (McNulty et al., 2004).
Recommended recruiting methods:

- Ensure all research assistants are adequately trained, fully informed and supervised closely
- Liaise closely with clinic staff (administrative and clinical) and ensure they are fully informed about the recruiting process; set up a process to address any queries or concerns expediently
- Recruit in privacy, ensuring the participants feel comfortable discussing the study and feel confidentiality is assured
- Supply appropriate information about the study in plain folders
- Employ research assistants who are independent of the clinical relationship to remain clear of the patient doctor relationship.

Methods to maximise retention:

- Communicate regularly with participants, being particularly sensitive to maintain confidentiality
- Prompt participants prior to sending follow up to confirm contact details
- Maintain contact with participants using the same staff to engender familiarity and trust
- Provide easy access to study staff by email or a free-call telephone number, including being available after hours (until 9pm weeknights and on weekends)
- Manage positive results efficiently, respectfully and at no cost to the participant
- Provide small incentive payments and small gifts when appropriate.
While our assessment of the effectiveness of the individual methods used has been subjective, there has been some evaluation and discussion in the literature about methods that are more likely to increase recruiting and retention in sexual health research. Strategies such as prompting participants to confirm their contact details prior to sending out follow up have been demonstrated to increase the return of postal surveys (Atherton et al., 2010), other studies also suggest that having a dedicated research team and being flexible and creative help to increase recruitment rates (Atherton et al., 2007, Gabbay and Thomas, 2004) and interestingly, whilst gifts and money provide incentives to be involved, young women are only likely to be part of a study if they feel it is an altruistic thing to do (Atherton et al., 2006, Gabbay and Thomas, 2004).

5.6 Conclusion

The challenges identified in this study included the nature of the research (sexual health), the required follow up (sending vaginal swabs through the post) and the mobility of the participants in the study (at least 35% moved one or more times during the 12 months). However, this methodology was very successful in terms of retention and recruitment, both of which are crucial to the success and validity of a cohort study. Further, the methods used resulted in negligible retention bias, also crucial in terms of the usefulness of the study results although further research is needed to improve participation from less well-educated women. Even though we were unable to test our methodology using a randomised design, other researchers may benefit from adopting some of our methods and clearly more evaluation of effective methods is warranted.
CHAPTER 6.

THE DIFFERENCE IN DETERMINANTS OF CHLAMYDIA TRACHOMATIS AND MYCOPLASMA GENITALIUM IN A COMMUNITY BASED SAMPLE OF YOUNG AUSTRALIAN WOMEN


6.1 Introduction

Genital Chlamydia trachomatis ('chlamydia') infection is a significant public health problem among young Australian women, with notification rates increasing from 74 per 100 000 people per year in 1997, to 287 per 100 000 people per year in 2009 (Department of Health and Ageing, 2009). Prevalence estimates among young Australian women range from 3% to 5% in community-based samples (Hocking et al., 2006b, Kong et al., 2009), but these estimates are based on small sample sizes with limited precision. In light of Australia’s future national chlamydia testing pilot program (Hocking et al., 2008b), there is an urgent need for reliable chlamydia prevalence estimates that can be used to both inform the design of the pilot and monitor its performance.

M. genitalium is another important sexually transmitted pathogen that is associated with urethritis (Jensen et al., 1993), cervicitis (Lusk et al., 2010), endometritis (Cohen et al., 2002), pelvic inflammatory disease (PID), tubal factor infertility (Clausen et al.,
2001), and an increased risk of HIV transmission (Mavedzenge, 2009) which has also been reported in women from Australian sexual health centres (Lusk et al., 2010). Recent studies internationally report varying prevalence estimates for *M. genitalium* in women; 0.8% (95% CI: 0.4, 1.6) among 18-27 year old sexually-active women in the US (Manhart et al., 2007); 2.3% (95% CI: 1.3, 3.2) in 21-23 year old women in Denmark (Andersen et al., 2007); and 3.4% (95% CI: 2.7, 4.3) in sexually-active university students in the UK (Hay et al., 2009). Freezing the specimens can reduce the overall sensitivity of the test and lead to an underestimation of prevalence which might account for the lower prevalence in the samples in the US study (Carlsen and Jensen, 2010). Generally, *M. genitalium* prevalence has been found to be consistently lower than chlamydia in the same population (Andersen et al., 2007, Manhart et al., 2007, Hay et al., 2009), although recent results from testing women in an Australian termination of pregnancy service has found similar prevalence estimates for *M. genitalium* [prevalence estimate: 4.1% (95% CI: 1.8, 6.3)] and chlamydia [prevalence estimate 5.2% (95% CI: 2.3, 8.0)] (Marceglia et al., 2010). Otherwise, in Australia, *M. genitalium* testing is not widely available and there are no population data available for women. Understanding the burden of disease that might be attributable to *M. genitalium* in young Australian women is necessary to inform clinical practice and policy and will contribute to the discussion about the introduction of a commercially available test.

### 6.2 Aims

This chapter aims to describe and compare the epidemiological characteristics of chlamydia and *M. genitalium* in the CIRIS cohort of sexually active young women at the commencement of the study in order to gain insights into the epidemiology and transmission dynamics of these two infections within the same population. This chapter also aims to determine prevalence estimates and the clinical and behavioural factors associated with both infections and aims to identify chlamydia serotypes and organism loads for both infections exploring any associations with these factors.
6.3 Methods

6.3.1 Recruitment

The data presented in this chapter were collected as part of a longitudinal study of young women - the Chlamydia Incidence and Re-infection Rates Study (CIRIS). The primary aim of CIRIS was to measure chlamydia prevalence, incidence and re-infection during a 12 month study period and a secondary aim was to measure *M. genitalium* prevalence, incidence and re-infection. Women in the study were recruited from 29 primary health clinics (including general practice, sexual health and family planning clinics) in three states in Australia between May 2007 and August 2008. Women were eligible for inclusion if they were aged 16 to 25 years, had ever had vaginal sex, were not pregnant at recruitment, were competent to understand written English, and were able to be contacted by post within Australia during the 12-month study. A dedicated research assistant recruited consecutive women attending the clinic during a six week period. Informed consent was obtained for each participant prior to their recruitment into the study. The methods are described in detail in Chapter 5. The prevalence estimates and other data presented here are based on testing and data collection at the time of recruitment (baseline).

Women were asked to complete a self-administered questionnaire at the time of recruitment. This collected demographic, sexual behaviour data (including number of sex partners), and recent antibiotic and contraceptive use. It also included questions about the presence of any genital symptoms during the month prior to recruitment, including abnormal vaginal discharge and pelvic pain (Appendix U).

6.3.2 Testing

At baseline, each participant provided two self-collected vaginal swabs. One swab was tested for chlamydia by the clinic’s preferred pathology testing laboratory using nucleic acid amplification techniques (NAAT). The second swab, a flocked swab (www.microrheologics.com), was forwarded to Royal Women’s Hospital (RWH), Melbourne, Victoria for *M. genitalium* testing. The swabs were analysed further if
they tested positive, including quantifying the organism load of both chlamydia and *M. genitalium* and identifying the serovar for chlamydia positive specimens.

*M. genitalium* testing was conducted by rotating the swab in 400μl of PBS and 200μl was extracted using the automated MagNA Pure LC (Roche Molecular Biochemical, Mannheim, Germany) with the DNA Isolation Kit 1 protocol. Detection of *M. genitalium* was performed using the extracted DNA amplified by real-time PCR targeting a 517bp region of the 16S rRNA gene (Yoshida et al., 2002) and human beta-globin was used as a measure of sample adequacy as an internal control to detect the presence of possible inhibitors (Resnick et al., 1990). Any remaining specimen was stored at -80°C. All the participants were tested for *M. genitalium* at baseline and 12 months throughout the study period.

The *M. genitalium* test results were validated by retesting a random sample of 845 stored study samples from 761 women from the study including all *M. genitalium* positive samples. The samples had been stored at -80°C for a median of 25 months (average=22.2; range=1-29 months). The samples were tested at the conclusion of the study using a real-time PCR assay that was directed at the adhesion protein gene (MgPa) (Jensen et al., 1991, Jensen et al., 2004). Of the samples tested, 38 (88.4%) were positive using both assays, 2 (4.7%) by the MgPa assay only, and 3 (7.0%) by the 16S rRNA assay only. A total of 43 samples were found to be positive by one or both assays giving a sensitivity of 95.0% (95% CI: 0.831 to 0.994) and specificity of 99.6% (95% CI: 0.989 to 0.999) when comparing the 16S rRNA gene assay to the MgPa assay; or a kappa score of 0.935 (95% CI: 0.879 to 0.992). This indicated there was virtually no difference between the two assays (Twin et al., 2011). At baseline, women were given a positive *M. genitalium* diagnosis if they tested positive using either assay; this accounted for any possible DNA degradation of the sample during the storage period, and also, in the absence of a clear gold standard for the diagnosis of *M. genitalium*, it was clinically important to treat all women who were *M. genitalium* positive by either assay.
6.3.3 Organism load and serovars

Quantification of chlamydia load was determined by a quantitative PCR (qPCR) system targeting the *omp1* gene using published methodology (Stevens et al., 2010). The chlamydial load in each tested sample was quantified by comparing the crossing-threshold of each sample to the crossing-threshold of a standard curve constructed by amplifying different known copy numbers of the *omp1* gene. This method also determined whether any mixed infections were present, and identified the chlamydia serovar(s) of each infection through a series of qPCR assays using serovar-specific probes. Confirmation of each chlamydia serovar, and detection of genotypic variants were determined by DNA sequencing across all four variable domains of the *omp1* gene that encodes for the antigenic major outer membrane protein as previously described (Stevens et al., 2004).

The *M. genitalium* concentration of each sample was quantified using a qPCR (TaqMan® MGB Probe) assay targeting the MgPa gene (Edberg et al., 2008). Quantification was carried out using a LightCycler 480 Real-Time PCR System (Roche Diagnostics, Mannheim, Germany) by comparing the quantification cycle of each sample to the quantification cycle of a standard curve constructed by amplifying different known copy numbers of target gene. Organism loads were presented as copies per swab.

6.3.4 Management of participants

Women who tested positive for chlamydia at baseline were managed by the clinic from where they were recruited. The treating clinicians were provided with up-to-date chlamydia treatment guidelines (1g of azithromycin for uncomplicated chlamydia infection), partner notification material (Australasian College of Sexual Health Physicians, Accessed 2005 [online] http://www.ashm.org.au), information about websites that could be used for partner notification (www.letthemknow.org.au), and access to a free call telephone number for clinicians to call a sexual health physician if they required clinical advice. All clinics were supplied with azithromycin to treat the positive baseline patients free of charge.
Women who tested positive at baseline were followed up three months later by the research team which included sending a questionnaire to determine if treatment had been taken and if partner(s) had been treated (Appendix W), and a swab to re-test for chlamydia.

All women who tested positive for *M. genitalium* were managed by the research team and a sexual health physician. The research team contacted the woman as indicated on their consent form, discussed their result and asked some preliminary clinical questions (Appendix LL). Then a telephone consultation was coordinated with a sexual health physician, and the medication, partner notification letter and patient information form about *M. genitalium* were sent out (Figure 6-1). Clinical symptoms and partner notification were discussed and support material and partner notification letters were provided (Appendix S and Appendix EE). Treatment with 1g of azithromycin (Mena et al., 2009) was provided if there were no symptoms to suggest PID. Women were sent a second vaginal swab and a questionnaire (Appendix NN) ‘a test-of-cure’ one month following treatment. If the test-of-cure was positive and no risk of re-infection was identified via telephone consultation, the patient was treated with 400mg moxifloxacin daily for 10 days (Bradshaw et al., 2008), otherwise a repeat 1g dose of azithromycin was prescribed (Bradshaw et al., 2008) and another test-of-cure was done a month later.

Women who tested negative were sent a letter to inform them (Appendix MM) and if a woman had indicated that she preferred to be treated and managed by her own clinician this was coordinated.
6.3.5 Data collection

Women were asked to complete a self-administered questionnaire at recruitment. This collected demographic, sexual behaviour data (including number of sex partners), and recent antibiotic and contraceptive use. It also included questions about the presence of any genital symptoms during the month prior to recruitment, including abnormal vaginal discharge and pelvic pain.
6.3.6 Statistical methods

Power calculations assuming a design effect of 2 suggested that a sample size of 1,000 would be sufficient to generate standard error of 0.8% and 0.6% for prevalence estimates of 5% and 2% respectively.

Data were analysed using STATA version 11.1 (Stata Corporation, 2009). All analyses were adjusted for clustering at the clinic level and for type of clinic (general practice versus sexual health/family planning clinic). Prevalence estimates and 95% confidence intervals (95% CIs) were calculated and odds ratios (OR) and robust standard errors were calculated to explore associations with chlamydia and M. genitalium. For the analysis of the associations with chlamydia or M. genitalium and symptoms, only women who had tested positive for one infection were included and women with a co-infection were excluded. Associations with organism load for both chlamydia and M. genitalium were explored using linear regression and organism load was logarithm transformed because of the skewed distribution of the raw data.

Ethics approval to conduct this study was obtained from ten Human Research Ethics Committees throughout Australia.

6.4 Results

6.4.1 Characteristics of sample

Overall, 66% of consecutive, eligible women agreed to participate in the study (n=1116) with two-thirds recruited from general practice clinics (20 out of 29 clinics); 1110 women were recruited into the sub-study. The participants had a median age of 21 years, and when compared with the most recent Australian census data for women in the same age group, the study participants were more likely to be Australian-born (89% versus 79%, \(p<0.01\)) (Australian Bureau of Statistics, 2006) and more well-educated (tertiary degree 44% versus 21% \(p<0.01\)) (Australian Bureau of Statistics, 2006). Compared with women of the same age in the ‘Australian Study of Health and Relationships’ (a nationally representative sexual behaviour survey), women in our study were more likely to report having had three or more sexual
partners in the last 12 months (33% versus 9.5%, \( p<0.01 \)) (Smith et al., 2003). There were no differences for all other reported demographics according to the Australian Bureau of Statistics census data (Australian Bureau of Statistics, 2006). More information about the sample is presented in Chapter 5.

### 6.4.2 Prevalence estimates and associations

A total of 55 women tested positive for chlamydia [prevalence: 4.9% (95% CI: 2.9, 7.0)] and 27 tested positive for \( M. \ genitalium \) [prevalence: 2.4% (95% CI: 1.5, 3.3)]. Two women were co-infected with both chlamydia and \( M. \ genitalium \) [0.2% (95% CI: 0.0, 0.4)]. Prevalence estimates were higher among women recruited from sexual health clinics and family planning clinics than from general practice clinics for both chlamydia [7.9% (95% CI: 4.1, 11.8) compared with 3.4% (95% CI: 1.5, 5.3) \( (p=0.01) \)], and \( M. \ genitalium \) [4.0% (95% CI: 2.7, 5.3) versus 1.6% (95% CI: 0.7, 2.6) \( (p<0.01) \)] respectively (Table 6-1).

Chlamydia was associated with younger age [AOR: 0.9 (95% CI: 0.8, 1.0)] whereas \( M. \ genitalium \) was not. \( M. \ genitalium \) was associated with Indigenous status [AOR: 4.5 (95% CI: 1.4, 14.9)] \( (n=2) \), but chlamydia was not. A strong association was found between chlamydia infection and increased numbers of sexual partners. The odds of testing positive for chlamydia were six times greater for women who had had two or more sexual partners in the preceding year compared with women with fewer partners [AOR: 6.4 (95% CI: 3.6, 11.3)], however the association was not as strong for \( M. \ genitalium \) [AOR: 2.2 (95% CI: 1.0, 4.6)]. In contrast, the odds of infection associated with the reported number of unprotected sex partners was far greater for \( M. \ genitalium \) [≥3 unprotected sex partners in the last 12 months: AOR: 16.6 (95% CI: 2.0, 138.0)] than for chlamydia [≥3 unprotected sex partners in the last 12 months: AOR: 3.1 (95% CI: 1.0, 9.5)]. Having being diagnosed with chlamydia in the past was also associated with testing positive for chlamydia [AOR: 2.0 (95% CI: 1.1, 3.9)], but not for \( M. \ genitalium \) (Table 6-1).

Self-reported use of any antibiotic in the prior two months was protective against chlamydia [AOR: 0.4 (95% CI: 0.2, 1.0)], but was not associated with \( M. \ genitalium \)
[AOR: 0.8 (95% CI: 0.3, 2.5)]. There were no associations with any other demographic characteristics collected (country of birth, employment status or education level) and chlamydia or *M. genitalium* (Table 6-1).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Characteristics n (%)</th>
<th>Chlamydia prevalence (95% CI) (no. positive/ no. total)</th>
<th>UOR&lt;sup&gt;d&lt;/sup&gt; (95% CI)</th>
<th>AOR&lt;sup&gt;e&lt;/sup&gt; (95% CI)</th>
<th>M. genitalium prevalence (95% CI) (no. positive/ no. total)</th>
<th>UOR (95% CI)</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&lt;sup&gt;a&lt;/sup&gt; (median age)</td>
<td></td>
<td>0.9 (0.8, 1.0)</td>
<td></td>
<td></td>
<td>1.7 (0.5, 5.2) (2/120)</td>
<td>1.0 (0.8, 1.3)</td>
<td>1.0 (0.8, 1.3)</td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Not Australian born</td>
<td>121 (11.5)</td>
<td>1.7 (0.4, 6.7) (2/121)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.8 (0.1, 6.0) (1/25)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Australian born</td>
<td>934 (88.5)</td>
<td>5.4 (3.5, 8.1) (50/934)</td>
<td>3.1 (0.6, 14.7)</td>
<td></td>
<td>1.0 (0.1, 18.0) (2/120)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indigenous status</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Not indigenous</td>
<td>1059 (97.7)</td>
<td>4.8 (3.2, 7.3) (51/1059)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.4 (1.4, 3.4) (25/1059)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Indigenous</td>
<td>25 (2.3)</td>
<td>4.0 (0.5, 27.2) (1/25)</td>
<td>1.0</td>
<td>1.0</td>
<td>8.0 (2.4, 23.2) (2/25)</td>
<td>3.6 (0.9, 13.5)</td>
<td>4.5 (1.4, 14.9)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
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<tr>
<td>up to year 12&lt;sup&gt;f&lt;/sup&gt;</td>
<td>609 (56.1)</td>
<td>5.9 (2.9, 9.9) (36/609)</td>
<td>1.0</td>
<td>1.0</td>
<td>3.1 (1.8, 4.4) (19/604)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Tertiary</td>
<td>477 (43.9)</td>
<td>3.6 (1.4, 5.7) (17/477)</td>
<td>0.6 (0.3, 1.2)</td>
<td>0.6 (0.3, 1.3)</td>
<td>1.7 (0.4, 2.9) (8/476)</td>
<td>0.5 (0.2, 1.1)</td>
<td>0.6 (0.3, 1.2)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Unemployed/Not working</td>
<td>418 (38.5)</td>
<td>4.8 (1.8, 7.8) (20/418)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.4 (0.7, 4.1) (10/416)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Employed</td>
<td>668 (61.5)</td>
<td>4.9 (2.7, 7.1) (33/668)</td>
<td>1.0 (0.6, 1.9)</td>
<td>1.0 (0.5, 1.9)</td>
<td>2.5 (1.6, 3.5) (17/664)</td>
<td>1.1 (0.5, 2.1)</td>
<td>1.0 (0.5, 2.1)</td>
</tr>
<tr>
<td>Clinic type</td>
<td></td>
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<tr>
<td>GP</td>
<td>738 (66.1)</td>
<td>3.4 (1.5, 5.3) (25/738)</td>
<td>1.0</td>
<td>N/A&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1.0 (0.7, 2.6) (12/735)</td>
<td>1.0</td>
<td>N/A&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>SHC/FP</td>
<td>378 (33.9)</td>
<td>7.9 (4.1, 11.8) (30/378)</td>
<td>2.5 (1.2, 4.9)</td>
<td></td>
<td>4.0 (2.7, 5.3) (15/375)</td>
<td>2.5 (1.4, 4.6)</td>
<td></td>
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<tr>
<td>No. partners last 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;2</td>
<td>553 (51.8)</td>
<td>1.3 (0.5, 2.1) (7/553)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.4 (0.6, 2.3) (8/551)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2+</td>
<td>515 (48.2)</td>
<td>8.5 (5.6, 11.5) (44/515)</td>
<td>7.3 (4.3, 12.2)</td>
<td>6.4 (3.6, 11.3)</td>
<td>3.7 (2.1, 5.3) (19/511)</td>
<td>2.6 (1.3, 5.3)</td>
<td>2.2 (1.0, 4.6)</td>
</tr>
<tr>
<td>Partners 12 months without condoms</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>301 (29.0)</td>
<td>3.0 (1.5, 6.1) (9/301)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.3 (0.0, 2.3) (1/299)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>1 - 2</td>
<td>599 (57.8)</td>
<td>4.3 (2.6, 6.6) (26/599)</td>
<td>1.5 (0.8, 2.9)</td>
<td>1.4 (0.7, 2.6)</td>
<td>2.5 (1.6, 3.9) (15/595)</td>
<td>7.7 (1.0, 62.4)</td>
<td>7.2 (0.9, 57.6)</td>
</tr>
<tr>
<td>3+</td>
<td>137 (13.2)</td>
<td>10.9 (6.4, 18.0) (20/216)</td>
<td>4.0 (1.6, 10.1)</td>
<td>3.1 (1.0, 9.5)</td>
<td>6.6 (3.7, 11.5) (9/137)</td>
<td>20.9 (2.6, 167.3)</td>
<td>16.6 (2.0, 138.0)</td>
</tr>
<tr>
<td>Past history of chlamydia diagnosis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>965 (89.4)</td>
<td>4.2 (2.2, 6.3) (41/965)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.4 (1.4, 3.4) (23/960)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>114 (10.6)</td>
<td>9.6 (5.1, 14.2) (11/114)</td>
<td>2.4 (1.2, 4.7)</td>
<td>2.0 (1.1, 3.9)</td>
<td>3.5 (0.3, 6.8) (4/113)</td>
<td>1.5 (0.6, 4.0)</td>
<td>1.3 (0.4, 3.6)</td>
</tr>
<tr>
<td>Antibiotics in last 2 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>807 (74.0)</td>
<td>5.7 (3.0, 8.4) (48/833)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.5 (1.6, 3.9) (21/802)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>283 (26.0)</td>
<td>2.5 (0.5, 4.4) (7/283)</td>
<td>0.4 (0.2, 1.0)</td>
<td>0.4 (0.2, 1.0)</td>
<td>2.1 (0.8, 5.5) (6/282)</td>
<td>0.8 (0.3, 2.6)</td>
<td>0.8 (0.3, 2.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> age as a continuous variable, <sup>b</sup> CI: confidence interval. <sup>c</sup> no.=number, <sup>d</sup> Unadjusted odds ratio. <sup>e</sup> Adjusted Odd Ratio: Adjusted for clinic type the participants were recruited from. <sup>f</sup> Year 12 is the final year of secondary education in Australia. <sup>g</sup> Data not available.
Chlamydia was not associated with any self-reported genital symptoms but *M. genitalium* was associated with self-reported ‘abnormal vaginal discharge’ [AOR: 2.1 (95% CI: 1.1, 4.0)] (Table 6-2). Women testing positive for *M. genitalium* reported a greater number of symptoms on average than women testing positive for chlamydia, although this did not reach statistical significance 91.9 symptoms versus 1.3; *p*=0.2) (Table 6-2). Two of the women who had tested positive for *M. genitalium* (and negative for chlamydia) had been clinically diagnosed as having pelvic inflammatory disease, and one was diagnosed with muco-purulent cervicitis prior to knowing their *M. genitalium* status.
Table 6-2  Associations between self-reported symptoms and infection with *Chlamydia trachomatis* or *Mycoplasma genitalium* (*M. genitalium*).

<table>
<thead>
<tr>
<th>Symptoms in last month</th>
<th>Chlamydia % (95% CI) (n/no. women)</th>
<th>UOR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
<th>AOR&lt;sup&gt;c&lt;/sup&gt; (95% CI)</th>
<th>M. genitalium % (95% CI) (n/no. women)</th>
<th>UOR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
<th>AOR&lt;sup&gt;c&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal discharge</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>4.6 (2.9, 7.2) (40/840)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.8 (1.1, 2.8) (15/836)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>4.8 (2.9, 7.8) (12/249)</td>
<td>1.0 (0.6, 1.7)</td>
<td>0.9 (0.6, 1.5)</td>
<td>4.0 (1.8, 6.2) (10/248)</td>
<td>2.3 (1.2, 4.6)</td>
<td>2.1 (1.1, 4.0)</td>
</tr>
<tr>
<td>Abnormal vaginal odour</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>4.3 (2.8, 6.5) (40/902)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0 (1.3, 3.2) (18/898)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>6.4 (3.0, 13.4) (12/187)</td>
<td>1.5 (0.7, 3.3)</td>
<td>1.4 (0.6, 3.1)</td>
<td>3.8 (1.7, 8.0) (7/186)</td>
<td>1.8 (0.7, 4.5)</td>
<td>1.7 (0.7, 4.2)</td>
</tr>
<tr>
<td>Burning when passing urine</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>4.3 (2.7, 6.6) (39/888)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.3 (1.6, 3.3) (20/883)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>6.5 (3.6, 11.4) (13/201)</td>
<td>1.5 (0.9, 2.8)</td>
<td>1.5 (0.8, 2.6)</td>
<td>2.5 (1.2, 5.3) (5/201)</td>
<td>1.0 (0.5, 2.2)</td>
<td>1.0 (0.5, 2.1)</td>
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<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>4.6 (3.0, 6.9) (36/770)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0 (1.2, 3.1) (15/762)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>5.0 (2.8, 8.8) (16/319)</td>
<td>1.1 (0.7, 1.8)</td>
<td>1.1 (0.6, 1.8)</td>
<td>3.1 (1.8, 5.4) (10/318)</td>
<td>1.6 (0.8, 3.4)</td>
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<td>Dyspareunia</td>
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<td></td>
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<td></td>
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<tr>
<td>No</td>
<td>5.1 (3.2, 7.9) (45/849)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.1 (1.4, 3.1) (18/860)</td>
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<td>Yes</td>
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<td>0.6 (0.3, 1.4)</td>
<td>0.6 (0.2, 1.4)</td>
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<tr>
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<td>4.8 (3.2, 7.3) (43/874)</td>
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<td>1.0</td>
<td>2.0 (1.3, 3.0) (17/865)</td>
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<td>1.8 (0.7, 4.4)</td>
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<td>Number of symptoms</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>0</td>
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<td>1.0</td>
<td>1.0</td>
<td>1.3 (0.6, 2.6) (6/456)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
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<td>1</td>
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<td>1.1 (0.6, 2.1)</td>
<td>2.7 (1.4, 5.2) (6/222)</td>
<td>2.1 (0.8, 5.6)</td>
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<td>2</td>
<td>6.4 (3.2, 12.2) (13/204)</td>
<td>1.6 (0.8, 3.2)</td>
<td>1.5 (0.7, 3.0)</td>
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<td>1.9 (0.5, 7.0)</td>
<td>1.8 (0.5, 6.4)</td>
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<tr>
<td>3</td>
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<td>1.3 (0.5, 3.4)</td>
<td>1.2 (0.5, 3.1)</td>
<td>4.3 (1.7, 9.9) (4/94)</td>
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<td>3.1 (0.8, 11.2)</td>
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<td>4</td>
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<td>1.5 (0.2, 10.8) (1/65)</td>
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<td>5</td>
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<td>0.7 (0.1, 4.9)</td>
<td>10.0 (3.3, 26.5) (3/30)</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td>0.0 (0/11)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> CI: confidence interval.  
<sup>b</sup> Unadjusted odds ratio.  
<sup>c</sup> Adjusted Odd Ratio: Adjusted for clinic type the participants were recruited from.
6.4.3 Self-reported symptoms

An audit was done comparing clinicians’ notes with self-reported symptoms on the questionnaire. This revealed that the number of self-reported symptoms on a questionnaire was much higher (163 symptoms) than the number of symptoms being detailed than from clinician-elicited symptoms on the same day (58 symptoms) with a complete concordance in only 44% of cases.

6.4.4 Infectious load and serovars

Overall, 52 chlamydia positive samples and 22 M. genitalium positive samples were analysed to determine their respective infectious loads. The median M. genitalium organism load was 100 times lower (5.7 x 10^4/swab) than the median chlamydia organism load (5.6 x 10^6/swab) (p<0.01), and the quantitative range reported for M. genitalium was smaller (1.9 x 10^3/swab to 2.1 x 10^6/swab) than for chlamydia (4.2 x 10^3/swab to 2.6 x 10^9/swab) (Figure 6-2)

![Figure 6-2](image_url)  
Chlamydia trachomatis (chlamydia) organism load and Mycoplasma genitalium (M. genitalium) organism load per swab (log).
The chlamydia serovar was identified for 52 of 55 positive chlamydia specimens and 27 (51.9%) of these were serovar E and shared a 100% homology in their \textit{omp1} gene sequencing (Table 6-3). No cases of mixed chlamydia serovar were detected.

<table>
<thead>
<tr>
<th>Table 6-3</th>
<th>Serovars detected in \textit{Chlamydia trachomatis} positive samples. \textit{a} – based on reference strain \textit{omp1} sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chlamydia genotype</strong></td>
<td><strong>Frequency N (%)</strong></td>
</tr>
<tr>
<td>D</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>E</td>
<td>27 (49.0)</td>
</tr>
<tr>
<td>E variant\textsuperscript{b}</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>F</td>
<td>12 (21.8)</td>
</tr>
<tr>
<td>G</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>G variant\textsuperscript{c}</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Ia</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>J</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>K</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td>N/A\textsuperscript{d}</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
</tr>
</tbody>
</table>

\textit{b} – E variant has 100% homology to Genbank sequence GU903922 (\textit{C. trachomatis} strain 1969 from Australian MSM population)
\textit{c} – G variant has 100% homology to Genbank sequence FJ261928 (G/IU-FW0267)
\textit{d} - N/A: serovar unable to be determined.
The organism load was significantly higher for serovar D than serovar E ($p=0.04$) and higher for serovar E than for serovar F ($p=0.06$). No other differences were found (Figure 6-3).

![Figure 6-3](image)

**Figure 6-3**  *Chlamydia trachomatis* organism load per swab (log) for each chlamydia serovar detected.

### 6.4.5 *M. genitalium* test-of-cure

Of the 27 women who were sent a second swab and a questionnaire in the mail for an *M. genitalium* test-of-cure one month after azithromycin treatment, 20 (74%) returned swabs for testing. Of these, 17 tested negative, and three (15%) tested positive. The three women with persistent *M. genitalium* had further telephone consultations with a sexual health clinician who after a thorough consultation, determined they all had adhered to treatment, two had had partners concurrently treated with 1g azithromycin, and one had no sexual contact since her diagnosis. These women were considered likely to have had treatment failure rather than a new infection [azithromycin failure: 15% (95% CI: 3.2, 37.9)] and were prescribed 400mg moxifloxacin daily for ten days. A second test-of-cure was performed one
month later on two of the three women and both were negative, but the third woman failed to return a second test-of-cure.

6.5 Discussion

6.5.1 Key findings

This chapter presents the largest community-based estimate of chlamydia prevalence among young Australian women and Australia’s first *M. genitalium* prevalence survey. Consistent with previous international reports, we found the chlamydia prevalence (4.9%) was higher than the *M. genitalium* prevalence (2.4%) among young women (Andersen et al., 2007, Manhart et al., 2007, Hay et al., 2009). We also found some important clinical and epidemiological differences between chlamydia and *M. genitalium* in this cohort, suggesting there might be different transmission dynamics for both infections.

Firstly, it is possible that *M. genitalium* is less infectious than chlamydia requiring a greater “exposure” or direct genital or cervical contact to acquire *M. genitalium*. This is supported by the 100 fold lower organism load among samples from women with *M. genitalium* compared with chlamydia, and the finding that *M. genitalium* was more strongly associated with unprotected sex than chlamydia. Clearly, further partner studies are needed to investigate the transmission dynamics for *M. genitalium* and chlamydia to determine if and how transmission dynamics differ.

The clinical features associated with *M. genitalium* and chlamydia also differed, *M. genitalium* was associated with vaginal discharge, but chlamydia showed no associations with any reported symptoms. Studies of the association between *M. genitalium* and specific genital symptoms have been somewhat conflicting with some studies determining an association between *M. genitalium* and genito-urinary symptoms including vaginal discharge and dysuria (Pepin et al., 2005), and other studies finding no association with symptoms (Anagrius et al., 2005). Overall, published data suggests that *M. genitalium* appears to be somewhat similar to chlamydia (Gomes et al., 2006, Korte et al., 2006, Anagrius et al., 2005, Andersen et al., 2007). Further to this, no associations were found between organism load and
reported symptoms for either chlamydia or *M. genitalium*, which was also consistent with the other studies (Gomes et al., 2006).

Younger women were more likely to have a prevalent chlamydia infection which is consistent with other research (Hocking et al., 2006b), although younger age was not associated with *M. genitalium* infection.

Antibiotic use in the two months prior to being tested demonstrated a protective effect against chlamydia but not for *M. genitalium*. This is most likely because chlamydia has been shown to be sensitive to a number of commonly prescribed antibiotics (O'Rourke et al., 2009), and *M. genitalium* is less likely to be sensitive to the same antibiotics as it is resistant to a number of commonly prescribed antibiotics (Mena et al., 2009, Bradshaw et al., 2006b, Bjornelius et al., 2008, O'Rourke et al., 2009).

We also found that *M. genitalium* but not chlamydia was associated with Indigenous status (Australian Aboriginal and Torres Strait Islander women). The number of Indigenous women in our study (n=25) limited further exploration in the analysis. Nonetheless, these are the first prevalence estimates for *M. genitalium* in Indigenous Australian women and given that STI rates are generally higher in Indigenous women in Australia this is not a surprising *M. genitalium* finding (National Centre in HIV Epidemiology and Clinical Research The University of New South Wales, 2010).

Unlike other studies, we did not find any associations between chlamydia organism load and age or past history of chlamydia infection (Batteiger et al., 2010, Gomes et al., 2006). We did find evidence to suggest that chlamydia serovar was associated with organism load. However, this was based on a small number of cases. Nevertheless, given that others have not found any association between serovar and organism load (Gomes et al., 2006), and uncertainty remains as to whether serovar is associated with disease severity, further studies with larger sample sizes are needed to investigate serovar and organism load.
6.5.2 Limitations and strengths

There were a number of limitations to our study. Firstly, our sample had a higher proportion of Australian-born, well-educated and sexually-active women than the general background population in Australia for the same age (Australian Bureau of Statistics, 2006, Smith et al., 2003), however, these are common findings in similar research studies investigating sexual health issues (Smith et al., 2009, Hocking et al., 2006b). It is difficult to assess the impact this may have had on our prevalence estimates because increased number of partners is often associated with increased prevalence (LaMontagne et al., 2004b, Hocking et al., 2006b) and higher education levels tend to be associated with reduced prevalence. We also were unsuccessful in recruiting 34% of the eligible women who were approached in the clinics, and while there were no associations between age and participation, we have no other information about the women we were unable to recruit. Nevertheless, this participation compares favourably with other chlamydia prevalence surveys (Fenton et al., 2001a, Miller et al., 2004, Low et al., 2004a).

Another limitation was relying on self-reported genital symptoms; these have been found to be highly subjective, non-specific and frequently poorly associated with cervical STIs. Self-reporting of genital symptoms on questionnaires also do not always correlate well with clinician elicited symptoms (Lister et al., 2008). We audited the clinical notes of a sub-set of 100 women and found very poor correlation with genital symptoms reported in the clinical notes. Women were far more likely to self-report symptoms on their study questionnaire than were recorded by their clinicians in their clinical notes at the time of recruitment. It is possible that clinicians record only clinically relevant symptoms at the time of the consultation or that women are uncomfortable telling their clinicians genital symptoms and more comfortable disclosing symptoms on a questionnaire. A combination of both these factors might contribute to the discordance in our audit.

There were limitations to the organism load analysis. Samples were self-collected and therefore the equal efficiency of sampling could not be assured, and as positive samples were subjected to a number of assays, the mean organism loads were not
able to be normalized to number of cells per sample. However, we did find that the serovars detected in our study were consistent with those reported in international data (serovar E followed by serovar F) (Gomes et al., 2006, Morré et al., 2000).

There were a number of strengths to this study including the large sample size, the high participation rate of 66% and the broad range of geographical locations and socio-economic areas from where the women were recruited. Also, considering 66% of the women were recruited from general practice, and between 80 to 90% of young Australian women visit a general practice clinic each year (Hocking et al., 2008b), the study method chosen was likely to provide a broadly representative sample.

6.5.3 Comparisons with other research

The prevalence of chlamydia in our study was higher (4.9%) compared with the only other Australian population-based chlamydia prevalence study for women in the same age range (3.7%) (Hocking et al., 2006b) but was similar to a small community-based study (Kong et al., 2009), and other studies involving young women (Williams et al., 2003, Heal et al., 2002). Importantly these data suggest chlamydia prevalence is still somewhat lower in Australia than some other countries, most notably the UK (Pimenta et al., 2003b).

These are the first population data on M. genitalium prevalence in Australia and these findings are very similar to the population data to date from international studies[2.3% (95% CI: 1.3, 3.2)] (Andersen et al., 2007), and [3.4% (95% CI: 2.7, 4.3)] (Hay et al., 2009), but are somewhat higher than a study in the U.S [0.8% (95% CI: 0.4, 1.6)] (Manhart et al., 2007). This result is less than the prevalence found at the pregnancy termination service in Melbourne [4.1% (95% CI: 1.8, 6.3)] although not statistically, however these women were older than our cohort (12 to 46 years old) and possibly a higher risk population (Marceglia et al., 2010).
6.5.4 Implications of these results

As increasing evidence supports a role for *M. genitalium* in PID and tubal factor infertility, *M. genitalium* is emerging as an important treatable STI in women. Our estimate for treatment failure was consistent with current Australian research which reports that 1g of azithromycin appears to be 85% effective at best for uncomplicated *M. genitalium* (Bradshaw et al., 2008, Bradshaw et al., 2006b). Further, *M. genitalium* is less responsive to the doxycycline and cefoxitin based regimens used in the presumptive treatment with in women with PID (Haggerty, 2008). Clearly these data provide evidence that *M. genitalium* is not uncommon in young women in Australia, and impetus is needed for the commercialization of a diagnostic assay to improve the management of *M. genitalium*. This study also contributes to understanding the *M. genitalium* organism load in clinical samples. However, further studies are needed to be done to understand this compared with other STIs such as chlamydia and if there is any relationship between copy number and pathogenicity.

6.6 Conclusions

This is the first large and broadly representative chlamydia prevalence survey and first *M. genitalium* prevalence survey in Australian women. Chlamydia prevalence was high in young sexually-active women in Australia and largely asymptomatic, supporting the need for further chlamydia control activities. There is also a significant burden of *M. genitalium* in this population, but importantly, this study identified that there are important differences in the epidemiology of chlamydia and *M. genitalium* and possibly in the transmission dynamics of these two infections. This is important information which contributes to the scant population data on *M. genitalium*, an emerging pathogen in young women.
CHAPTER 7.

THE INCIDENCE OF GENITAL CHLAMYDIA TRACHOMATIS IN A COMMUNITY BASED SAMPLE OF YOUNG AUSTRALIAN WOMEN

7.1 Introduction

*Chlamydia trachomatis* (*‘chlamydia’*) is the most commonly notified sexually transmitted infection (STI) in Australia. Both men and women can be infected by chlamydia causing urethritis and epididymitis in men and cervicitis in women (Schachter and Stephens, 2008, Peipert, 2003, Jones, 1995, Paavonen et al., 1985). If left untreated, chlamydia can lead to upper genital tract infections including pelvic inflammatory disease (PID) with tubal factor infertility being the most serious sequelae of an untreated chlamydia infection (Peipert, 2003).

Chlamydia incidence estimates among women vary according to the population. In one study, the incidence among women recruited from general practice clinics in the UK was estimated at 4.9 (95% CI: 2.7, 8.8) per 100 person years, however the incidence was higher in women recruited from family planning clinics [6.4 (95% CI: 4.2, 9.8) per 100 women years] and even higher again in women recruited from genitourinary medicine clinics (sexual health clinics) [10.6 (95% CI: 7.4, 15.2) per 100 women years] (LaMontagne et al., 2007). High incidence rates have also been reported among women from a sexual health clinic in Denver [11.4 per 100 person years] (Rietmeijer et al., 2002) and up to 34 per 100 women years among adolescents aged between 14 and 17 years old in the US (Batteiger et al., 2009).

Predictors for incident chlamydial infection in women have been identified and include younger age (Geisler et al., 2004, van den Broek et al., 2010, LaMontagne et al., 2007, Rietmeijer et al., 2002), having had a previous sexually transmitted infection (Geisler et al., 2004, LaMontagne et al., 2007, Rietmeijer et al., 2002, ...
Batteiger et al., 2009), and having an increased number of sexual partners (Geisler et al., 2004, Batteiger et al., 2009, Rietmeijer et al., 2002).

Re-infection with chlamydia is also very common (Batteiger et al., 2009). In the United Kingdom, a prospective cohort of 16 to 24 year old women had a re-infection rate of 29.9 (95% CI: 19.7, 45.4) per 100 person years in women recruited from general practice clinics, 22.3 (95% CI: 15.6, 31.8) per 100 person years from family practice clinics and 21.1 (95% CI: 14.3, 30.9) per 100 person years from GUM clinics. (LaMontagne et al., 2007). A recent review of the literature estimated a peak re-infection rate for chlamydia of 19% to 20% of cases, 8 to 10 months after an initial diagnosis, and a median re-infection rate of 13.9% (Hosenfeld et al., 2009).

Population based studies have reported a re-infection rate between 4 to 51 per 100 women years (Oh et al., 1996, Veldhuijzen et al., 2005, Xu et al., 2000, Schillinger et al., 2003) with a median of 13.9% (Hosenfeld et al., 2009). Other studies of specific groups have also reported re-infection rates ranging from 1.7% for a cohort of women from sexual health centres study in the US (Peterman et al., 2006), 7% in a multi-centred cohort study after 4 months (Whittington et al., 2001), 26.3% in female adolescents from school based clinics (Gaydos et al., 2008) to 34% in US army recruits although the latter were a ‘high risk’ group and retesting occurred after 30 days only (Barnett and Brundage, 2001). In a recent US longitudinal study Batteiger et al reported 84.2% of repeated infections were probable re-infections, however 13.7% were due to probable treatment failure, and 2.2% were persistent infections without treatment (Batteiger et al., 2009).

Predictors of re-infection are similar to predictors of incident chlamydia including younger age (Xu et al., 2000, Gaydos et al., 2008, Peterman et al., 2006), non-white women compared with white women in the US (Xu et al., 2000, Peterman et al., 2006) and the UK (LaMontagne et al., 2007) having a previous STI (Oh et al., 1996, Peterman et al., 2006, LaMontagne et al., 2007, Kjaer et al., 2000), having an increased number of sexual partners (Peterman et al., 2006, LaMontagne et al., 2007), or new sexual partner(s) (LaMontagne et al., 2007), and not having a current partner treated adequately (LaMontagne et al., 2007).
In Australia, follow up chlamydia testing after an initial infection to ensure there is no repeat infection is a clinical recommendation of the professional medical organisations (RACGP, 2009, Australasian College of Sexual Health Physicians, Accessed 2005 [online] http:www.ashm.org.au), which is particularly important since there is evidence that the risk of developing PID and other serious upper genital tract sequelae are associated with repeat infections (Hillis et al., 1993, Weström, 1994).

A follow up positive result can also be from an infection that has persisted despite appropriate treatment and no risk of chlamydia exposure after taking treatment (Horner, 2006). It can be difficult to determine unequivocally whether a repeat is a true re-infection or persistent infection following treatment failure or antibiotic resistance (Batteiger et al., 2009, Horner, 2006). Azithromycin resistance appears to be very rare for chlamydia infection (Dean et al., 2000, Horner, 2006), although it has been identified in vitro (Misyurina et al., 2004). The use of increasingly specific molecular typing, in particular genotyping and multi-locus sequence typing (MLST) (Jurstrand et al., 2010), will be important in identifying antibiotic resistant chlamydia as well as identifying true re-infections.

There are currently no published chlamydia incidence rates or re-infection rates for women in Australia and understanding the degree of infection and re-infection in Australia will help to determine the optimum testing interval recommended in young, sexually active Australian women.

7.1.1 Aims

This chapter primarily aims to determine Australia’s first chlamydia incidence estimates and re-infection rates among young women aged 16 to 25 years. The secondary aim for this chapter is to determine the clinical and epidemiological characteristics associated with incident chlamydia infection and re-infection, and determine any associations between organism load, serovar and clinical presentation.
7.2 Methods

7.2.1 Recruitment

Young Australian women were recruited into the Chlamydia Incidence and Re-infection Rates Study (CIRIS), a 12 month longitudinal study that primarily aimed to measure chlamydia incidence and re-infection rates in 16 to 25 year old women. Participants were recruited consecutively from primary health care clinics in south-eastern Australia and were eligible for the study if they were not pregnant at the time of recruitment, had ever had vaginal sex with a man, were able to understand written English, and were able to be contacted by post within Australia during the 12 month period of the study. The methods for the study are described in detail in Chapter 5.

7.2.2 Testing

At the time of recruitment (baseline), women were tested by their clinician’s pathology provider using either a self-collected vaginal swab or first pass urine specimen using nucleic acid amplification techniques (NAAT). During the study, women were tested for chlamydia at six months and 12 months using a self-collected swab (www.microrheologics.com) that was sent through the Australian postal system. For women who tested positive, it was important to retest them three months after they had been treated, so they were sent a follow up swab to test for re-infection in between. Positive tests were further analysed by the Royal Women’s Hospital (RWH), Melbourne, Victoria to determine the chlamydia serovar and organism load for each specimen.

7.2.3 Organism load

Quantification of chlamydia load was determined by a quantitative PCR (qPCR) system targeting the omp1 gene using published methodology (Stevens et al., 2010). The chlamydial load in each tested sample was quantified by comparing the crossing-threshold of each sample to the crossing-threshold of a standard curve constructed by amplifying different known copy numbers of the omp1 gene. This method also
determined whether any mixed infections were present, and identified the chlamydia serovar(s) of each infection through a series of qPCR assays using serovar-specific probes. Confirmation of each chlamydia serovar, and detection of genotypic variants were determined by DNA sequencing across all four variable domains of the \textit{omp1} gene that encodes for the antigenic major outer membrane protein as previously described (Stevens et al., 2004).

### 7.2.4 Management of participants

Women who tested positive at baseline were managed by their clinician. The research team provided free azithromycin and all the clinicians were given an education pack with the latest treatment guidelines (Workowski and Berman, 2006), partner notification support and a telephone number they could call to discuss clinical management of sexually transmissible infections with a sexual health physician (detailed in Chapter 5). If a participant tested positive during the course of the study, they were contacted by the research team who coordinated a telephone consultation with a sexual health physician. Medication was sent to the participant free of charge along with partner notification letters and information sheets about chlamydia (Appendix R and DD). Three months after treatment, another swab was sent which was tested and if positive the women were managed similarly. Treatment of 1g of azithromycin (Workowski and Berman, 2006) was provided unless the clinician decided more clinical intervention was required, which was then coordinated by the research and clinical staff to ensure the woman had a face to face consultation with a clinician.

### 7.2.5 Definitions for an incident infection, a re-infection, and a persistent infection

An incident infection was defined as any new infection during the study period; this included repeat infections if the previous infection had been treated effectively.

Any repeat infection during the study was classified as either a re-infection or a persistent infection using an algorithm (Figure 7-1) based the work done by Batteiger et al (Batteiger et al., 2009). In summary, if a woman had two infections with
different genotypes, then the second infection was considered a definite re-infection. If there had been a confirmed negative test between two positive test results, the second infection was also considered a definite re-infection. If women had taken and absorbed the correct antibiotics but had had unprotected sex with her untreated partners or new partners, the second infection was also considered a probable re-infection. A follow up positive result was considered a persistent infection if they had not been treated and/or the patient had always used condoms or they had abstained from sex between two positive results which was determined from their questionnaire data (Appendix W) and consultation with a clinician (Figure 7-1).
Figure 7-1  Algorithm to differentiate *Chlamydia trachomatis* re-infection and persistent infection; adapted from Batteiger et al (2009)
7.2.6 Data collection

Women were followed up at three-monthly intervals during a 12 month period. At recruitment, women were asked to complete a self-administered questionnaire which collected demographic data (Appendix U). Questionnaires were also sent at every three months that asked questions about sexual behaviour (number of sex partners and condom use), recent antibiotic and contraceptive use, and any pregnancies including termination and/or miscarriages. It also included questions about the presence of any recent genital symptoms, including abnormal vaginal discharge, abnormal vaginal odour, burning on urination, pelvic pain and abnormal bleeding. Questionnaires were different if a woman had previously tested positive including extra questions about treatment, partner notification and partner treatment (Appendix V and Appendix W). If women identified she had tested positive in between follow ups or she had taken antibiotics for any reason, a ‘release of information form’ was sent to allow the study team to contact the doctor for the release of these data (Appendix OO).

7.2.7 Statistical methods

Power calculations assuming a design effect of 2 suggested that a sample size of 1,000 would be sufficient to generate incidence estimates of 4 per 100 women years and a re-infection rate of 20% with adequate precision.

Data were analysed using STATA version 11.1 (Stata Corporation, 2009). Chlamydia incidence estimates and 95% confidence intervals (95% CIs) were calculated and adjusted hazard ratios (AHR) and robust standard errors were calculated to explore factors associated with chlamydia incident infection. Hazard ratios were adjusted for type of clinic from which the participant was recruited (general practice clinic or sexual health/family planning clinic), age, education level, recent antibiotic use, and numbers of sexual partners. Re-infection rates were calculated as a proportion of repeat infections where the women had had an infection previously during the study period. Persistent infections were calculated as a proportion of infections that presented twice without effective treatment in between during the study.
Ethics approval to conduct this study was obtained from ten Human Research Ethics Committees throughout Australia.
7.3 Results

7.3.1 Sample characteristics

A total of 1116 women agreed to participate in the study, 79\% of whom provided a specimen at the study end. A total of 1056 person years contributed to the analysis. Refer to Chapter 5 for more information on the sample and an analysis of women retained in the study.

7.3.2 Chlamydia incidence

Overall, during the follow up period, there were 50 positive results of which 47 were classified as incident infections [incidence rate of 4.4 per 100 women years (95\% CI: 3.3, 5.9)], one persistent infection [rate of 0.1 per 100 women years (95\% CI: 0.0, 0.7)], one false positive diagnosis [rate of 0.1 per 100 women years (95\% CI: 0.0, 0.7)] and one potential treatment failure [rate of 0.1 per 100 women years (95\% CI: 0.0, 0.7)].

Univariate analysis predicted that having more than two new sexual partners [HR: 4.2 (95\% CI: 2.0, 8.9)] was a predictor for having a chlamydia infection. Older age [HR: 0.3 (95\% CI: 0.1, 0.5)], being more well-educated [HR: 0.3 (95\% CI: 0.2, 0.6)] and recent use of antibiotics [HR: 0.1 (95\% CI: 0.0, 0.6)] were protective against having an incident infection. Multivariate analysis predicted that older age [AHR: 0.4 (95\% CI: 0.2, 0.8)] and recent use of antibiotics [AHR: 0.1 (95\% CI: 0.0, 0.6)] were protective factors against having an incident infection. Having two or more sexual partners during the study [AHR: 4.0 (95\% CI: 1.9, 8.6)] was a predictor of a chlamydia infection. Use of condoms, previously having chlamydia, and other demographic characteristics were not associated with incident infection (Table 7-1).

Women who reported having an ‘abnormal vaginal discharge’ [HR: 2.0 (95\% CI: 1.0, 4.1)], ‘vaginal odour’ [HR: 4.7 (95\% CI: 2.1, 10.4)], ‘burning on urination’ [HR: 2.0 (95\% CI: 1.0, 3.8)] or ‘abdominal pain’ [HR: 2.4 (95\% CI: 1.3, 4.3)] were more likely to have an incident chlamydia infection, although once adjusted for a diagnosis of Bacterial vaginosis only vaginal odour [AHR: 3.9 (95\% CI: 1.7, 9.0)] and abdominal
pain [AHR: 2.1 (95% CI: 1.1, 3.9)] were predictors of a chlamydia infection (Table 7-2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.(^2) with variable /No. cases (%)</th>
<th>Unadjusted Hazard Ratio (95% CI(^b))</th>
<th>Adjusted Hazard Ratio(^c) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 20</td>
<td>34/47 (72)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>21 to 25</td>
<td>13/47 (28)</td>
<td>0.3 (0.1, 0.5)</td>
<td>0.4 (0.2, 0.8)</td>
</tr>
<tr>
<td>Australian born</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1/47 (2)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46/47 (98)</td>
<td>5.7 (0.7, 45.1)</td>
<td></td>
</tr>
<tr>
<td>Area of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>19/47 (40)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>28/47 (60)</td>
<td>1.0 (0.6, 1.9)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to year 12</td>
<td>37/47 (79)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Tertiary</td>
<td>10/47 (21)</td>
<td>0.3 (0.2, 0.6)</td>
<td>0.6 (0.3, 1.2)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed/Not working</td>
<td>13/47 (28)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>34/47 (72)</td>
<td>1.6 (0.8, 3.1)</td>
<td></td>
</tr>
<tr>
<td>Clinic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>14/47 (30)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>SHC/FP</td>
<td>33/47 (70)</td>
<td>1.2 (0.7, 2.1)</td>
<td>1.6 (0.9, 2.9)</td>
</tr>
<tr>
<td>Number of new partners</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;2</td>
<td>19/47 (40)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2+</td>
<td>28/47 (60)</td>
<td>4.2 (2.0, 8.9)</td>
<td>4.0 (1.9, 8.6)</td>
</tr>
<tr>
<td>Recently had antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45/46 (98)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1/46 (2)</td>
<td>0.1 (0.0, 0.6)</td>
<td>0.1 (0.0, 0.6)</td>
</tr>
<tr>
<td>Use of hormonal contraception</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9/37 (24)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28/37 (76)</td>
<td>1.4 (0.7, 2.7)</td>
<td></td>
</tr>
<tr>
<td>Use of condoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24/46 (52)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22/46 (48)</td>
<td>1.5 (0.8, 2.8)</td>
<td></td>
</tr>
<tr>
<td>Previous positive chlamydia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40/45 (89)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5/45 (11)</td>
<td>1.0 (0.4, 2.9)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)No.= number; \(^b\) Confidence interval; \(^c\) Adjusted for age, education level, clinic type, number of sexual partners during the study, recent use of antibiotics.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>No.(^a) with symptom/No. cases (%)</th>
<th>Unadjusted Hazard Ratio (95% CI(^b))</th>
<th>Adjusted Hazard Ratio(^c) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>36/46 (78)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>10/46 (22)</td>
<td>2.0 (1.0, 4.1)</td>
<td>1.6 (0.9, 3.1)</td>
</tr>
<tr>
<td><strong>Odour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32/46 (70)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>14/46 (30)</td>
<td>4.7 (2.1, 10.4)</td>
<td>3.9 (1.7, 9.0)</td>
</tr>
<tr>
<td><strong>Burning with urination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>39/46 (85)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>7/46 (15)</td>
<td>2.0 (1.0, 3.8)</td>
<td>1.4 (0.7, 3.0)</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30/46 (65)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>16/46 (35)</td>
<td>2.4 (1.3, 4.3)</td>
<td>2.1 (1.1, 3.9)</td>
</tr>
<tr>
<td><strong>Dyspareunia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>37/46 (80)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>9/46 (20)</td>
<td>1.8 (0.9, 3.4)</td>
<td>1.6 (0.8, 3.4)</td>
</tr>
<tr>
<td><strong>Spotting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>39/46 (85)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>7/46 (15)</td>
<td>1.4 (0.6, 3.4)</td>
<td>1.2 (0.5, 3.1)</td>
</tr>
<tr>
<td><strong>Tested positive for BV(^d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30/37 (81)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>7/37 (19)</td>
<td>1.9 (0.9, 4.0)</td>
<td>1.9 (0.9, 4.0)</td>
</tr>
</tbody>
</table>

\(^a\)No. = number; \(^b\) Confidence interval; \(^c\) Adjusted for clinic type (general practice or sexual health centre/family planning clinic) and diagnosis of Bacterial vaginosis; \(^d\) Bacterial vaginosis; \(^e\) adjusted for clinic type (general practice or sexual health centre/family planning clinic) only.
7.3.3 Re-infection

There were 14 re-infections with a risk of re-infection of 20.3% (95% CI: 11.6, 31.7) for those who tested positive at least once during the study period; 7 were considered ‘definite’ re-infections in women who had had either a negative test in between two positive tests or different serovars for each test, and 7 were ‘probable’ re-infections in women who had had unprotected sex in between positive results. This corresponded to a re-infection rate of 20.0 (95% CI: 11.9, 33.8) per 100 women years.

No associations with re-infection and participant characteristics were found (Table 7-3). Women who had a re-infection were more likely to report having an ‘unusual vaginal odour’ [AHR: 5.9 (95% CI: 1.6, 23.1)] and ‘abdominal pain’ [AHR: 2.8 (95% CI: 1.1, 7.0)] but there were no other symptoms associated with re-infection (Table 7-4). These were not adjusted for Bacterial vaginosis as there were too few cases.
Table 7-3  Hazard ratios determining associations between characteristics and *Chlamydia trachomatis* reinfections.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. with variable/No. cases (%)</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 20</td>
<td>11/14 (79)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>21 to 25</td>
<td>3/14 (21)</td>
<td>0.4 (0.1, 1.1)</td>
<td>0.3 (0.1, 1.1)</td>
</tr>
<tr>
<td><strong>Australian born</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0/14 (0)</td>
<td>Insufficient data$^d$</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Yes</td>
<td>14/14 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Area of residence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>5/14 (36)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Metropolitan</td>
<td>9/14 (64)</td>
<td>2.1 (0.6, 7.1)</td>
<td>2.2 (0.7, 7.0)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to year 12</td>
<td>10/14 (71)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Tertiary</td>
<td>4/14 (29)</td>
<td>0.7 (0.3, 1.7)</td>
<td>0.7 (0.3, 1.6)</td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed/Not working</td>
<td>3/14 (21)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Employed</td>
<td>11/14 (79)</td>
<td>2.1 (0.8, 5.9)</td>
<td>2.0 (0.6, 6.0)</td>
</tr>
<tr>
<td><strong>Clinic type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>8/14 (57)</td>
<td>1.0</td>
<td>N/A</td>
</tr>
<tr>
<td>SHC/FP</td>
<td>6/14 (43)</td>
<td>0.5 (0.1, 1.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of new partners during study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>11/14 (79)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2+</td>
<td>3/14 (21)</td>
<td>0.4 (0.1, 1.0)</td>
<td>0.4 (0.1, 1.2)</td>
</tr>
<tr>
<td><strong>Recently had antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13/14 (93)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1/14 (7)</td>
<td>0.5 (0.1, 3.5)</td>
<td>0.5 (0.1, 3.4)</td>
</tr>
<tr>
<td><strong>Use of hormonal contraception</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1/11 (9)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>10/11 (91)</td>
<td>2.0 (0.4, 10.9)</td>
<td>2.7 (0.5, 14.0)</td>
</tr>
<tr>
<td><strong>Use of condoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9/14 (64)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>5/14 (36)</td>
<td>1.0 (0.3, 3.4)</td>
<td>1.1 (0.3, 4.6)</td>
</tr>
<tr>
<td><strong>Test positive for Bacterial vaginosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5/6 (83)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1/6 (17)</td>
<td>0.9 (0.1, 6.7)</td>
<td>1.0 (0.1, 9.8)</td>
</tr>
</tbody>
</table>

$^a$No. = number; $^b$ Confidence interval; $^c$ Adjusted for clinic type (general practice or sexual health centre/family planning clinic); $^d$ no cases with this variable.
Table 7-4  Hazard ratios determining associations between symptoms and *Chlamydia trachomatis* re-infection.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. with symptom/No. cases (%)</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10/14 (71)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>4/14 (29)</td>
<td>2.0 (0.7, 5.5)</td>
<td>1.8 (0.6, 4.8)</td>
</tr>
<tr>
<td>Odour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7/14 (50)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>7/14 (50)</td>
<td>5.2 (1.4, 18.9)</td>
<td>6.0 (1.6, 23.1)</td>
</tr>
<tr>
<td>Burning with urination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11/14 (79)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>3/14 (21)</td>
<td>2.0 (0.5, 8.7)</td>
<td>2.2 (0.5, 9.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9/14 (64)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>5/14 (36)</td>
<td>2.5 (1.0, 5.9)</td>
<td>2.8 (1.1, 7.0)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11/14 (79)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>3/14 (21)</td>
<td>2.3 (0.6, 8.1)</td>
<td>2.6 (0.7, 9.3)</td>
</tr>
<tr>
<td>Spotting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12/14 (86)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>2/14 (14)</td>
<td>1.3 (0.3, 6.9)</td>
<td>1.6 (0.3, 8.6)</td>
</tr>
</tbody>
</table>

*a* No. = number;  
*b* Confidence interval;  
*c* Adjusted for clinic type (general practice or sexual health centre/family planning clinic)

7.3.4  Persistent infections, treatment failure and ‘false positives’

One persistent infection was identified in a woman who had not taken the prescribed antibiotics despite having them prescribed and sent to her; one possible treatment failure was identified with a woman who had always had protective sex with condoms; and one false positive was found, a participant who tested positive at her follow up test despite taking antibiotics and having no risk of re-exposure. This third case was sent another swab which tested negative, and we concluded from her low risk of re-infection that her first test had been a ‘false positive’ result. She was prescribed azithromycin as a precaution. All behavioural data provided for the algorithm were based on self-reported questionnaire data and a thorough consultation with a sexual health physician.
7.3.5 Organism load for incident infections

The 47 incident infections were analysed to determine the organism load per swab. The chlamydia organism load ranged between $6.1 \times 10^6$/swab and $2.6 \times 10^9$/swab with a median of $1.4 \times 10^6$/swab. Load was not associated with increased likelihood of reporting any symptoms, and the organism load was significantly lower in incident infections relative to prevalent infections ($p=0.004$)(Figure 7-2). This was also the case with the organism load and re-infections ($p=0.002$) (Figure 7-3).

![Figure 7-2 Chlamydia organism load for prevalent infections and incident infections.](image-url)
Figure 7-3  Chlamydia organism load for prevalent infections and re-infections.
7.3.6 Serovars

The chlamydia serovar was detected in the 39 of the 47 positive incident chlamydia samples; 64% were serovar E (n=28), 11% were serovar F (n=5), 7% were serovar D (n=3), 5% were serovar G (n=2) and 2% were serovar H (n=1) (Table 7-5). The chlamydia serovars detected in the re-infection samples were primarily serovar E (n=12, 86%), one was serovar D (7%) and one was serovar F (7%) (Table 7-6). Overall, there were no associations between serovar and organism load for all the infections found (Figure 7-4).

Table 7-5 Genotypes detected in *Chlamydia trachomatis* incident samples.

<table>
<thead>
<tr>
<th>Chlamydia genotype</th>
<th>Frequency N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>3 (7)</td>
</tr>
<tr>
<td>E</td>
<td>28 (64)</td>
</tr>
<tr>
<td>F</td>
<td>5 (11)</td>
</tr>
<tr>
<td>G</td>
<td>2 (5)</td>
</tr>
<tr>
<td>H</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
</tr>
</tbody>
</table>

Table 7-6 Genotypes detected in *Chlamydia trachomatis* re-infection samples

<table>
<thead>
<tr>
<th>Chlamydia genotype</th>
<th>Frequency N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>1 (7)</td>
</tr>
<tr>
<td>E</td>
<td>12 (86)</td>
</tr>
<tr>
<td>F</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
</tr>
</tbody>
</table>
Figure 7-4 Box plot showing organism load (log per swab) per chlamydia serovar for all incident cases infections.
7.4 Discussion

7.4.1 Key findings

These results are the first chlamydia incidence and re-infection data for Australian women. The chlamydia incidence was estimated at 4.4 per 100 women years, and 20.3% of women who tested positive, tested positive again for chlamydia at some stage during the study giving a re-infection rate of 20.0 per 100 women years. found that younger women (16 to 20 years old compared with 21 to 25 years old) and women who had had more sexual partners during the study were more likely to have an incident chlamydia infection but no more likely to have a re-infection. Recent use of antibiotics was protective against an incident infection but this was expected as women who tested positive were provided with antibiotics. Antibiotic use was not protective against a re-infection though although this is more likely explained by the low numbers of re-infections in the analysis. Increased numbers of sexual partners was not a predictor of re-infection, because most re-infections were probably from a current partner who was not treated concurrently (7/14 re-infections).

Women who presented with an incident infection were more likely to report symptoms such as abdominal pain than women with a prevalent infection (Chapter 6). It is possible that these symptoms correlate with upper genital tract infection from an acute lower genital tract chlamydia infection rather than as a consequence of a chronic infection, and might demonstrate a closer temporal association with acute rather than with a chronic chlamydia infection. However abdominal pain is a very non specific symptom that can be attributed to many conditions of which upper genital tract infection is a small proportion. There were no associations with upper genital tract infections and re-infections.

7.4.2 Duration of infection

The duration of infection for chlamydia can be estimated from the prevalence and incidence estimates within the one population (incidence = duration of infection x prevalence). We found a baseline prevalence of 4.9% (refer to Chapter 6) and an
incidence of 4.4 per 100 women years which suggests a mean duration of infection for chlamydia would be about one year long.

7.4.3 International incident rates

The incident rate in this study are similar to findings in a recent cohort study in the United Kingdom which report an incidence of 4.9 (95% CI: 2.7, 8.8) per 100 women years among 16 to 24 year old women from general practice clinics (LaMontagne et al., 2007). Research findings vary widely with reported incidence rates ranging between 3 and 34 per 100 women years (Burstein et al., 1998, Batteiger et al., 2009, Rietmeijer et al., 2002, Richey et al., 1999), although many of these studies have been researched in high risk populations. There are few population based estimates because prospective cohort studies are costly and logistically very difficult to implement which increases the importance of these data.

7.4.4 Predictors of incident infection

Overall predictors for chlamydia incidence include younger age (Geisler et al., 2004, van den Broek et al., 2010, LaMontagne et al., 2007, Rietmeijer et al., 2002), history of chlamydia infection (Geisler et al., 2004, LaMontagne et al., 2007, Rietmeijer et al., 2002), history of other STIs (Batteiger et al., 2009), inconsistent condom use (Rietmeijer et al., 2002), increased number of recent sexual partners (Geisler et al., 2004, Batteiger et al., 2009), and acquisition of new sexual partner (Rietmeijer et al., 2002) (unless they used a condom which was protective against chlamydia) (LaMontagne et al., 2007). The CIRIS study found younger age and new sexual partners were predictors for incident chlamydia but not lack of condom use or having a history of chlamydia; data about other STIs were not collected.

7.4.5 International re-infection results

Even though the incidence of chlamydia is considerable, the most alarming result in this study was the high proportion of women who had a re-infection. Approximately 20% of women who had chlamydia during the study were re-infected at some stage during the study period. Again our results are similar to those found in the recent UK
general practitioner cohort study of in 16 to 25 year old women which found a re-infection rate of 29.9 (95% CI: 19.7, 45.4) per 100 person years (LaMontagne et al., 2007). Other population based studies vary between 4 to 51 per 100 women years (Oh et al., 1996, Veldhuijzen et al., 2005, Xu et al., 2000, Schillinger et al., 2003) and a more recent US longitudinal study found that out of 268 repeat infections, 84.2% were defined as definite or probable re-infections (Batteiger et al., 2009). However these results reflect high risk women in the US and are not comparable with our results.

There is evidence to support that repeated infections are more likely to cause the more serious sequelae of an acute episode of chlamydia including PID or salpingitis (Hillis et al., 1997) and therefore a high re-infection rate will potentially cause an increase in upper genital tract infection incidence. Reducing re-infection is an important factor in chlamydia control, and strategies to reduce re-infection should be included in chlamydia control strategies, particularly adequate partner treatment and retesting after an initial diagnosis.

### 7.4.6 Predictors of re-infection

Predictors for re-infection include younger age (Xu et al., 2000, Gaydos et al., 2008, Peterman et al., 2006), having a previous infection with chlamydia or having had a previous infection with another STI (Oh et al., 1996, Peterman et al., 2006, LaMontagne et al., 2007, Kjaer et al., 2000), having increased numbers of sexual partners (Peterman et al., 2006, LaMontagne et al., 2007), a rapid acquisition of new sexual partners (LaMontagne et al., 2007) and incomplete partner treatment (LaMontagne et al., 2007). There were no predictors identified for re-infection although it was quite possibly largely due to incomplete partner treatment. A comprehensive analysis to determine predictors of re-infections was limited by sample size.

### 7.4.7 Persistent infections and treatment failure

Persistent infections are more difficult to define; particularly considering molecular typing is limited to differentiating different organisms and confirming re-infection.
This study identified one persistent infection and one treatment failure. There were fewer persistent infections and fewer treatment failures than Batteiger et al which reported 13.7% of repeat infections were due to probable treatment failure, and 2.2% were persistent infections without treatment, although our study was done in a population of lower risk women so was not directly comparable (Batteiger et al., 2009). Larger population based samples of women would provide greater power to achieve estimates for rates of persistent infections and treatment failure, and also provide information about the potential effect of organism load on treatment failure. This is of particular interest considering the level of in vivo azithromycin resistance is unknown (Wang et al., 2005), and the potential effect of organism load causing heterotypic resistance warrants further investigation (Horner, 2006).

7.4.8 Limitations and strengths

There were some limitations to our results. Firstly, our algorithm is partially dependent on self reported sexual behaviour which is potentially influenced by social desirability bias. The degree of clinical enquiry required to determine definite re-infection from persistent infection will always compromise any definitive answer to the degree of treatment failure and/or azithromycin resistance in a population. Increasingly specific molecular analysis such as the use of MLST is being developed to help reduce this error.

Secondly, self-reporting of symptoms has been demonstrated to be likely to be overestimated. An audit of a sub-sample of the questionnaires found the clinician-elicited symptoms for each participant resulted in far fewer symptoms being reported (refer to Chapter 6). This was either due to lack of disclosure of symptoms by the participants, or clinicians reporting only clinically relevant symptoms.

The limitations to the organism load analysis are discussed in Chapter 6, and in summary, the samples were self-collected which potentially caused discrepancies in the samples between women, and the loads were unable to be quantified to number of cells per sample. Also, the sample size was too small to capture a large number of re-infections which limited the analysis.
There were a number of strengths to this study including the high participation rate and the high retention of the sample (79%).

7.4.9 Implications for these results

These data provide a strong argument to support the current RACGP and Australasian College of Physicians Chapter of Sexual Health Medicine that women who test positive for chlamydia should be tested at least three months after treatment (RACGP, 2009, Australasian College of Sexual Health Physicians, Accessed 2005 [online] http:www.ashm.org.au). Our results also confirm the importance of partner notification and patient delivered partner therapy which in combination have proved effective at decreasing re-infection (Trelle et al., 2007) and is acceptable to clinicians and patients (Bilardi et al., 2010b, Bilardi et al., 2009).

7.5 Conclusions

Clearly, chlamydia is a common infection in young Australian women and considering the high proportion of women who re-infect within a short period of time, recommendations for more effective partner treatment, repeat testing and follow up is particularly pertinent for chlamydia control. It is also recommended that further molecular analysis is warranted to determine the degree of treatment failure and/or azithromycin resistance. Further research into the effects of organism load and serovar may also demonstrate an effect on the pathogenesis of chlamydia in the population.
CHAPTER 8.

THE INCIDENCE OF GENITAL MYCOPLASMA GENITALIUM IN A COMMUNITY BASED SAMPLE OF YOUNG AUSTRALIAN WOMEN

8.1 Introduction

*Mycoplasma genitalium* (*M. genitalium*) is an emerging sexually transmitted infection (STI) that infects both men and women. *M. genitalium* is an established cause of urethritis and cervicitis in women (Jensen et al., 1993, Anagrius et al., 2005, Hjorth et al., 2006, Bradshaw et al., 2006a) and there is evidence to suggest that *M. genitalium* is associated with endometritis (Cohen et al., 2002), tubal factor infertility (Clausen et al., 2001, Svenstrup et al., 2007) and pelvic inflammatory disease (PID) (Haggerty, 2008); although may be less likely to cause PID than chlamydia (Oakeshott et al., 2010a). *M. genitalium* has also been associated with HIV infection by meta-analysis with a two-fold increased odds of HIV infection with HIV infected individuals (Cohen et al., 2005, Mavedzenge, 2009).

There are few population data for *M. genitalium* infection in women, and the predictors of infection are largely unknown. Prevalence estimates vary widely, with recently studies estimating prevalence of *M. genitalium* between 0.8% (95% confidence interval [CI]: 0.4-1.6) among 18-27 year old sexually-active women in the US (Manhart et al., 2007), 2.3% (95% CI: 1.3-3.2) in 21-23 year old women Denmark (Andersen et al., 2007) and 3.4% (95% CI: 2.7-4.3) in sexually-active students in the UK (Hay et al., 2009), the same UK study reported an *M. genitalium* incidence of 0.9% (95% CI, 0.5%-1.6%) (Oakeshott et al., 2010a). *M. genitalium* testing is not widely available in Australia however some large sexual health services have accessed *in house* assays and test males with symptoms of urethritis and women for *M. genitalium* with cervicitis or pelvic inflammatory disease particularly if they are chlamydia negative (Lowe, 2009). One public hospital pregnancy termination service
in Melbourne has also begun testing women presenting for a termination for *M. genitalium* and reports a prevalence of 4.1% (95% CI: 1.8, 6.3) (Marceglia et al., 2010).

Given the limited published data on *M. genitalium* infection in women, further understanding of the epidemiology of the infection in young women will help inform STI testing recommendations and future control activities.

### 8.1.1 Aims

The aims of this chapter are to determine Australia’s first community-based *M. genitalium* incidence estimates and re-infection data for young women aged 16 to 25 years. A second objective is to describe the clinical and epidemiological characteristics associated with incident *M. genitalium* infection and re-infection and determine associations between *M. genitalium* organism load and clinical presentation. The chapter also aims to calculate an estimate of azithromycin treatment failure among young women.

### 8.2 Method

#### 8.2.1 Recruitment

Young women were recruited as part of the Chlamydia Incidence and Re-infection Rates Study (CIRIS), a 12 month longitudinal study that aimed to measure chlamydia incidence in Australian women aged 16 to 25 years recruited from primary care clinics; a secondary aim of the study was to measure *M. genitalium* incidence, the results of which are presented here. The methods are described in detail elsewhere in this thesis (Chapter 5). In summary, consecutive women were recruited from 29 primary health clinics (including general practice, sexual health and family planning clinics) in the Australian States and Territories of New South Wales (NSW), Victoria and the Australian Capital Territory (ACT) between May 2007 and August 2008. A research assistant was employed to approach women in these clinics, irrespective of their reasons for having a medical consultation, determine their eligibility and gain informed consent for the study. Women aged 16 to 25 years who were not pregnant
at the time of recruitment, had ever had vaginal sex with a man, were competent in written English and were able to be contacted by post within Australia during the 12-month study were invited to be in the study, and if they consented to the primary study, they were also invited to be involved in the sub-study. Follow up was completed in December 2009.

8.2.2 Testing

Women provided a self collected flocked vaginal swab (www.microrheologics.com) at baseline and 12 months. Swabs collected at baseline were given to the research assistant at the clinic and all follow up swabs were sent through the regular Australian post as described in Chapter 5. Swabs collected at baseline and 12 months were tested for *M. genitalium* in real time and results provided to the participants. All testing was done by the Royal Women’s Hospital (RWH), Melbourne, Victoria and if the swab tested positive, further studies were performed including organism load quantification.

*M. genitalium* testing was conducted by rotating the swab in 400μl of PBS and 200μl was extracted using the automated MagNA Pure LC (Roche Molecular Biochemical, Mannheim, Germany) with the DNA Isolation Kit 1 protocol. Detection of *M. genitalium* was performed using the extracted DNA amplified by PCR targeting a 517bp region of the 16S rRNA gene (Yoshida et al., 2002). Any remaining specimen was stored at -80°C.

8.2.3 Evaluation of assays for *M. genitalium* testing

As described above in Chapter 5, the 16S rRNA assay was used to diagnose *M. genitalium* for women enrolled in the sub-study. To validate this assay we tested a subsample of 845 swabs, including all the samples that had tested positive using the 16S rRNA assay, by retesting the samples with real-time PCR assay that was directed at the adhesion protein gene (MgPa) (Jensen et al., 1991). This was done at the completion of the study after all the samples had been stored at -80°C for a median of 25 months (average=22.2; range=1-29 months). A total of 43 samples were found to be positive by one or both assays giving a sensitivity of 95.0% (95% CI: 0.831 to
0.994) and specificity of 99.6% (95% CI: 0.989 to 0.999) when comparing the 16S rRNA gene assay to the MgPa assay; or a kappa score of 0.935 (95% CI: 0.879 to 0.992) and we were satisfied that this meant that there was virtually no difference between the two assays (Twin et al., 2011).

8.2.4 Organism load

The *M. genitalium* concentration of each sample was quantified using a qPCR (TaqMan® MGB Probe) assay targeting the MgPa gene (Edberg et al., 2008). Quantitation was carried out using a LightCycler 480 Real-Time PCR System (Roche Diagnostics, Mannheim, Germany) by comparing the quantification cycle of each sample to the quantification cycle of a standard curve constructed by amplifying different known copy numbers of target gene.

8.2.5 Management of participants

All women who tested positive for *M. genitalium* were managed by the research team who organised a telephone consultation with a sexual health physician (refer to Figure 6.1) which included detailed questions about any symptoms the woman might be experiencing. The clinician discussed treatment and support material including partner notification letters specific to *M. genitalium*, were provided for sexual partners (Appendix S and Appendix EE). Treatment of 1g of azithromycin (Mena et al., 2009) was provided and if there were symptoms to suggest PID or there were any other clinical concerns, a face to face consultation with a clinician was arranged.

A test-of-cure was sent one month after treatment to all the women who tested positive for *M. genitalium*. The test-of-cure included a swab for self-collection and a questionnaire to confirm they had taken azithromycin 1g *stat*, and to determine if their recent sexual partners had been treated, and they had not had unprotected sex with infected partners before both had been simultaneously treated (Appendix NN). When a participant had a positive test-of cure, they had another consultation with a sexual health physician who determined if there had been any risk of re-infection.
To ascertain if treatment failure had occurred, an algorithm was designed based on an algorithm for repeat infections with chlamydia by Batteiger et al (Batteiger et al., 2009) which distinguished between re-infection and persistent infection, and in the case of *M. genitalium*, if treatment failure was likely to have occurred (Figure 8-1). Treatment failure was identified when a positive result was diagnosed after treatment with azithromycin and there had been no possibility of re-infection from an untreated sexual partner. If the persistent infection was deemed not likely to be due to re-infection or non-adherence and more likely to be due to azithromycin resistance, the patient was treated with 400mg moxifloxacin daily for 10 days (Bradshaw et al., 2006b, Bradshaw et al., 2008), otherwise a repeat 1g dose of azithromycin was prescribed (Bradshaw et al., 2008). A second test-of-cure was done a month after the second treatment.

**8.2.6 Definitions for incident infection, re-infection, persistent infection**

The same algorithm was used to differentiate re-infections from persistent infections. Re-infection with *M. genitalium* was defined as a second positive *M. genitalium* result after testing positive at baseline with a confirmed negative test in between. A persistent infection was defined as a positive result at 12 months preceded by a positive result at baseline but without any confirmation of treatment or confirmed negative test in between. An incident infection was defined as a new infection during the study period with no prior *M. genitalium* positive result; re-infections were also included in the analysis of incident infections (Figure 8-1).
Two episodes of *M. genitalium* infection

YES/N/A

**Negative test of cure**

YES

**Definite re-infection**

NO

**Antibiotics taken?**

YES

**Persistent infection**

NO

**Possible treatment failure**

**Condoms used with all coitus?**

YES

**Probable re-infection**

NO

**Coitus with same partner?**

YES

**Probable re-infection**

NO

**Coitus with different partner?**

**Figure 8-1** Algorithm to differentiate *Mycoplasma genitalium* re-infection and persistent infection adapted from Batteiger et al (2009).

8.2.7 Data collection

Women were followed up at three-monthly intervals during the 12 month study period. At recruitment, women were asked to complete a self-administered questionnaire which collected demographic data (Appendix U). Questionnaires asked about sexual behaviour (number of sex partners and condom use), recent antibiotic and contraceptive use, and any pregnancies including termination and/or miscarriages that might have occurred since the previous questionnaire. It also included questions about the presence of any recent genitai symptoms, including abnormal vaginal discharge, abnormal vaginal odour, burning on urination, pelvic pain and abnormal bleeding (Appendix V and Appendix W). Any associations between reported symptoms, behavioural data and demographic characteristics and
incident infection were analysed. If women identified she had tested positive in between follow ups or she had taken antibiotics for any reason, a ‘release of information form’ was sent to allow the study team to contact the doctor for the release of these data (Appendix OO).

### 8.2.8 Statistical methods

Power calculations suggested that a sample size of 1,000 would be sufficient to generate standard error of 1.0% for incidence estimates of 2%.

Data were analysed using STATA version 11.1 (Stata Corporation, 2009). All analyses were adjusted for clustering at the clinic level. *M. genitalium* incidence estimates and 95% confidence intervals (95% CIs) were calculated and hazard ratios (HR) and robust standard errors were calculated to explore factors associated with *M. genitalium* incident infection. Hazard ratios were adjusted for type of clinic from which the participant was recruited (general practice clinic or sexual health/family planning clinic).

Re-infection was calculated as the proportion of *M. genitalium* infections where the women had had an *M. genitalium* infection previously during the study period but was treated and had tested negative in between. Persistent infections were calculated as a proportion of infections that presented twice without a negative result in between during the study. Azithromycin failure was calculated as a proportion of infections that were diagnosed and treated for *M. genitalium* and were found to have treatment failure according to our algorithm.

Ethics approval to conduct this study was obtained from ten Human Research Ethics Committees throughout Australia. Informed consent was obtained from every participant prior to being in the study.
8.3 Results

8.3.1 Sample characteristics

A total of 1110 women agreed to provide specimens for *M. genitalium* testing, providing a total of 1056 person years of follow up. Two-thirds of the sample was recruited from general practice clinics and the median age was 21 years old and apart from being slightly more well-educated and more likely to be Australian born, the sample was representative of the comparative Australian background according to the latest Australian census data (Australian Bureau of Statistics, 2006). For more information about the sample refer to Chapter 5.

8.3.2 Prevalence and incidence

A total of 27 women tested positive for *M. genitalium* at baseline [prevalence: 2.4% (95% CI: 1.5, 3.3)]; factors associated with a prevalent *M. genitalium* infection are described in Chapter 6. Overall, 10 incident infections were identified with an incidence rate of 1.1 per 100 person years. (95% CI: 0.4, 1.6). Univariate analysis found that the type of clinic (sexual health centre or family planning clinic as opposed to a general practice clinic) from which a participant was recruited from was strongly associated with having an incident infection [HR: 4.5; (95% CI: 1.4, 14.7)] Having two or more sexual partners during the study [HR: 5.2 (95% CI: 1.0, 26.5)] or having a past history of chlamydia [HR: 4.2 (95% CI: 1.1, 16.5)] were associated with increasing risk of having incident *M. genitalium*, but once adjusted for type of clinic from which the participant was recruited, these associations were not significant. Use of condoms, recent antibiotic use and other demographic and clinical characteristics were not associated with incident infection (Table 8-1 and Table 8-2).
Table 8-1  Hazard ratios determining the predictors of *Mycoplasma genitalium* incident infection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.² with variable/No. cases (%)</th>
<th>Unadjusted Hazard Ratio (95% CI)²</th>
<th>Adjusted Hazard Ratio (95% CI)²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 21</td>
<td>5/9 (55.6)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>21 to 25</td>
<td>4/9 (44.4)</td>
<td>0.6 (0.1, 2.4)</td>
<td>0.7 (0.2, 2.6)</td>
</tr>
<tr>
<td><strong>Area of residence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>6/9 (66.7)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Metropolitan</td>
<td>3/9 (33.3)</td>
<td>0.3 (0.1, 1.2)</td>
<td>0.5 (0.2, 1.3)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to year 12</td>
<td>6/9 (66.7)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Tertiary</td>
<td>3/9 (33.3)</td>
<td>0.6 (0.1, 2.4)</td>
<td>0.7 (0.2, 2.5)</td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed/Not working</td>
<td>3/9 (33.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Employed</td>
<td>6/9 (66.7)</td>
<td>1.1 (0.3, 4.1)</td>
<td>1.1 (0.3, 3.9)</td>
</tr>
<tr>
<td><strong>Clinic type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>3/9 (33.3)</td>
<td>1.0</td>
<td>N/A</td>
</tr>
<tr>
<td>SHC/FP</td>
<td>6/9 (66.7)</td>
<td>4.5 (1.4, 14.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of new partners during study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>2/6 (33.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2+</td>
<td>4/6 (66.7)</td>
<td>5.2 (1.0, 26.5)</td>
<td>3.9 (0.6, 25.7)</td>
</tr>
<tr>
<td><strong>Recently had antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3/6 (50.0)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>3/6 (50.0)</td>
<td>4.3 (0.7, 28.5)</td>
<td>4.7 (0.8, 29.3)</td>
</tr>
<tr>
<td><strong>Use of hormonal contraception</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2/5 (40)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>3/5 (60)</td>
<td>0.8 (0.2, 3.3)</td>
<td>0.8 (0.2, 2.9)</td>
</tr>
<tr>
<td><strong>Use of condoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4/6 (66.7)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>2/6 (33.3)</td>
<td>0.7 (0.1, 5.2)</td>
<td>0.7 (0.1, 5.7)</td>
</tr>
<tr>
<td><strong>Previous positive result for chlamydia ever</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6/9 (66.7)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>3/9 (33.3)</td>
<td>4.2 (1.1, 16.5)</td>
<td>2.8 (0.7, 12.0)</td>
</tr>
</tbody>
</table>

²No. = number; ²Confidence interval; ²Adjusted for clinic type (general practice or sexual health centre/family planning clinic)
Table 8-2  Hazard ratios determining associations between symptoms and *Mycoplasma genitalium* incident infection.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. a with symptom/No. cases (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>Adjusted Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5/6 (83.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1/6 (16.7)</td>
<td>1.3 (0.2, 10.6)</td>
<td>1.0 (0.1, 6.6)</td>
</tr>
<tr>
<td><strong>Odour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5/6 (83.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>1/6 (16.7)</td>
<td>1.8 (0.2, 15.7)</td>
<td>1.9 (0.3, 12.7)</td>
</tr>
<tr>
<td><strong>Burning with urination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6/6 (100)</td>
<td>Insufficient data b</td>
<td>Insufficient data</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
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<td></td>
</tr>
<tr>
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<td>5/6 (83.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
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<td>1/6 (16.7)</td>
<td>1.0 (0.1, 8.3)</td>
<td>1.3 (0.2, 9.2)</td>
</tr>
<tr>
<td><strong>Dyspareunia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>6/6 (100)</td>
<td>Insufficient data b</td>
<td>Insufficient data</td>
</tr>
<tr>
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<td>0/6 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spotting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5/6 (83.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
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<td>1/6 (16.7)</td>
<td>1.5 (0.3, 8.9)</td>
<td>2.2 (0.3, 14.4)</td>
</tr>
</tbody>
</table>

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*a* No.: number; *b* Confidence interval; *c* Adjusted for clinic type (general practice or sexual health centre/family planning clinic); *d* there were no cases of women with incident *M. genitalium* and these symptoms.

### 8.3.3 Re-infections and persistent infections

One participant tested positive at 12 months after a positive baseline result and negative test of cure [re-infection rate of 10.0 per 100 women years (95% CI: 0.3, 44.5)]. There were no persistent infections.

### 8.3.4 Organism load for incident infections

The 10 incident infections were analysed to determine the organism load per swab. The *M. genitalium* organism load ranged between $3.5 \times 10^3$/swab and $1.0 \times 10^6$/swab with a median of $2.4 \times 10^4$/swab. Load was not associated with increased likelihood of reporting any symptoms, and there was no significant difference between the organism load found in prevalent infections compared with incident infections ($p=0.5$).
8.3.5 Treatment failure

A test-of-cure was sent to all positive women to determine if azithromycin treatment had been effective; four women had a positive test-of-cure (12.1%). From the questionnaire data and a comprehensive follow-up telephone consultation with a sexual health physician, all four women were considered more likely to have had treatment failure than a new infection [treatment failure: 12.1% (95%CI: 3.4, 28.2)] as all had adhered to treatment and none had had sex with an untreated sexual partner. The women were prescribed 400mg moxifloxacin daily for ten days and a second test-of-cure one month later was returned by three of the four women, all of whom tested negative.

Organism load for *M. genitalium* was identified was significantly higher in cases with azithromycin failure (mean organism load: $9.8 \times 10^5$/swab) compared with cases that were ‘azithromycin susceptible’ *M. genitalium* (mean organism load: $1.5 \times 10^5$/swab) ($p=0.006$) (Figure 8-2). Work is in progress with our collaborators to develop an azithromycin resistance assay which will enable us to determine whether known azithromycin resistance mutations were present in cases experiencing treatment failure.
The differences in *Mycoplasma genitalium* organism load per swab (log) between infections that were not effectively treated with 1 gram azithromycin and those infections that were treated effectively by azithromycin.
8.4 Discussion

8.4.1 Incidence and duration of infection

At the time of writing this thesis, there were no published *M. genitalium* incident data for young women in Australia. We identified 26 (2.2%) cases of *M. genitalium* at baseline, and during the 12 month follow up period we identified 10 incident cases (*M. genitalium* incidence: 1.0 per 100 person years); one re-infection (10%) and four azithromycin treatment failures (12%). Co-infection with chlamydia during the study was rare (n=2, 0.2%). The duration of infection was estimated from the prevalence and incidence data obtained within the same population (prevalence = incidence x duration of infection) (Webb et al., 2005) as being close to two years (refer to Chapter 6 for *M. genitalium* prevalence data).

8.4.2 Predictors of infection

The only demographic characteristic identified as a predictor of *M. genitalium* incident infection was the type of clinic the participant had been recruited from (sexual health centre/family planning clinic). Increased number of sexual partners, lack of condom use and having a previous chlamydia infection were not predictors for *M. genitalium* incident infection once adjusted for the clinic type. There was no association with an increased likelihood of reporting symptoms and having an incident infection, however the small number of infections limited this analysis.

8.4.3 Treatment failure

Clinical information was used to determine if azithromycin failure had occurred in cases where women had a positive test-of-cure (12.1%). The results of the quantitative analysis suggest that a higher load of *M. genitalium* was present in those cases experiencing treatment failure indicating that the amount of infectious organism may influence the effectiveness of azithromycin against *M. genitalium*.
8.4.4 Comparison with international studies

Internationally, our findings are similar to other recent population data that reported *M. genitalium* prevalence was somewhat lower than chlamydia prevalence (Manhart et al., 2007, Hay et al., 2009), and our incidence estimates were very similar to a recent study in the UK which found an incidence of 0.9% in young sexually active female university students (Oakeshott et al., 2010a).

The UK study identified increased number of sexual partners as a risk factor associated with having an incident infection (Oakeshott et al., 2010a), however the small number of incident cases in our study limited our analysis. Research of other STIs (in particular chlamydia) has demonstrated incident infections were more likely in women who attended sexual health centres, women who had a greater number of recent sexual partners, women who had previously been diagnosed with an STI, and women who had had recent unprotected sexual intercourse (LaMontagne et al., 2007). In our study, only women from sexual health and family planning clinics were more likely to have had an incident infection, whilst increased sexual behavior, area of residence and previous STI infection were not independently associated with an incident infection. Recent unprotected sex was not a predictor for *M. genitalium* infection which suggests further investigation with partner studies may be useful in investigating potential differences in infectivity and transmission of *M. genitalium* compared to other STIs.

8.4.5 Organism load

There are scarce data about the effect of organism load on the clinical presentations of *M. genitalium*. Clinical presentations in men have shown increased load is associated with signs of urethritis in men, but another study found no association in with women between organism load and clinical cervicitis or urethritis (Hogdahl and Kihlstrom, 2007). There are also scarce data about the association between organism load and treatment failure for *M. genitalium*. Horner et al (2006) postulate that increased chlamydia infectious load can cause ‘heterotypic’ resistance to azithromycin, which was demonstrated by large trachoma trials where treatment
failure was been associated with high organism load (Horner, 2006, West et al., 2005). Some but not all the data suggest that a 5 day regimen of azithromycin (1.2g) may be more effective than a single 1g dose, however the effect of a higher dose or prolonged treatment with azithromycin in M. genitalium cases as well as in chlamydia cases with a higher organism load warrants further research in larger populations. Our finding of 12.1% treatment failure is consistent overall with the findings of other Australian and international studies which have found azithromycin to be effective in approximately 85% of cases (Bradshaw et al., 2006b, Bradshaw et al., 2008, Mena et al., 2002, Bjornelius et al., 2008).

8.4.6 Limitations and strengths

There were a number of limitations to our study. Firstly, our sample had a higher proportion of well-educated and sexually-active women than the general background population in Australia for the same age (Smith et al., 2003, Australian Bureau of Statistics, 2006), which is common in population research for this age group and sexual health (Smith et al., 2009, Hocking et al., 2006b); this has been discussed further in Chapter 5. Also we were particularly limited by the small number of incident cases (n=10) in this analysis.

There were limitations to consider when interpreting associations with organism load. Equal efficiency of self-collected sampling could not be assured and positive samples were subjected to a number of assays depleting the sample each time. We were also unable to substantiate azithromycin resistance with molecular analysis despite having very good clinical information collected by a sexual health physician at the time of consultation. The study strengths were the large sample size, the high retention rate (78%), and the broadly representative sample.

8.4.7 Implications

M. genitalium is emerging as an important STI in women as increasing evidence demonstrates an association with M. genitalium and upper genital tract infection (Haggerty, 2008, Svenstrup et al., 2007). Currently, there is no available commercial assay and the majority of M. genitalium infections worldwide in women go
undiagnosed and untreated. Whilst 1g of azithromycin appears to be 85% effective at best for uncomplicated *M. genitalium* infections in men and women (Bradshaw et al., 2006b, Bradshaw et al., 2008, Mena et al., 2002, Bjornelius et al., 2008), it appears azithromycin resistance or failure might be higher than this in different populations and even increasing (Bradshaw, 2010). *M. genitalium* treatment might also be complicated by variable organism load and whilst moxifloxacin appears to be highly effective, worryingly, a small number of cases of moxifloxacin failure have recently been identified (Bradshaw, 2010).

Our results also support other research which has found that that *M. genitalium* is not uncommon in young women and is often not associated with clinical symptoms. More research is required to inform our clinical management of *M. genitalium* but there is increasing evidence to support the development of a commercially available assay. More research is also warranted into the potential effect of organism load on treatment efficacy and determining the prevalence of azithromycin resistance mutations in treatment failures. Studies with larger populations will provide more information about transmission dynamics and duration of infection which are both important factors in understanding the management of *M. genitalium* in the population.

### 8.5 Conclusion

*M. genitalium* incidence is a concern for sexually active young Australian women particularly since it is likely to be left undiagnosed in asymptomatic women and ineffectively treated in a significant proportion of symptomatic women. It appears that *M. genitalium* might have a longer duration of infection than chlamydia and *M. genitalium* infection might have be associated with different predictors for infection than chlamydia. This may suggest the two organisms have different transmission dynamics and/or infectivity. These study results can inform further research and clinical strategies for managing *M. genitalium* infection in Australia and internationally.
CHAPTER 9.

YOUNG AUSTRALIAN WOMEN’S THOUGHTS ABOUT CHLAMYDIA SCREENING: A PSYCHOSOCIAL ANALYSIS

9.1 Introduction

9.1.1 Background

Genital *chlamydia trachomatis* is the most common notifiable sexually transmitted infection in Australia and is increasing steadily over time (Department of Health and Ageing, 2009). Chlamydia infection is often asymptomatic in women and can be associated with significant morbidity, including tubal factor infertility and ectopic pregnancy (Peipert, 2003). Opportunistic testing of young women is recommended by the relevant professional medical organisations in Australia (RACGP, 2009, Royal Australasian College of Physicians, 2010), however, still only 12% of women under 25 are being tested annually (Health Insurance Commission, 2008). The Australian government is currently piloting a national screening program for chlamydia to determine the effectiveness, feasibility and acceptability of chlamydia testing in young people with a view to introduce opportunistic chlamydia testing in Australia (Hocking et al., 2009).

For any screening program to be successful, the test has to be acceptable to the constituency tested as well as being acceptable to clinicians. Previous research on women’s attitudes to chlamydia testing consistently demonstrate that women experience a number of barriers to testing, including concerns about confidentiality being breached (Dixon-Woods et al., 2001, Blake et al., 2003, Heritage and Jones, 2008), fear of being stigmatised about having a test (France et al., 2001, Christianson et al., 2003, Ford et al., 2004a, Henning et al., 2007, Mills et al., 2006, Pavlin et al., 2008, Piercy, 2006), anxiety and embarrassment caused by being tested, and apprehension about others knowing that they have been tested for a sexually
transmitted infection (Duncan et al., 2001, Ford et al., 2004b, Mills et al., 2006, Mulholland and Van Wersch, 2007). If they test positive, women worry about their partner’s reaction, become concerned about their future fertility, and experience shame, guilt and embarrassment (Kangas et al., 2006, Pavlin et al., 2006, France et al., 2001). This is also complicated by clinicians poor understanding of the potential psychosocial impact testing might have as well as the lack of public knowledge about the benefits of chlamydia testing (Piercy, 2006, France et al., 2001, Cook et al., 2001, Temple-Smith et al., 2009, McNulty et al., 2004).

Most research about the psychosocial implications of chlamydia testing have been conducted outside Australia, involve qualitative interviews with small numbers of women (Devonshire et al., 1999, Pavlin et al., 2006, Andersson-Ellstrom and Milsom, 2002) or are not specific to women (Duncan et al., 2001, Blake et al., 2003, Mulholland and Van Wersch, 2007, Piercy, 2006), or involve older women rather than younger women who are at greater risk of infection (Devonshire et al., 1999, Mills et al., 2006, Tilson et al., 2004, Duncan et al., 2001, Ford et al., 2004a), or have focused on chlamydia positive women only (Dixon-Woods et al., 2001, Devonshire et al., 1999, Tilson et al., 2004, Fenton et al., 2001a).

Results from the few Australian studies that have been published are consistent with international research findings despite the limited data. More comprehensive research in a large sample of young Australian women will provide a greater understanding of the issues associated with having a chlamydia test and having a positive test. A larger sample can also identify if there are any differences in the psychosocial behaviour between women who test positive and women who test negative for chlamydia.

Testing rates are low in Australia, and screening policies and programs internationally have not been demonstrated to be successful in reducing chlamydia in the population, so more research about how women want to be tested and barriers to screening are warranted, particularly any information specific to the Australian context.
9.1.2 Aims

This chapter aims to determine the psychosocial implications, barriers and screening preferences of young Australian women tested for chlamydia based on the results of a psychosocial questionnaire sent to all women at the end of the CIRIS study. The chapter also aims to determine any psychosocial differences between women who tested negative and women who tested positive.

9.2 Methods

Women were recruited from 29 primary health care clinics (general practice and sexual health/family planning clinics) between May 2007 and August 2008, as part of the Chlamydia Incidence and Re-Infection Rates Study (CIRIS), a longitudinal study aiming to determine incidence and re-infection estimates for chlamydia. The study involved a cohort of sexually active, 16 to 25 year old women (n=1116) who were followed up at three monthly intervals by post, for a period of 12 months. Women were tested for chlamydia at the time of recruitment (baseline), 6 months and 12 months, and extra testing was done in between if they tested positive at any stage. The methods for the study are explained in detail in Chapter 5. The study, including the final psychosocial questionnaire, was approved by ten ethics committees in Australia.

9.2.1 Data collection

Demographic and sexual behaviour data were obtained at recruitment and every 3 months using self completed questionnaire; psychosocial data were obtained from a questionnaire sent at the conclusion of the study. The psychosocial questionnaire contained 45 to 48 questions, and depending on whether the participant had tested positive or negative for chlamydia during the study. Variations in wording were designed to capture women’s actual (those testing positive at least once) verses anticipated (those who always tested negative) thoughts and attitudes about testing positive for chlamydia (Appendix X and Appendix Y).
Women were asked about their experience of chlamydia testing, their views or experiences about testing positive for chlamydia, what barriers they might anticipate to having a chlamydia test, which testing methods were preferable, what they considered would be the ideal way to promote chlamydia testing, and who they would talk to if they had questions about chlamydia. Women were also asked how they felt about being involved in the study and whether being involved in the study had changed their sexual behaviour. Most items were scored using a 5 point Likert scale graded from ‘strongly agree’ to ‘strongly disagree’ or ‘never’ to ‘always’. A number of questions required ‘yes’ or ‘no’ responses, while others allowed for extra comments. Two questions were open ended and exploring how women felt about discussing their sexual history with their doctor and what preferences they had for collecting specimens for testing.

9.2.2 Data Analysis

Associations with chlamydia test results during the study (patients testing positive versus patients testing negative) were explored using odds ratios with robust standard errors; odds ratios were adjusted for clustering at the clinic level. Descriptive frequencies and quotations were used to describe questionnaire responses and to highlight the main themes. All data were de-identified to protect confidentiality and were analysed using STATA version 11.1 (Stata Corporation, 2009). The two open ended questions were subjected to thematic analysis.

9.3 Results

9.3.1 Key study results

Overall, 1116 (66%) of eligible women were consecutively from 29 recruitment sites agreed to participate in the study and after 12 months 79% of women were retained in the study. The final psychosocial questionnaire was completed by 872/1116 (78%) women in the study, 67 of whom tested positive at some stage during the study. More details about the sample characteristics are detailed in Chapter 5.
During the study, 55 women tested positive for chlamydia at the beginning of the study [prevalence: 4.9% (95% CI: 2.9, 7.0)] and there were 47 incident infections [incidence rate of 4.4 per 100 women years (95% CI: 3.3, 5.9)], one persistent infection [rate of 0.1 per 100 women years (95% CI: 0.0, 0.7)], one false positive diagnosis [rate of 0.1 per 100 women years (95% CI: 0.0, 0.7)] and one potential treatment failure [rate of 0.1 per 100 women years (95% CI: 0.0, 0.7)] during the study period. For more information about the prevalence of chlamydia in the cohort, refer to Chapter 6 and for more details about the incidence and re-infection results, refer to Chapter 7.

9.3.2 Psychosocial implications of testing positive for chlamydia

Many women who completed the final questionnaire, irrespective of their test result, reported having some psychosocial response to having a chlamydia test and the possibility of having a positive result. Most women experienced anxiety [85% (95% CI: 82%, 87%)], embarrassment [84% (95% CI: 82%, 87%)], were concerned about what their sexual partner’s response might be [78% (95% CI: 75%, 81%)], what other people’s reactions might be [64% (95% CI: 61%, 67%)], and how a positive result might affect their future health [80% (95% CI: 77%, 82%)] if they tested positive. Older women were more likely to report anxiety about having a positive test than younger women [AOR: 2.3 (95% CI: 1.2, 4.6)].

Compared to women who tested negative, women who tested positive were more likely to change their future sexual behaviour [AOR: 5.1 (95% CI: 3.0, 9.0)], talk to other people about their positive test result [AOR: 2.6 (95% CI: 1.6, 4.2)], have less concern around the impact a positive test would have on their future health, [AOR: 0.4 (95% CI: 0.2, 0.8)] and were less concerned about their partner’s response to their diagnosis [AOR: 0.4 (95% CI 0.2, 0.9)] (Table 9-1).

The majority of women who tested positive for chlamydia were pleased to have had the test [98% (95% CI: 95%, 100%)], felt that it was easy to notify their sexual partners [62% (95% CI: 50%, 70%)] and talked to their friends about their positive result [52% (95% CI: 40%, 60%)]. Women aged 16 to 20 years were more likely to talk
to other people about their result than women aged 21 to 25 years of age (AOR: 0.6 (95% CI: 0.3, 1.0)].
<table>
<thead>
<tr>
<th>Psychosocial factors</th>
<th>AOR$^a$ (95% CI)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Will change future sexual behaviour</strong></td>
<td></td>
</tr>
<tr>
<td>Negative$^c$</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive$^d$</td>
<td>5.1 (3.0, 9.0)</td>
</tr>
<tr>
<td><strong>Will talk with someone about positive result</strong></td>
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<tr>
<td>Negative</td>
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</tr>
<tr>
<td>Positive</td>
<td>2.6 (1.6, 4.2)</td>
</tr>
<tr>
<td><strong>Concerned about future health</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive</td>
<td>0.4 (0.2, 0.8)</td>
</tr>
<tr>
<td><strong>Worried about partner’s reaction to a positive result</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive</td>
<td>0.4 (0.2, 0.9)</td>
</tr>
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<td><strong>Anxious about testing positive</strong></td>
<td></td>
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<tr>
<td>Negative</td>
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</tr>
<tr>
<td>Positive</td>
<td>1.3 (0.6, 3.0)</td>
</tr>
<tr>
<td><strong>Worried about how others would perceive them</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
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</tr>
<tr>
<td>Positive</td>
<td>0.7 (0.3, 1.4)</td>
</tr>
<tr>
<td><strong>Embarrassment about testing positive</strong></td>
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<tr>
<td>Negative</td>
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</tr>
<tr>
<td>Positive</td>
<td>0.6 (0.3, 1.4)</td>
</tr>
<tr>
<td><strong>Feel fear associated with testing positive</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive</td>
<td>0.9 (0.5, 1.6)</td>
</tr>
</tbody>
</table>

$^a$AOR= Adjusted odds ratio, $^b$CI= Confidence intervals, $^c$negative means the women always tested negative for chlamydia during the study, $^d$positive means the women tested positive at least once during the study.
9.3.3 Barriers to chlamydia testing

Nearly all women thought testing for chlamydia was a good idea [97% (95% CI: 96%, 98%)], but despite this, there were still a number of reasons women would not seek out a test in future. Half the women [47% (95% CI: 44%, 50%)] reported they were uncomfortable raising sexual health issues with a general practitioner, and a quarter of women [25% (95% CI: 23%, 29%)] were concerned about what their sexual partner’s reaction would be to having a test. There were also practical barriers to having a test. Almost half the women [46% (95% CI: 43%, 49%)] reported that finding the time to attend an appointment would be a barrier, 41% of the women [41% (95% CI: 38%, 45%)] were prevented by the perceived cost of testing and treatment, and about a quarter [27% (95% CI: 24%, 30%)] reported they would not know where to go for a test (Figure 9-1) These barriers were the same for women who tested negative and women who tested positive. There was a difference between rural and metropolitan women; women attending rural clinics were less likely to find time to attend a clinic appointment [AOR: 0.7 (95% CI: 0.5, 0.8)] and know where to have a chlamydia test [AOR: 0.5 (95% CI: 0.4 0.8)] than women attending metropolitan clinics. Women who tested positive and attended rural clinics were the least likely to know where to go for a chlamydia test [AOR: 0.6 (95% CI: 0.4, 1.0)].

![Figure 9-1 Barriers to testing reported by women in the study.](image_url)
9.3.4 Privacy, knowledge and home testing

Women reported they would be more open to having a chlamydia test if they could do a self test in the privacy of their own home [92% (95% CI: 89%, 93%)], if they knew chlamydia was easy to treat [91% (95% CI: 88%, 92%)], if they were aware that it is common [72% (95% CI: 69%, 75%)], if they knew more about chlamydia [71% (95% CI: 67%, 74%)] and if chlamydia was part of a national health screening program [67% (95% CI: 64%, 70%)]. Most women had heard of chlamydia [97% (95% CI: 93%, 98%)] however were not necessarily well informed about the cause, duration, symptoms or treatment of chlamydia.

Quote: [I was] aware that chlamydia was an STI, but unaware of affects, symptoms, treatment etc.

Just over half of the women [55% (95% CI: 51%, 58%)] suggested having available support such as a nurse at the medical visit would be beneficial. Women who tested positive for chlamydia were less likely to report that having available support was important for encouraging testing for chlamydia [AOR: 0.5 (95% CI: 0.2, 1.0)] than women who tested negative.

9.3.5 Communication with doctors

Most women [88% (95% CI: 86%, 90%)] reported that they would be willing to have an annual chlamydia test if offered one by their doctor, but almost half the women [47% 95% CI: 44%, 50%] would be uncomfortable with doctors asking about their sexual history. Some women suggested the most important factors that would facilitate discussions about sexual health with their health practitioner were if they had a female doctor (33%) and a non-judgemental doctor (34%). Social stigma, patient attitude and more education were reported to a lesser degree (15%).

Quote: Unfortunately I think gender makes a difference. As a woman I feel more comfortable with women doctors.

Quote: The doctor & patient have to have a good relationship. The doctor must make the patient comfortable and be very open and understanding.
Quote: ...I think it is a societal issue. If you are female and having sex with more than one partner there is fear of being treated badly. Even by health professionals.

9.3.6 Resources and contacts for support

If women had any questions or concerns about chlamydia, most indicated they would talk to a sexual health physician [88% (95% CI: 86%, 90%)] or their own doctor [84% (95% CI: 82%, 87%)]. Over half of women indicated that if the option were available, they would speak with sexual health staff on a free-call professional sexual health line [59% (95% CI: 56%, 62%)]. Women who tested positive for chlamydia indicated that they would be less likely to talk to their doctors than women who tested negative [AOR 0.3 (95% CI: 0.1, 0.4)].

9.3.7 Sample collection

Self collected vaginal swabs were the preferred method of sample collection [64% (95% CI: 61%, 68%)], followed by urine testing [51% (95% CI: 48%, 55%)], some women preferred physician collected swabs [11% (95% CI: 9%, 13%)] and few women preferred tampon specimens [5% (95% CI: 3%, 6%)] (Figure 9-2). Women who tested positive were much more likely to report a preference for self collected swabs than women testing negative [AOR: 1.8 (95% CI: 1.1, 2.9)].

![Figure 9-2](image)

**Figure 9-2** Women’s preference for specimen they prefer to use for chlamydia testing.
9.3.8 Advertising for chlamydia

When asked about the best way to inform young women about chlamydia, most women reported that they would prefer television advertisements [84% (95% CI: 82%, 87%)], advertising in school or tertiary institutions [72% (95% CI: 69%, 75%)] or advertising in magazines [64% (95% CI: 61%, 67%)]. Less popular forms of advertising included website advertising [39% (95% CI: 35%, 42%)], advertising in pubs or clubs [34% (95% CI: 31%, 38%)], radio advertising [37% (95% CI: 34%, 40%)] or included as a story line in a television soap opera [33% (95% CI: 30%, 36%)]. The least popular places to advertise included bus stops [21% (95% CI: 19%, 24%)], in the work place [20% (95% CI: 17%, 23%)] and at sporting events [5% (95% CI: 3%, 6%)] (Figure 9-3).

![Preferred advertising site/method](image)

**Figure 9-3** Women's suggestions as the most effective form of advertising for chlamydia testing.
9.4 Discussion

9.4.1 Key findings

This study examined the effects of testing in a large cohort of young women who were all tested at least once for chlamydia. The results demonstrated that having a chlamydia test can have a psychosocial impact irrespective of the result, although largely in anticipation of having a positive result. Women reported they were concerned about how the test would impact on their relationship with other people, including their partners, and also on the impact a positive result might have on their health. Despite this, when women tested positive for chlamydia they were much less likely to worry about their partner’s reaction to their positive result, less likely to be concerned about their future health and more likely to seek out support than women who tested negative anticipated they would be. Positive women had talked with their friends about their result and found it was relatively easy to contact their partners. They were also more likely to report a change in their sexual practice than women who tested negative as a result of the study.

Despite the high proportion of anxiety about having a test, the overwhelming majority of women were happy to have had a test, and nearly all the women (98%) who tested positive were pleased to have had the test. The women in the study were provided with plain language information about any infection they were tested for, they were given access to a website that was established for the study with more information, and the participants also had access to the research team by free-call phone number and email. Women who tested positive were provided with extra information (written and verbal), had a comprehensive consultation with an experienced sexual health physician, were provided with partner notification material and assistance if required, and were sent free medication and follow up swabs to ensure treatment had been effective and to test for re-infection. It was possible that the extra resources offered by the research team helped to reduce the psychosocial impact of having a test, which was supported by the large proportion of women who remained in the study (close to 80%) and had repeat chlamydia tests during the study period.
9.4.2 Barriers to testing

The barriers to testing for chlamydia evident in our study, have also been noted in other studies (Duncan et al., 2001, France et al., 2001, Blake et al., 2003, Ford et al., 2004a, Kangas et al., 2006, Mills et al., 2006, Pavlin et al., 2008). The large majority of women were accepting of an annual chlamydia test, including those who tested positive, however many identified that they were uncomfortable discussing their sexual history with their doctors and would generally prefer to talk with female doctors about having a chlamydia test and many emphasised the importance of having a non-judgemental doctor which is a common theme other studies also (Temple-Smith et al., 1996, Pavlin et al., 2008). The clinical relationship was not the only barrier to seeking out a test, women reported that time, money and knowing where to go to were likely to have a test, would be a barrier to having a test, and this was particularly the case for rural women. This has also been reported in other research (Dixon-Woods et al., 2001, Henning et al., 2007, Chacko et al., 2008)

9.4.3 Specimen type

Unlike previous studies (Piercy, 2006, Pimenta et al., 2003a, Hsieh et al., 2003) more women in our study preferred vaginal swabs than other methods for specimen collection to do a chlamydia test. It is possible that women who were not comfortable with swabs self-selected out of the study, nonetheless, the women found using the swabs, particularly with clear instructions provided by the research team, very acceptable.

9.4.4 Limitations and strengths

Limitations of the sample are discussed in Chapter 5, but in summary the women recruited into the study were more well educated and more sexually active than the background Australian population for the same age group (Tilson et al., 2004, Bilardi et al., 2010a) Also, a few of the positive women did not complete the psychosocial questionnaire as they tested positive at the final stage of the study and either continued their follow up with their own clinician or failed to return the questionnaire that was sent out with a follow up test 3 months after the study was
completed. There was also potential social desirability bias inherent in self completed sexual health surveys, positive women for example are likely to report that they will change their behaviour after testing positive and it is not possible to confirm whether or not they did contact their sexual partners after testing positive.

This study has a number of strengths, including the large sample size across three Australian states and high participation rate and high retention rate. To our knowledge, no previous studies have compared the views and experiences of women testing negative to chlamydia with those testing positive.

9.4.5 Implications for these results

Considering women are concerned about testing positive for chlamydia, the attitude of the practitioner who is doing the testing is important to allay fears and normalise sexual experiences for young women. A common theme that arises from other research is the desire for chlamydia testing and management to be destigmatised (Duncan et al., 2001, Blake et al., 2003, Christianson et al., 2003, Kangas et al., 2006, Piercy, 2006, Chacko et al., 2008). Some women suggested a preference for home based collection which might be one way to circumvent the reported discomfort with doctors. Despite the issues with clinicians, many of the women reported that they would seek information about chlamydia from their doctor suggesting doctors are perceived to be an important source of information.

This study explores the thoughts of young women about testing for chlamydia and highlights some practical and psychosocial issues women have around testing. It may be surmised that providing adequate support for women who test positive will reduce the psychosocial impact of testing positive. These results can inform education programs which might consider the perceived consequences around testing might be greater than the actual experience and suggests that women who have experienced a positive test would be likely to play an important role in educating other young women. Other methods might be explored further to reduce the psychosocial impact of having a test including some of these methods used in the research study.
These findings might also be utilised on television campaigns targeting chlamydia, which was the preferred medium of advertising observed by women in this study. Future research might compare the psychosocial experiences of young women who visit general practice clinics for chlamydia testing with women who have home testing and explore the differences women attending rural and metropolitan clinics might experience.

9.5 Conclusion

There are definite psychosocial implications to having a chlamydia test that will need to be addressed before testing can become completely acceptable to young women. Sensitive clinical management of women when they test positive can encourage behaviour change, communication and reduce unnecessary concern about future health outcomes. Differences between what women perceive they will experience can be different to what actually happens when women test positive for chlamydia. Clinicians might observe the need to address anxiety surrounding having a chlamydia test for all women presenting for a test.
CHAPTER 10.

THE INCIDENCE OF INDUCED ABORTION IN A PROSPECTIVE COHORT STUDY OF 16 TO 25 YEAR OLD AUSTRALIAN WOMEN.


10.1 Introduction

10.1.1 Background

The number of induced abortions (IA), defined as ‘medically or surgically induced’ abortions’, in Australia is difficult to accurately quantify (Pratt et al., 2005). Currently in Australia, three states are mandated to notify IAs (South Australia, Western Australia and Northern Territory), but of these only one state, South Australia, publishes annual statistics (Chan and Keane, 2004). The remaining states and territories estimate IA rates from the number of claims made through the Australian national health provider ‘Medicare’ by the number of specific services claimed by Medical Benefits Scheme (MBS) item numbers; specifically MBS item numbers 35643 (‘evacuation of the contents of the content of the gravid uterus by curettage or suction curettage’) and 16525 (‘management of second trimester labour, with or without induction, for intrauterine foetal death, gross foetal abnormality or life threatening maternal disease’) (Australian Government Department of Health and Ageing, 2009). Unfortunately the usefulness of this estimate is limited. Firstly, these MBS item
numbers are not exclusive to IA and might also be used for surgical management of spontaneous abortion, foetal death in utero, or other maternal medical conditions (Pratt et al., 2005). Secondly, women without access to Medicare, including women living in Australia on specific visas, cannot access MBS items and some women choose not to claim from Medicare, potentially underestimating IA by up to 34% (Adelson et al., 1995, Nickson et al., 2004). Thirdly, medical abortions and third trimester surgical abortions do not qualify for a specific MBS item number so these are not included in the recorded data. Lastly, IA performed in the public hospital system cannot be counted as they are not funded through the MBS (Pratt et al., 2005).

In addition to the lack of reliable IA rate estimates in Australia, there is scant information available about the women who seek to have an IA. Data from the UK on women aged under 20 years, show pregnancies are more common in the socioeconomically disadvantaged, but those seeking to have an IA are more likely to be from higher socioeconomic backgrounds (Smith, 1993).

In view of the lack of reliable data about the rate of IA in Australia, accurate estimates of IA data would be valuable for informing policy and allocating resources. Legislation is different in every State and Territory in Australia and has been challenged recently in Victoria and Queensland which will benefit from more accurate data about the incidence of IA in Australia.

10.1.2 Aims

The aims of this chapter are to determine IA estimates and epidemiological associations with IA among the CIRIS cohort of sexually active young Australian women, providing some of the first population based IA data for young Australian women.
10.2 Methods

10.2.1 Recruiting

The CIRIS study aimed to determine the prevalence, incidence and re-infection rates of chlamydia *M. genitalium* in sexually active 16 to 25 year old women during a 12 month period (Chapters 6 to 8). Participants were recruited in 2007 and 2008 from 29 primary health clinics (20 general practice clinics and 9 sexual health/family planning clinics) in the Australian States and Territories of Victoria, New South Wales (NSW) and the Australian Capital Territory (ACT) rural and urban areas. The location of clinics was selected to ensure that a broad socio-demographic profile of young Australian women was recruited and the participant’s residential postcode was used as a measure of their socio-economic advantage (stratified from low to high) (Australian Bureau of Statistics, 2006).

10.2.2 Data collection

Demographic, sexual behaviour data and contraceptive use were collected at the time of recruitment with a ‘baseline’ questionnaire (Appendix U) and again at every three months period during the 12 month period which were sent to the participants through the post (Appendix V and Appendix W). The three monthly questionnaires also included questions about pregnancies conceived, and whether or not they had remained pregnant or were still pregnant, had had a spontaneous abortion or had had an IA during the study period. No information was collected about any pregnancies or IAs prior to being involved in the study. Women were eligible for participation if they were aged between 16 and 25 years old, had ever had vaginal sex with a man and intended to reside in Australia for the next 12 months. Women who were pregnant at the time of recruitment were ineligible for participation, although women were not tested for pregnancy at the time. Women who became pregnant during the study were encouraged to remain in the study.
10.2.3 Statistical analysis

IA rates and 95% confidence intervals were calculated using exact Poisson methods. Univariate hazard ratios and 95% confidence intervals were calculated to examine factors associated with IA. Pregnancy rates and 95% confidence intervals and associations were also explored. As participants were recruited from 29 clinics, all analyses were adjusted for clustering at the clinic level. It was not possible to conduct multivariate analyses because of the relatively small number of IAs and pregnancies reported by participants. All analyses were performed using STATA 11.1 (Stata Corporation, 2009). Ethics approval for the study was granted from ten human research ethics committees throughout Australia.

Chapter 5 of this thesis discusses the methods for the longitudinal study in more detail.

10.3 Results

10.3.1 Key results

Overall, 1116 women participated in the study with a response rate of 66%. Of these 1116, 877 (79%) completed the 12 month follow up. The mean age of the participants was 21 years old and the cohort was more well-educated and sexually active than the women of the same age group in Australia (Stata Corporation, 2009).

10.3.2 Pregnancy and induced abortion rates

During the course of the study, 72 women conceived 76 pregnancies during 1055.8 person years of follow up. The pregnancy rate for the study period was 7.2 per 100 woman years (95% confidence interval [CI]: 5.7, 9.0). Of these 76 pregnancies, 37 (49%) pregnancies were continued, 22 (29%) resulted in an IA, 11 (14%) spontaneously aborted, five (7%) women reported they were no longer pregnant but did not provide a reason why, and the outcome of one pregnancy (1%) was unknown. Four women had more than one pregnancy during follow-up and of these one had two IAs, two women had both a spontaneous abortion and an IA, and one woman had a spontaneous abortion and was pregnant again at last contact (Figure
The overall IA rate among women participating in this study was 2.1 per 100 women years (95% confidence interval: 1.4, 3.2), with an IA rate per 100 pregnancies of 28.9 (95%CI: 19.1, 40.5). There was a significant difference in the IA rate between the states with NSW [n=14, 3.5 per 100 women years (95% CI: 2.1, 6.0)] being significantly higher than ACT [n=2, 0.8 per 100 women years (95% CI: 0.1, 5.5)]. No differences were found between NSW or ACT and Victoria [n=7, 1.3 per 100 women years (95% CI: 0.6, 2.8)]. However, the IA rate per 100 pregnancies did not vary between the States [NSW 33.3% (95% CI: 19.6, 49.5), Victoria 26.9% (95% CI: 11.6, 47.8) and the ACT 13% (95% CI: 0.3, 52.6)].

Figure 10-1  Flowchart of numbers of pregnancies and outcomes during the study.
The ages of the women who had an IA during the study period were evenly distributed with a median age of 21 years. No demographic characteristics were found to be significant predictors for IA and there were no specific behavioural characteristics that were predictors for IA (Table 10-1).

Women who became pregnant during the study were more likely to be less well educated [HR=0.5; 95% (CI: 0.3, 0.8)] and in a relationship [HR=3.9; (95% CI: 1.7, 9.3)]. Socioeconomic status was not a predictor of pregnancy [HR: 1.2, (95% CI: 0.6, 2.4)] and there was no statistically significant association with age, employment status, number of new sexual partners, recruitment site or being born in Australia (Table 10-1).
Table 10-1  Unadjusted hazard ratios for women who had an induced abortion and pregnancy during the study period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women who have had an induced abortion</th>
<th>Women who have had a pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (% of women)</td>
<td>Unadjusted hazard ratio (95% CI(^a))</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21 years</td>
<td>12 (56%)</td>
<td>1.0 (0.6, 1.1)</td>
</tr>
<tr>
<td>&gt;20 years</td>
<td>10 (45%)</td>
<td>0.6 (0.3, 1.1)</td>
</tr>
<tr>
<td>Recruitment site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP clinic(^b)</td>
<td>15 (68%)</td>
<td>1.0 (0.3, 3.2)</td>
</tr>
<tr>
<td>SHS(^c)</td>
<td>7 (32%)</td>
<td>1.0 (0.3, 3.2)</td>
</tr>
<tr>
<td>Number of new partners(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 partners</td>
<td>13 (59%)</td>
<td>1.0 (0.9, 4.4)</td>
</tr>
<tr>
<td>1+ partners</td>
<td>9 (41%)</td>
<td>2.0 (0.9, 4.4)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 12 or less</td>
<td>15 (68%)</td>
<td>1.0 (0.2, 1.2)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>7 (32%)</td>
<td>0.6 (0.2, 1.2)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed/not working</td>
<td>7 (32%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Employed</td>
<td>15 (68%)</td>
<td>1.3 (0.4, 4.2)</td>
</tr>
<tr>
<td>Australian born</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3 (14%)</td>
<td>1.0 (0.2, 3.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>18 (86%)</td>
<td>0.8 (0.2, 3.0)</td>
</tr>
<tr>
<td>Socio-demographic status(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>15 (68%)</td>
<td>1.0 (0.6, 2.4)</td>
</tr>
<tr>
<td>High</td>
<td>7 (32%)</td>
<td>1.2 (0.6, 2.4)</td>
</tr>
<tr>
<td>In relationship (at baseline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3 (14%)</td>
<td>1.0 (0.8, 8.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>19 (86%)</td>
<td>2.5 (0.8, 8.5)</td>
</tr>
<tr>
<td>Area of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>7 (32%)</td>
<td>1.0 (0.4, 5.1)</td>
</tr>
<tr>
<td>Metro</td>
<td>15 (68%)</td>
<td>1.5 (0.9, 25.2)</td>
</tr>
<tr>
<td>State in Australia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT</td>
<td>1 (5%)</td>
<td>1.0 (0.4, 8.6)</td>
</tr>
<tr>
<td>Victoria</td>
<td>7 (32%)</td>
<td>4.7 (0.9, 25.2)</td>
</tr>
<tr>
<td>NSW</td>
<td>14 (64%)</td>
<td>4.7 (0.9, 25.2)</td>
</tr>
</tbody>
</table>

\(^a\) 95% confidence interval. \(^b\) General practice clinic. \(^c\) Sexual health service/Family Planning clinic. \(^d\) Number of new partners per stage of the study. \(^e\) Socio-economic status based on participant’s home address, using the ABS SEIFA indexes (Australian Bureau of Statistics, 2006)
10.4 Discussion

10.4.1 Key findings

We found an IA rate of 2.1 per 100 women years, a pregnancy rate of 7.2 per 100 women years and an IA rate per 100 pregnancies of 28.9% (95% CI: 19.1, 40.5) among sexually active women aged 16 to 25 year in this cohort of young Australian women. This IA rate is similar to the only reliable Australian data, the IA rate reported in South Australia of 2.2% among 15 to 24 year old women (Chan et al., 2007). If we compare these data with other developed countries, the Australian IA rate is slightly less than the rate reported in the United States (2.5% IA rate in 15 to 24 year old women in 2006) (Pazol et al., 2009), and the UK (2.8% in 15 to 24 year old women) (U.K. Department of Health, 2009).

10.4.2 Characteristics of women having an induced abortion

Significantly, women from NSW had the highest IA incidence, followed by Victorian women and then women from the ACT. This might be explained by women travelling interstate to have an IA which is common practice in Australia in particular women travel from the ACT and Queensland into NSW, and from Tasmania into Victoria. The reason for travelling is to ensure privacy and also perceived better clinical services (Nickson et al., 2004). The State or Territory demographic is not a reliable indicator for where services should be targeted and future policies and services should accommodate for this.

Despite not being statistically significant, there was some evidence to suggest that older women (21 to 25 years) had a lower IA rate compared with younger women (16 to 20 years) [HR=0.6 (95% CI: 0.3, 1.1)], and that women with a higher educational level had a lower IA rate [HR=0.6 (95%CI: 0.2, 1.2)] although this latter finding was likely to be confounded by age. There was also some evidence that women who had had at least one new sexual partner during the study, had a higher IA rate [HR=2.2 (95%CI: 0.9, 4.4)], but again this was not statistically significant. There was also some evidence to show that younger age was associated with pregnancy [HR=0.7 (95% CI: 0.4, 1.1)].
10.4.3 Comparison with other induced abortion data

There is limited information about the epidemiology of women in Australia who seek to have an IA (Abigail and Power, 2008). An analysis of the South Australian data reported that pregnancies in teenage women occur more frequently in lower socio-demographic regions however, teenage women having an IA are more likely to be from higher socio-demographic areas (Van der Klis et al., 2002). This is consistent with findings in the United Kingdom (Smith, 1993). Our analysis found no association between socioeconomic status and either IA or pregnancy.

10.4.4 Study context

These results have to be understood in the context of the CIRIS study aims. The CIRIS study was designed to determine chlamydia and *M. genitalium* incidence and not specifically IA incidence. No information was collected about the participants’ prior obstetric history including previous pregnancies and/or IAs and women which would have provided information about the incidence of primary IA. Also, women who were pregnant at the time of recruitment were ineligible for the study and the outcomes of those pregnancies were unknown. Another limitation was that we made an assumption that women who had decided to remain pregnant would not have an IA later in the pregnancy after leaving the study, yet younger women are much more likely to seek an IA at a later gestational stage than older women (Rowe et al., 2009).

10.4.5 Limitations and strengths

Another limitation was that our cohort only included sexually active women, and the most recent sexual behaviour data available estimate that about 44% of Australian women aged 16 to 19 years and 10% of women aged 20 to 24 years have never had sexual intercourse with a man (Smith et al., 2003). The South Australian rate of 2.2% is a population rate where the denominator includes both ever and never sexually active women; on this basis, it is likely that the IA rate in this study underestimates the actual IA rate in the underlying population of sexually active Australian women aged 16 to 25 years.
A further limitation was that we were unable to conduct any multivariate analysis because of the relatively small number of IAs and pregnancies. Future research would be beneficial with a greater number of women over a longer period of time.

The strength of this study was that this it is a large cohort study of young sexually active Australian women with a high participation rate (66%), a well represented population sample and a very high retention rate (79%). These are the first IA incidence estimates for Australian women from a community based cohort study.

10.5 Conclusion

As there is little information about IA in Australia, these data increase the overall knowledge about the number of young Australian women having IAs. In order to be able to direct services appropriately, further information would be required to understand the characteristics of the population of young Australian women who have IAs.
CHAPTER 11.

CONCLUSIONS

*Chlamydia trachomatis* is the most common bacterial sexually transmissible infection in young Australian women. Notifications only capture data for women who are tested and considering testing rates are low, notification data are very likely to underestimate the burden of chlamydia in the population. Currently, the Australian Government is piloting a chlamydia screening program to determine the most effective ways increase opportunistic chlamydia testing in general practice. Understanding the prevalence and incidence of chlamydia in the population will be crucial to the design of the pilot and to measure the effectiveness of the pilot.

Another sexually transmissible infection found in young women is *Mycoplasma genitalium*. *M. genitalium* also has been associated with upper genital tract infection including PID and tubal factor infertility, and increasing HIV transmission. In Australia *M. genitalium* testing is restricted to several sexual health and family planning clinics where testing is limited to symptomatic women or sexual contacts of people with *M. genitalium*. *M. genitalium* is not notifiable in Australia and there are no routinely collected epidemiological data. To date there have been no population based estimates for *M. genitalium* in young women and as a consequence the burden of disease attributable to *M. genitalium* in young Australian women is also unknown.

This thesis covered a three-year program of research in order to further understanding of the epidemiology of genital chlamydia and *M. genitalium*. The results of these studies provided the first population based prevalence estimates for *M. genitalium* and the first incidence estimates for chlamydia and *M. genitalium* in young Australian women. These data will inform the design of a future chlamydia screening program and *M. genitalium* policy including whether or not the time has come to develop a commercially available test for *M. genitalium*. 
11.1 The C-Alert Trial

The C-Alert trial was the first study in the thesis. This RCT demonstrated that a simple intervention such as a computer alert in general practice can increase general practitioners’ chlamydia testing rates in young women. Chlamydia testing rates in general practitioners are increasing gradually over time, however it is estimated that the testing rate would have to increase to 30% of 15 to 24 year old women annually to affect a change in chlamydia prevalence. In this RCT, the doctors in both arms of the trial increased their chlamydia testing rates during the trial period; importantly however, the doctors in the intervention clinics increased their testing rates significantly by 27% relative to the doctors in the control group. This was a small but significant increase in testing and demonstrated that the alert was effective. In practice, general practitioners will require more intervention than a computer alert, and considering the alert failed to load in a number of practices, it would not work as a standalone intervention for all clinics. The alert would be best utilised as one of many evidence based interventions to have a maximum effect. Other interventions which have led to successfully increasing preventive health measures in general practice include the use of incentive payments, utilising staff to drive particular preventive health programs such as practice nurses, increasing awareness of particular diseases and actively recalling patients when preventive activities are due. Designing a multi-faceted intervention including computer alerts, tailor made for each general practice would be the recommended approach for a comprehensive chlamydia intervention tool to increase general practitioners screening rates.

11.2 The CIRIS study

11.2.1 Chlamydia

The CIRIS study was the second study in the thesis. The results of the CIRIS study provided important population based prevalence, incidence and re-infection rates for chlamydia and *M. genitalium* in young sexually active women in Australia. Understanding the burden of disease associated with chlamydia is essential for chlamydia control. Incidence rates of 4.4% and a duration of infection of one year suggest annual screening would be effective, however the understanding the natural
history of chlamydia, in particular the temporal association between acquiring an infection and developing PID, will be essential for the determining the incidence of upper genital tract infection affected by the screening program. Our results suggest that symptoms of upper genital tract infection might occur within 12 months of acquiring an infection, however these assumptions were based on self-reported symptoms not confirmed diagnoses and therefore not substantiated. Further research exploring the temporal association between infection and upper genital tract infection are required to further explore this. Antibiotic use in Australia was also implicated as having a protective effect against chlamydia which might indicate that the incidence in Australia would otherwise be higher.

The most alarming finding of the CIRIS study was the high chlamydia re-infection rate, with approximately 20% of women who had a chlamydia infection at some stage testing positive again during the course of the study. This was despite patient education and supported partner notification. The high re-infection rate presents a major chlamydia control issue particularly considering repeat infections are more likely to be associated with upper genital tract infection. This high re-infection rate highlights the crucial need for retesting positive women for chlamydia 3 to 6 months after an infection which is likely to require increased effort and possibly more innovative methods, particularly considering chlamydia is commonly asymptomatic. The high re-infection rate also emphasises the importance of partner treatment, and the introduction of novel methods such as the use of the internet for partner notification. Considering the high degree of acceptability of patient delivered partner therapy (PDPT) by both patients and doctors, changing the legislation to allow PDPT might be applicable.

11.2.2 M. genitalium

The results from this study have provided the first epidemiological data for *M. genitalium* in young Australian women. The study results demonstrated that *M. genitalium* was found in up to 3% of young, sexually active women and had a mean duration of infection of up to two years. This is concerning as *M. genitalium* can cause upper genital tract infection and it is unlikely that a woman with an
asymptomatic infection would be tested for it in Australia. Also, unlike chlamydia, common background antibiotic use was not protective against *M. genitalium* as *M. genitalium* is resistant to many commonly prescribed antibiotics. This means that *M. genitalium* is unlikely to be treated indirectly when antibiotics are prescribed for another infection.

The CIRIS study also provided treatment failure rates for *M. genitalium* and further molecular analysis will determine if these treatment failures were due to infection with azithromycin resistant bacteria. Interestingly, treatment failure was associated with increased organism load, which could have implications for treatment of *M. genitalium*. Treatment for *M. genitalium* with an increased organism load might require an increased dose or longer course of azithromycin, or treatment with moxifloxacin might be recommended in these cases. Internationally there is evidence to suggest that azithromycin resistant *M. genitalium* is becoming more prevalent and further research is required with larger sample sizes to determine if organism load is contributor to this.

### 11.2.3 Comparison between the two infections

The study had the advantage of comparing two infections within the one population of women. Chlamydia prevalence was demonstrated to be about double *M. genitalium* prevalence (55:27) which was consistent with international data, and chlamydia incidence was about four times that of *M. genitalium*, suggesting the duration of infection of chlamydia was half that of *M. genitalium*. Interestingly unprotected sex was associated with both infections, however the strength of association was stronger with *M. genitalium* than for chlamydia which suggested the two pathogens might have different transmission dynamics. From the results it might be hypothesised that *M. genitalium* is less infectious than chlamydia requiring a greater “exposure” or direct genital or cervical contact to acquire an *M. genitalium* infection. This is supported by the 100 fold lower organism load among samples from women with *M. genitalium* compared with chlamydia.
11.2.4 Psychosocial consequences

The study identified that overall, women were glad to have had a test for chlamydia, however many women suggested they would not necessarily have another test in the future. Despite being pleased to have had a test, women who tested negative anticipated they would have a negative psychosocial impact from testing positive, and overall, all women were anxious and felt embarrassed by doing a test. Interestingly, the women who did test positive were less affected by having a positive result than negative women anticipated they would be. These results suggest there are still barriers that will need to be addressed before testing can become completely acceptable to young women. We might hypothesis that women were less affected than expected by a positive result because of their clinical management which they indicated was important on their questionnaires. We suggest from our analysis that sensitive clinical management of women when they test positive encouraged behaviour change, increased communication with others about testing positive, and reduced unnecessary concerns about future health outcomes. This is an important finding considering anxiety about having a test was a common experience when having a test, and if clinicians can be educated about the importance of addressing women’s concerns, this might increase their likelihood of having future tests.

11.2.5 Induced abortion

Data about pregnancies, induced abortions and miscarriages was collected from each follow up questionnaire which provided an incidental finding of the incident rate for induced abortion. Significantly, women from NSW had the highest IA incidence, followed by Victorian women and then women from the ACT. It appeared women travelled interstate to have an IA, in particular women from the ACT and Queensland into NSW, and from Tasmania into Victoria. This was hypothesised as being for privacy and also perceived better clinical services. These results have demonstrated that the State or Territory are not a reliable indicators for where services should be targeted and future policies should take this into consideration when directing appropriate services and funding.
11.3 Implications

This thesis demonstrates there is significantly more chlamydia in the population of young Australian women than is captured by current testing methods and that chlamydia control is essential. Currently, the government is pilot testing chlamydia screening in a randomized controlled trial and information generated from this trial will be essential to inform the design of a future chlamydia screening program, should it be decided to go ahead. It is likely that novel ways to increase testing and re-testing should be explored and tested to determine their effectiveness in reducing the prevalence of chlamydia in the population. Clearly re-infection is also a major concern and it is crucial that any chlamydia control must address re-infection and include partner notification strategies and retesting guidelines.

*M. genitalium* is not well understood in Australia with minimal testing and available data. These data indicate that *M. genitalium* is prevalent in young Australian women and the benefits of developing a commercially available assay for more extensive *M. genitalium* testing should be debated.

Recommended interventions

- Addressing the psychosocial implications of testing, educating both general practitioners and the women being tested to reduce anxiety and make testing more acceptable
- Discuss the option of legislating for the use of PDPT to reduce re-infection
- Include partner notification guidelines and recommended retesting intervals in all preventive guidelines for general practitioners and other clinicians involved in sexual health

Further research:

- Further explore the natural history of chlamydia, determine a standardized diagnosis for PID and ascertain the temporal association between acute infection and upper genital tract infection for both chlamydia and *M. genitalium*
• Determine the level of testing required to make chlamydia screening effective in young women

• Determine the most effective interventions or the most effective multi-faceted intervention to increase chlamydia screening effectiveness and reduce chlamydia prevalence and related upper genital tract incidence

• Investigate further the transmission dynamics, organism load and associations with clinical presentations and/or persistence of infection or re-infection for both chlamydia and *M. genitalium*

• Determine the effect of *M. genitalium* organism load on treatment failure and explore relative treatment options

• Further studies into novel methods for partner notification and decreasing the barriers to testing for both the women tested and general practitioners

• Identify gaps in general practitioner knowledge and increase specific education
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APPENDICES

Appendix A  Divisions of general practice advertising C-Alert

Chlamydia Trial

General practitioners are being recruited for a world-first trial which University of Melbourne researchers hope will triple chlamydia testing rates among participating clinics.

The trial involves a computer alert system which will remind doctors to discuss chlamydia testing with sexually-active women aged 16 to 24 when they access their medical records via the widely-used patient management and prescribing system Medical Director.

General practitioners participating in the trial, which is expected to start in March 2006, will be divided into two groups and the testing rates of doctors using the alert system compared to those who do not.

Project manager Dr Jane Hocking said researchers hoped the alert would triple testing rates among the high risk 16 to 24-year-old group, and prove an easy, cost-effective method of detecting the largely symptom-free but potentially debilitating infection.

“Up to 65 per cent of people with chlamydia do not have any symptoms but it is a leading cause of pelvic inflammatory disease and tubal infertility in women,” she said.

“The tragedy is that many of these complications could be avoided with a simple urine test and single dose of antibiotics.”

Dr Hocking, who produced Australia’s first statistics on the prevalence of chlamydia in the community, said women aged 16 to 24 were at greatest risk.

“Women aged 16 to 24 account for almost two-thirds of the 21,000 chlamydia cases reported in Australia every year among women, but less than 7 per cent of women in this age group are tested,” she said.

“In Victoria 3.7 per cent of sexually active women aged 16 to 24 have chlamydia and the rate of infection increases with an increasing number of sexual partners. Among those who have three or more partners in a year, the rate is 14.3 per cent. As about 12 per cent of the women in this age group reported having three or more partners in a year, this suggests there are a considerable number of undiagnosed infections in the community.”

The chlamydia computer alert trial is funded by the National Health and Medical Research Council and will be run in partnership by the University of Melbourne, Suniel Institute and Melbourne Sexual Health Centre.

Dr Hocking said researchers hoped that the trial could become used as a model for a future national chlamydia screening program.

CONTACTS:
Dr Jane Hocking
Tel: (03) 8344 9354
Mob: 0416 376 838
Email: j.hocking@unimelb.edu.au

Ms Jennifer Walker
Tel: 03 9341 6265
Email: jwalker@mshc.org.au
Appendix B C-Alert letter of introduction to general practitioners.

Genital chlamydia infection - announcing a study to investigate chlamydia testing in general practice.

Chlamydia trachomatis infection is the most common notifiable sexually transmissible infection in Australia, with over 30,000 infections notified in 2003. Infection with chlamydia can have considerable complications, particularly for women – it is a leading cause of pelvic inflammatory disease and tubal infertility. Unfortunately, as many as 85% of people with infection do not have any symptoms, so are unaware they have chlamydia; yet chlamydia is easy to diagnose with urine tests and easy to treat with single dose antibiotics. Over 65% of infections diagnosed in women are among those aged 16 to 24 years. Internationally, screening programs for chlamydia have reduced the number of people with the infection and the rate of complications arising from infection. However, Australia does not have a screening program and only tests about 6% of 16 to 24 year old women, the largest group at risk of infection, each year.

The National Health and Medical Research Council (NHMRC) has funded the Sexual Health Unit and the Department of General Practice at the University of Melbourne to undertake a randomized controlled trial to investigate the affect of a computer-based alert on chlamydia testing rates in general practice. This alert is designed to prompt general practitioners to discuss chlamydia testing with sexually active women aged 16 to 24 years. General practices will be randomly allocated to have the alert installed on their computers and chlamydia testing rates among 16 to 24 year old women will be observed over a 12 month period. GPs are eligible for participation in this study if their practice is based in Melbourne and they use Medical Director as their medical records database. Participating GPs will receive a chlamydia educational program and will be eligible to apply for RACGP QA&CPD points.

Further information about this study or GPs interested in participating in this study can contact Professor Christopher Fairley at the Sexual Health Unit (ph: (03) 9341 6236; email: cfairley@unimelb.edu.au) or Ms Jenny Walker at the University of Melbourne (ph: (03) 9341 6265 or email: jwalker@mshc.org.au)
Appendix C  
C-Alert consent form

PROJECT TITLE:

A computer alert to increase chlamydia testing of high risk women in general practice: a randomised controlled trial. Funded by National Health and Medical Research Council.

Name of investigator(s): Professor Christopher K Fairley, Dr Jane Hocking, A/Prof Jane Gunn, Dr Lyle Gurrin, A/Prof Robert Carter, Dr Marie Pirotta.

I have read, and I understand the Plain Language Statement of the above-mentioned research project.

I consent to participate in the project named above, the particulars of which include allowing an alert to be placed on Medical Director, completing two questionnaires, providing permission for de-identified data to be collected from Medical Director and the pathology providers for the chlamydia testing. I understand any information I provide will be kept confidential subject to legal limitations.

I understand that the project is voluntary and that I am free to withdraw at any time, or to withdraw any information that I have previously supplied.

I freely agree to participate in this project according to the conditions in the Plain Language Statement. I have a copy of the Plain Language Statement to keep.

Participant’s Name (please print)…………………………………………

Signature: Date:

Witness to Signature (please print) ………………………………………

Signature: Date:

Please note: If you would like a summary report of this project please indicate this by selecting the appropriate box:  YES □  NO □
Appendix D  Release of pathology request form

Pathology Provider Request Form

I, Dr_____________________________, (Provider no.:______________).

Time period: __/__/____ to __/__/____

request that the following de-identified data be released to The University of Melbourne for the 12 month duration of the C-Alert trial including 12 months prior to the commencement of the trial:

The number of women aged 16 to 24 years who have at least one chlamydia test ordered:

________

The number of chlamydia tests ordered for 16 to 24 year old women:

________

The number of women who have had at least one positive chlamydia test.

________

The number of positive chlamydia test results among 16 to 24 year old women.

________

Please return this copy to the University of Melbourne in the reply paid envelope.

Sincerely,

_________________________

(signed)

________

(date)
Appendix E  C-Alert Plain language statement

**Title:** A computer alert to increase chlamydia testing of high risk women in general practice: a randomised controlled trial. Funded by National Health and Medical Research Council.

**Principal investigators:** Professor Christopher Fairley*, Dr Jane Hocking, A/Prof Jane Gunn, Dr Lyle Gurrin, A/Prof Robert Carter, Dr Marie Piratta.

*Contact details:* Melbourne Sexual Health Centre,
580 Swanston Street Carlton, 3053.
Telephone 9341 6236, Mobile 0438 155 536,
email: cfairley@unimelb.edu.au

**The project:**
You are invited to take part in this research project the aim of this project is to determine if an electronic alert on Medical Director will increase testing for genital chlamydia infection among women between 16 and 24 years of age who attend your practice. Research has shown that testing of these women identifies a significant number with chlamydia and prevents long term complications such as infertility, ectopic pregnancy and chronic pelvic pain. Currently only about 6% of women in this age group are tested despite chlamydia testing being widely implemented overseas. This project therefore addresses the issue of how to increase testing for chlamydia among young women.

**What the project will involve for you:**
If you choose to participate in the study your practice will be randomised to one of two groups. The first group will have an electronic alert installed on Medical Director and the other group will not. Both groups will receive information with an education package about the prevention of chlamydia and other STIs. The duration of the study is 12 months.
The alert:
The alert will be activated every time you see a woman between 16 and 24 years of age and will read:

Think Chlamydia – The RACGP ‘Red Book’ recommends a first pass urine test or self collected vaginal swab for all sexually active women under 25 years.

We have obtained permission from the Health Insurance Commission who has indicated that testing for chlamydia along the lines indicated above does not represent “screening” and is allowed under the HIC guidelines.

You will also be asked to:

- Complete two questionnaires about your knowledge, attitudes and practices about chlamydia other STIs.
- Provide permission for data to be extracted from Medical Director, and your general practice pathology provider(s) for the year before the study, and year of the study. The data will include: the age/sex profile of the patients, the number of 16 to 24 year old women seen at the practice, the number of consultations with 16 to 24 year old women, the number of women aged 16 to 24 years who have at least one chlamydia test ordered, and the number of positive chlamydia test results among 16 to 24 year old women. Only de-identified data will be extracted. No patient identifying information will be obtained or used. No clinical information about patients will be collected.

As part of the project we will provide all practices who participate with:

- An educational package on chlamydia free of charge, at a time that suits you. This will attract RACGP QA&CPD points.
- Provide you with a 1800 number direct to a Sexual Health Physician at Melbourne Sexual Health Centre for questions relating to the study or Sexual Health.
- $150 for any costs associated with the study.
Privacy, confidentiality and disclosure of information:

Your participation in this study is confidential.

All data will be stored in a locked cabinet in the research unit at Melbourne Sexual Health Centre (MSHC) or on password protected computers and password protected files at MSHC. Following completion of the study all related documents or information would be archived for 15 years, in accordance with the NHMRC statement of clinical research.

Results of project:

The results will be published in a medical journal but without any identifying information. If you would like a summary report of this project please indicate this to us on the consent form.

Further information or any problems:

If you have any queries about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

Name: Christopher K Fairley
Position: Professor of Sexual Health, University of Melbourne,
         Director, Melbourne Sexual Health Centre
Telephone: (03) 9341 6236

If you have any complaints or concerns about the conduct of this study, please contact the Executive Officer, Human Research Ethics, The University of Melbourne, 8344 2073; fax: 9347 6739.

Participation is voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the study at any stage.

If you decide to withdraw from this project we would be grateful if you could notify a member of the research team promptly rather than waiting until the next follow-up contact.

Ethical Guidelines

This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.
Appendix F  GP education and information folder

1. Cover of the education package including the DVD
Dear General Practitioner,

Thank you for participating in the chlamydia ‘C-Alert’ study. Please read the enclosed ‘plain language statement’ which explains the background and the conditions for the trial. Once you have read the plain language statement, sign the consent form and return it to the C-Alert team. There is a letter for you to send to the pathology provider/s that you use for chlamydia testing requesting the release of de-identified data to the research team, and once this has been done, please complete the initial questionnaire and return it in the enclosed ‘Reply Paid’ envelope.

As part of your involvement in the trial, you will be given an education package which contains information about chlamydia and other sexually transmissible infections. There is a pen with a contact number for the Sexual Health Advice Hotline for clinicians and the website address for the Melbourne Sexual Health Centre, which is free of charge. There is also a list of references should you require any further information about any other sexual health issues.

For your clients that test positive for chlamydia there is a letter to forward to their previous sexual partners, as well as a pamphlet explaining some basic information about chlamydia. Treating the sexual partners of someone with a positive chlamydia diagnosis is an important component of chlamydia management and more information about partner notification can be found at the Melbourne Sexual Health Centre website.

This Clinical Audit activity has been approved by the RACGP QA&CPD Program. Total CA Points for Steps 1-5: 30 (Category 1). On completion of your participation in the trial, the investigators will submit an application for credit for 30 QA&CPD points with the RACGP on your behalf.

For further information please contact the 1800 number or refer to the list of resources enclosed. For more information about the trial please contact Professor Christopher Fairley on 9341 6236 or Jennifer Walker on 9341 6265.

Sincerely,

Christopher Fairley
Professor of Sexual Health
University of Melbourne
Director Melbourne Sexual Health Centre
580 Swanston Street
Carlton Vic 3053
Appendix G  National Management Guidelines for STIs’ booklet cover
Appendix H  Letter for partner notification

Information for Sexual Partners of People with Genital Chlamydia Infections

Dear [Partner's given name only],

Date

A sexual partner of yours has just been treated for a sexually transmitted infection. This means that you may also be infected. The infection is called *chlamydia* (C. trachomatis) and most cases of chlamydia are easily cured with antibiotics.

Chlamydia bacteria can infect the womb (cervix) in women and the tube inside the penis (urethra) in men. Sometimes it can infect the throat and anus of both men and women. Many people do not know they have the infection, as there may be no signs or symptoms.

**In women the symptoms may be:**
- a vaginal discharge;
- a burning feeling when passing urine;
- deep pain or bleeding during or after vaginal sex.

**In men the symptoms may be:**
- a white or clear fluid discharge from the penis;
- a burning feeling when passing urine;
- long term irritation within their penis, or testicles;
- pain in the joints.

If left untreated, chlamydia can cause pelvic inflammatory disease (PID) in women, which can lead to chronic pain and future difficulty in becoming pregnant.

**Partners of people with chlamydia need to be treated even if they have no symptoms.** If partners are not treated then there is a possibility of becoming infected again during sex. If your tests show that you are also infected then any sexual partners you had unsafe sex with (without condom use) are at high risk of the infection.

**Please see a doctor and show them this letter.** The doctor will need to do a urine or swab test, and give you antibiotics. If treated early chlamydia can be easily cured with a single dose of antibiotics. Advanced chlamydia and PID in women may need longer courses of antibiotics.

**Information for Your Doctor**

The majority of patients with chlamydia will be asymptomatic. However, patients may present with a number of clinical symptoms and signs, including urethral discharge, dysuria, abdominal or pelvic pain, mucopurulent cervicitis, vaginal discharge and irregular vaginal bleeding.

It is recommended that sexual partners of a person with genital chlamydial infection should be tested, and treated at the time of presentation and regardless of the absence of symptoms to reduce the risk of further spread of the infection. The currently recommended treatment for asymptomatic cases or uncomplicated cervicitis and urethritis is:

- Azithromycin 1g orally as a single dose OR Doxycycline 100mg orally 12-hourly for 7-10 days

For recommendations on alternative antibiotic regimens, the treatment of pregnant women and the treatment of complicated chlamydial infections, please refer to the latest edition of the *Antibiotic Guidelines* and the *National Management Guidelines for Sexually Transmissible Infections*.

If you or your patient have any questions or concerns please contact the Department of Human Services' partner notification officer on telephone (03) 9637 4114 or the Melbourne Sexual Health Centre's duty physician on (03) 9347 0244.

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2. Victorian Society of Infectious Diseases, National Guidelines for Gonorheal Infections, Victorian Society of Infectious Diseases, Melbourne.

October 2003  Page 1 of 1
5.2 Chlamydia

|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-----|

All sexually active females under 25 years of age should be screened opportunistically for chlamydia infection(A). Those infected should be screened again after 6-12 months because of the high risk of re-infection. Male partners of infected females should be treated (A) (Men who have sex with men should be screened for chlamydia and other STIs every 12 months (B) (158).

### Who is at higher risk?

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>What should be done?</th>
<th>How often</th>
<th>Level of evidence &amp; references</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sexually active women under 25 years of age</td>
<td>Urine or endo-cervical swab for ligase chain reaction (LCR) or polymerase chain reaction (PCR)</td>
<td>Opportunistically</td>
<td>IIA (158-161)</td>
</tr>
</tbody>
</table>

### High Risk

| All sexually active teenagers, particularly female, Aboriginal or Torres Strait Islander, and those with pattern of inconsistent or no condom usage, or with recent change in sexual partner | Urine or endo-cervical swab for LCR or PCR (consider screening for other STIs) | Every 12 months | IIA (158-161) |

### HIGH RISK MEN

| Men who have anal sex with men | Urine for PCR and blind rectal swab for PCR (consider screening for other STIs) | At least every 12 months | III B (162) |

### SEXUAL PARTNERS OF INFECTED WOMEN AND MEN

| Test and then treat immediately | Every 12 months | IIA (163, 164) |

### Intervention - Test Technique Site References

| PCR/LCR | Should be (20ml) first void urine (not mid stream) or at least one hour after last void. This has been found to be the best performing test in both sexes. Urine samples should be kept at under 4 degrees C. Room temperature reduces sensitivity of LCR. PCR endocervical or low vaginal swab (patient can self collect) also possible in females. There has been no validation of this technique for anal or throat swabs | Urine, endo-cervix or Vagina. | (162, 165) |

| Elisa swab | Inferior to PCR/LCR Cheap, variable sensitivity and specificity, stores at room temperature | Endo-cervix, urethra | (162, 165) |
Appendix J  Educational material provided in the educational package

Follow Up
If you have been diagnosed with chlamydia, your doctor or nurse will advise you to have repeat testing. It is important to have regular tests if you have new sexual partners because it is possible to be reinfected.

Safer Sex
Remember your best protection against sexually transmissible infections (STIs) is to use barrier protection such as condoms, female condoms and dams.

Family Planning Victoria
901 Whitehorse Road
Box Hill VIC 3128
Tel: 03 9255 9800
Fax: 03 9255 9801

Action Centre
Level 1, 14 Elizabeth Street
Melbourne 3000
Tel: 03 9654 4766
1800 033 962

Chlamydia

Contact: 03 9996 6700
Hoppers Crossing: 04 9922 4895
Shoppers World: 04 7230 2800

Sexual Health & Family Planning Victoria
National Secretariat Sydney: 02 8752 4340
International Programs Canberra: 02 6230 5255
www.fpv.vic.gov.au

* Lists state and territory contact details.
What is it?
Chlamydia is a common sexually-transmissible infection (STI), caused by bacteria called Chlamydia trachomatis. Both men and women can have chlamydia. If someone has chlamydia, they can pass it on to their sexual partners the people you have had sex with) through oral, vaginal and anal sex.
Chlamydia can be carried in the female cervix, the male urethra (tube in the penis which carries urine and sperm) and the throat and rectum of both sexes.

How do I know if I have it?
Chlamydia infection can cause a variety of symptoms ranging from no symptoms at all, to discharge from the vagina or penis, pain when passing urine and abdominal bleeding or pain in the lower abdomen. It is very common to have no symptoms at all.
This can mean that you are completely unaware of having chlamydia and unaware if you pass it on.
Tests:
Chlamydia can be tested for by either a urine or swab test. The doctor or nurse will explain which test is preferable for you and how it is done. The most common test done now for men is a urine test; women may have either a urine or swab test taken.

How do I prevent it?
The best protection against getting chlamydia is to use condoms (either male or female condoms) when having vaginal or anal sex. Condoms and dental dams can be used for oral sex to help prevent chlamydia infections. A dam is a thin latex sheet placed over any part off the body for safer oral sex.

How is it treated?
Chlamydia is treated with antibiotics (usually just two tablets). It is important to treat all partners who have chlamydia, as you can get chlamydia infections more than once. Remember, the treatment is simple, easy and effective but not receiving treatment can have serious results.

What happens if it is not treated?
If it is not treated, chlamydia can cause complications, the most important of which is infertility.
Women may get an infection (Pelvic Inflammatory Disease), in their uterus (womb) and tubes, which can prevent them from becoming pregnant in the future.
Men may experience complications e.g. testicular and lower abdominal pain.
For both sexes, the pain from the complications can be very distressing.
If a woman is pregnant and has chlamydia, it is possible to pass the infection on to a baby during delivery. This can affect the baby’s eyes, nose, throat or lungs. Chlamydia can be treated during pregnancy, which will protect the baby.

What happens to my partner/s?
If you are found to have chlamydia, it is very important that your sexual partners are tested and have treatment. As people can be unaware they have chlamydia, it may be difficult to know who you got it from and how you were infected. Your doctor or nurse can help you with contacting your partners, or can arrange for this to be done anonymously.
Appendix K  C-Alert general practitioner educational DVD
Appendix L  C-Alert questionnaire

c-alert: General Practitioner questionnaire

PART A: DEMOGRAPHICS
Please provide some demographic information and your interest in sexual health medicine (please fill in the boxes below):

1. Your age: _______ years
2. The year you graduated from medicine: _______
3. Years in general practice: _______ years
4. Number of hours you work in general practice, in an average week: _______ hours
5. Your usual clinical practice postcode: _______
6. Please list your RACGP number (this is required if you wish to claim the CPD points): _______
7. Do you have any of the following postgraduate qualifications (please tick one or more boxes)?
   □ Diploam of G&O
   □ FRACP
   □ FRACGP
   □ FAAPSHM
   □ PhD
   □ Other (please specify):

8. How much interest do you have in the management of sexually transmitted infections?
   □ Very Interested
   □ Moderately Interested
   □ Not very Interested

calert  [Institution Logo]  [Institution Logo]  [Institution Logo]  [Institution Logo]  [Institution Logo]
PART B: KNOWLEDGE OF CHLAMYDIA RISK

1. Below are three case histories of patients whom you may encounter in general practice. Please indicate whether you would consider screening them for chlamydia as part of their routine clinical management (please tick your best answer for each question).

a. 16 year old female. In a 6 month relationship, pregnant with a history of sexual activity from the age of 15, visits you for the first time.
   - Definitely
   - Probably
   - Probably not
   - Definitely not
   - Uncertain/don’t know

b. 40 year old married female with no symptoms while on the oral contraceptive pill.
   - Definitely
   - Probably
   - Probably not
   - Definitely not
   - Uncertain/don’t know

c. A sexually active 24 year old female presents with deep dyspareunia.
   - Definitely
   - Probably
   - Probably not
   - Definitely not
   - Uncertain/don’t know

2. Which one of the following risk factors for chlamydia is most strongly associated with a high prevalence of infection? (Please tick only one box).
   - New sexual partner
   - Young age (<26 years)
   - Use of the OC pill for contraception

PART C: DIAGNOSIS AND MANAGEMENT OF CHLAMYDIA IN GENERAL PRACTICE

We would like to know how you screen and treat genital chlamydia infection in your general practice (please tick your best answer for each question).

1. How often would you screen for chlamydia in:

a. A sexually active female under 25 years of age with a vaginal discharge?
   - Never
   - Sometimes
   - About 50% of the time
   - Usually
   - Always

b. A sexually active female under 25 years of age with no genital symptoms, who is attending for a non-sexually related complaint?
   - Never
   - Sometimes
   - About 50% of the time
   - Usually
   - Always

c. A sexually active male under 25 years of age with dysuria?
   - Never
   - Sometimes
   - About 50% of the time
   - Usually
   - Always

d. A sexually active male under 25 years of age with no genital symptoms, who is attending for a non-sexually related complaint?
   - Never
   - Sometimes
   - About 50% of the time
   - Usually
   - Always

2. In your clinical practice please specify the percentage of time you use different specimens to test for chlamydia.

a. in female patients? (% should add up to roughly 100).
   - % Cervical swab
   - % Pap smear
   - % High vaginal swab
   - % Urine specimen
   - % Pharyngeal swab
   - % Other (please specify):

b. in male patients? (% should add up to roughly 100).
   - % Urinalysis
   - % Urine specimen
   - % Pharyngeal swab
   - % Other (please specify):
   - % Do not test

3. When you screen a patient for chlamydia in your clinical practice, does it increase your consultation time on average?
   - Yes - if yes, how many minutes does it usually add to the consultation: ___ min
   - No

4. Do you ever use a practice nurse or counsellor to discuss chlamydia screening with any of your patients before a test is done?
   - Yes - if yes how often:
   - Sometimes
   - About 50% of the time
   - Usually
   - Always
   - No

5. Do you require patients to return for a second consultation to discuss their chlamydia test results (regardless of whether results are positive or negative)?
   - Yes
   - No

6. Do you require patients who test positive to return for a second consultation to discuss their results and prescribe treatment?
   - Yes
   - No
7. How do you usually inform patients of their chlamydia test results? (Please tick where appropriate).
   □ I will ask them to make an appointment for another consult
   □ I will telephone them with results
   □ I will mail the results to them
   □ Receptionist or nurse will telephone them with results
   □ Other (please specify):______________

8. Besides you, the general practitioner, are there any other members of staff that have a role in the management of chlamydia infected patients? If so, who are they? and what do they do?

9. What do you usually prescribe for an uncomplicated genital chlamydia infection? And what do you usually prescribe if a patient is pregnant? (Please include any generic names and doses).
   a) Usually prescribe:_________________________
   b) If pregnant prescribe:_____________________

10. Having given treatment for an uncomplicated infection of chlamydia to a patient, and assuming they present with no further symptoms or complications, do you usually require them to attend for an additional re-testing? If so, when?
    □ Yes - if yes, when: in ___ weeks OR in ___ months
    □ No

11. When you diagnose chlamydia, how often would you recommend testing their sexual partners?
    a. if partners were male?
       □ Never               □ Sometimes               □ About 60% of the time               □ Usually               □ Always
    b. if partners were female?
       □ Never               □ Sometimes               □ About 60% of the time               □ Usually               □ Always

12. How do you usually ask index cases to contact their partners?

13. How often would you treat partners empirically for chlamydia without actually testing them?
    a. if partners were female?
       □ Never               □ Sometimes               □ About 60% of the time               □ Usually               □ Always
    b. if partners were male?
       □ Never               □ Sometimes               □ About 60% of the time               □ Usually               □ Always

14. Have you ever used any services available to help with contact tracing following a chlamydia diagnosis? (Please tick where appropriate).
   □ Victorian Department of Human Services contact tracers
   □ Melbourne Sexual Health Centre advice
   □ Victorian Department of Human Services contact tracing letters
   □ Melbourne Sexual Health Centre letters
   □ Other please specify:______________________

15. How far back in months would you enquire about tracing sexual partners of a chlamydia infected patient? __ months

16. On average how many consultations would you be involved in the care of a patient who you test for chlamydia from initial contact to final consult? __ consultations

17. Approximately, what is the usual total time you spend with a chlamydia infected patient from initial contact to final consult? __ hours OR ___ minutes
Appendix M  Map showing the locations of the C-Alert clinics
Appendix N  Confidentiality agreement signed by the CIRIS research assistant

Clinic name: ______________________________

PRIVACY AND CONFIDENTIALITY AGREEMENT

PREAMBLE

- The Health Records Act came into effect in March 2002. All information collected in the course of providing a health service must be handled in accordance with the Health Privacy Principles extracted from the Act.
- Privacy is not just something we are required to do by law, but something we value, and it will continue to be an integral part of our professional, ethical and legislative obligations.
- The Health Records Act and our confidentiality agreement ensure that we are aware of the important issues related to recording and storing client information, and whom it is shared with. It will enable us to develop an awareness of the client’s perspective with regard to what information is accessible to them.

CONFIDENTIALITY DEED

This deed is made on: ______________________________ Date

I ____________, a ______________

Name     Occupation

with the Chlamydia Incidence and re-Infection Rates Study (CIRIS) am aware of the Health Privacy Principles extracted from the Health Records Act 2001 (Vic). I am aware of the following websites to seek information:


I am aware that this deed is offered to visiting professionals as a best practice strategy, and is designed to ensure that I am aware of my obligation to abide by the law regardless of signing.
Full Project Title: Chlamydia incidence and re-infection rates: a longitudinal study of young Australian Women.

☐ I have read, and I understand the Participant Information Form version 1.1 dated 15th January 2007.

☐ I freely agree to participate in this project according to conditions in the Participant Information Form.

☐ I will be given a copy of the Participant Information Form and Consent Form to keep.

☐ The researcher has agreed not to reveal my identity and personal details if information from this study is published or presented in any public form.

Part 1 – The Chlamydia Study

☐ I give my consent to participate in Part 1 – the Chlamydia Study.

☐ I give my consent to allow my doctor to give the results of my chlamydia test conducted today to the study investigators.

☐ I understand that future chlamydia tests conducted during the study are for research purposes only.

☐ If I test positive for chlamydia at any stage during the study, I give my consent to allow further tests on my sample to determine the genotype of the infection.

☐ I give my consent to allowing my samples to be stored for testing at a later stage.
Part 2 – Other Vaginal Infections

☐ I give my consent to participate in Part 2 – Other Vaginal Infections

Follow up

☐ I give my consent to being sent a questionnaire and a kit for collecting samples in the post at 3, 6, 9 and 12 months to the following address:

| Preferred Name: |  |
| Contact Address: |  |

☐ I give my consent to receive a reminder message from the study investigators at 3, 6, 9 and 12 months by:

☐ Telephone: Provide Number ________________________________

OR:

☐ SMS Text Messaging: Provide Number ____________________________

OR:

☐ E-mail: Provide address ____________ @ ____________

Receipt of Results

It is important that we give you your test results during the study. You can receive your test results from either your own doctor or from the study investigators. Please indicate how you would like to receive your test results.

☐ I wish to receive my test results from my own doctor: YES/NO

Please provide your doctors contact details:

| GP Name |  |
| Contact Address: |  |


I give my consent to the study investigators providing my doctor with my follow up test results

I wish to receive my test results from the study investigators **YES/NO**

**Please provide my results by:**

- Telephone: Provide Number (as above or list other) __________________________

**OR:**

- SMS Text Messaging: Provide Number (as above or list other) __________________________

**OR:**

- E-mail: Provide address (as above or list other) __________________________

_________________________ @ __________________________

I would like to be contacted if an organism (virus or bacteria), found on my stored vaginal swab, is found to be relevant to my health **Yes / No**

If yes, please contact me in the following way

_____________________________________________________

When the study is finished, I would like a copy of the summary study results sent to me: **Yes / No**

If Yes, write the address you would like this sent to:

- Email (as above or list other) ___________@_____________________

- Mail (as above or list other)
Withdrawal from study

I understand that I can withdraw from the study at any time by telephoning the study investigators of 1800 082 820

Participant name (printed) ________________________________

Signature:                                             Date: ....../....../

Name of Witness to Participant’s Signature (printed)

_____________________________________________________________

Signature:                                             Date: ...../....../......

Researcher’s Name (printed) ________________________________

Signature:                                             Date...../....../......
Project Title: Chlamydia incidence and re-infection rates: a longitudinal study of young Australian Women.

REVOCATION OF CONSENT FORM

Version 1.1 Dated 15 January 2007

I hereby wish to WITHDRAW my consent to participate in the research proposal described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with my health care provider.

Participant’s Name (printed) .................................................................

Signature Date:
PARTICIPANT INFORMATION FORM
Version 2.0; Dated: 8th October 2007 (Vic)

Project Title: Chlamydia incidence and re-infection rates: a longitudinal study of young Australian women (CIRIS).

Principal Researcher: Dr. Jane Hocking

Associate Researchers: Prof. Christopher Fairley, Prof. Frank Bowden, Prof. Basil Donovan, Dr. Marcus Chen, Prof. John Kaldor, Prof. Jane Gunn, Dr. Marie Pirotta, Dr. Veerakathy Harindra, Dr. Lyle Gurrin, A/Prof. Sepehr Tabrizi, Prof. Suzanne Garland, Dr. Kathleen McNamee, Mr. Hudson Birden, Dr. Catriona Bradshaw.

This Participant Information Form is five (5) pages long. Please make sure that you have all the pages.

1. We seek your consent to participate in this project

If you are aged between 16 and 25 years, you are invited to take part in this research project being conducted by the University of Melbourne in collaboration with Family Planning Victoria, Royal Women’s Hospital, Australian National University, National Centre in HIV Epidemiology and Clinical Research and Northern Rivers University Department of Rural Health. The project is funded by the Commonwealth Department of Health and Ageing.

This Participant Information Form contains detailed information about the research project. Please read this Form carefully. Feel free to ask any questions about any information in the Form before you decide whether you want to participate in this project.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign a Consent Form. By signing the Consent Form, you indicate that you give your consent to participate in this research project.
2. The purpose of the project

There are two parts to this project:

**Part 1 - Chlamydia**

The Chlamydia Incidence and Re-Infection Study (CIRIS) has two purposes – 1) to determine how often young women become infected with chlamydia infection over a year, and 2) to determine how many young women with chlamydia become re-infected (infected again) over a year.

Chlamydia is a common sexually transmitted infection in young people. People with chlamydia often don’t have symptoms and if it is left untreated, it can cause infertility. It is easy to diagnose with a urine sample or a vaginal swab that you collect yourself. It is simple to treat using antibiotics.

The information from this project will help decide how often young women in Australia should be tested for chlamydia.

**Part 2 - Other vaginal infections**

We are also seeking your permission to test for two other vaginal infections - bacterial vaginosis (BV) and *Mycoplasma genitalium* (MG). But please note, you can choose to participate in part 1 only - the Chlamydia Incidence and Re-Infection Study – it is up to you.

MG is another sexually transmitted infection. We think it may behave in a similar way to chlamydia as it is possible that it may also cause infertility in some women. We don’t know how many Australian women have this infection. Your participation in this part of the study would help us determine how common this infection is.

BV is a common vaginal condition. It sometimes causes an unusual vaginal discharge or odour, but many women with BV do not have any symptoms. Doctors generally don’t treat BV unless the woman has symptoms. We currently don’t know how common BV is in Australian women, and your participation in this project would help determine this.

A total of 1400 women will be recruited from clinics across Victoria, New South Wales and the Australian Capital Territory.
3. What participation will involve

Part 1 - Chlamydia

At today’s visit, a Research Assistant will explain the study to you, and if you agree to take part, you will be asked to sign the Consent Form. You will be asked to complete a questionnaire that will take about 5-10 minutes. This questionnaire will ask you questions about your sexual health and whether you have any genital symptoms. In addition, you will be asked to provide 2 specimens to be tested for chlamydia – either 2 vaginal swabs you collect, or if your doctor does a genital examination, he or she may take the swabs. One specimen will be tested for chlamydia by the laboratory that your doctor uses. The other specimen will be stored at the Royal Women’s Hospital and may used at a later date for further testing by the study investigators.

Self-collected vaginal swabs are easy to take - the Research Assistant will give you instructions on how best to do it; it is a bit like inserting a small tampon. If you are menstruating (having your period), it doesn't matter – please still provide a specimen.

Your doctor will give you your initial chlamydia result and provide you with treatment if necessary. Your doctor will tell you when the results will be available.

We would like to contact you by mail at 3, 6, 9 and 12 months and ask you to answer a questionnaire at each time. We will also ask you to collect another vaginal swab for chlamydia testing at least twice during the 12 months. The exact times for collecting the swab will depend on whether your last test for chlamydia was positive or negative. At a minimum, we will ask you to collect a swab at 6 and 12 months, but if a test is positive, it is recommended that you are tested again 3 months later. We will send you a swab collection kit in the mail when necessary. The kit will consist of a vaginal swab and instructions on how to take the swab. Your name and contact details will not be recorded on the questionnaire or vaginal swab container – only a non-identifying code will be used. We will ask you to post the swab and questionnaire in the supplied post pack and mail it in an Australian Post red mail-box. All postage will be prepaid. We will send you a message by telephone, SMS or email telling you to expect the specimen collection kit in the post shortly.
Unless you tell us otherwise, your doctor will give you your chlamydia results and provide you with treatment where necessary. Results should be available two weeks after you have posted the vaginal swab to the laboratory. We will supply the chlamydia treatment free of charge to your doctor.

If you test positive for chlamydia at any stage in the project, we would like to conduct further tests on the sample you provide to determine the genotype (strain) of the infection. Like the common cold and the flu, there are many different strains of chlamydia. This testing will help us understand which strains of chlamydia are present among Australian women.

You will be reimbursed $10 for returning the questionnaire and specimen (if requested) at 3 months, $20 at 6 months, $20 at 9 months and a further $50 at 12 months as recognition for your time and effort in participating in this project. These will be paid to you on receipt of your swab or questionnaire at each stage of the study.

We also seek your consent to keep your vaginal swabs at the Royal Women’s Hospital for future testing if for example, improved technology becomes available or if any future research detects bacterial and other organisms that might be the cause of vaginal infections. You need to indicate if you would like us to contact you in the future with the results of these tests if they are considered to be important. Only a non-identifying code will be recorded on these swabs.

**Part 2 – Other vaginal infections**

If you consent to participate in part 2 of the project, we will test your vaginal swabs for MG and BV.

The vaginal swab you provided for Part 1 will be able to be tested for these infections as well. However, you will also need to make a smear of the swab on a glass slide for testing for BV. This only means that the vaginal swab you have collected is also dotted or smeared onto a glass slide that we will give you. It is simple and quick, and we will give you instructions on how to do this.

Unless you tell us otherwise, your doctor will also give you your results for MG and provide treatment where necessary. Results should be available two weeks after you have posted the vaginal swab to the laboratory. If you are diagnosed with MG, you will be asked to provide an additional swab test a month after treatment to check whether treatment has been effective.
We will not be testing the swabs and glass slide for BV until the end of the study. This is because treatment is not recommended if you do not have any symptoms. If you have an unusual vaginal discharge or odour then please let your doctor know so that they can arrange for the appropriate tests to be done.

If you are diagnosed with chlamydia or MG, it is important that your sexual partner is also tested and treated to prevent you from becoming infected again. We will offer advice on how partners can be tested and treated should you be found to have chlamydia or MG.

Doctors and laboratories are required by law in every State and Territory in Australia to notify their health authority when detecting Chlamydia infection. This is a routine practice and will not breach your privacy as name and contact details are not required by the health authorities.

4. Possible Benefits

Testing for chlamydia helps to prevent complications caused by chlamydia such as pelvic inflammatory disease and infertility. It is possible that the same is true for MG but as yet, this has not been well studied. Participation also provides you with the opportunity to discuss any sexual health issues with the trained research assistant. If infection is found, you will be provided with treatment free of charge. You will be making a valuable contribution to the design of the future chlamydia screening program in Australia and will also be providing important information about how common both MG and BV are in Australian women.

5. Possible Risks

It is possible that you may feel some of the questions in the questionnaire are very personal or embarrassing. Or you might feel upset, embarrassed or angry at being diagnosed with a sexually transmitted infection. The research assistants are trained in speaking about sensitive subject material. There are trained counselling staff at the Melbourne Sexual health Centre and we can put you in contact with them if necessary.

6. Alternatives to Participation

If you decide not to participate in the study you will not be disadvantaged, and will receive the usual medical care from your doctor or nurse.
7. Privacy, Confidentiality and Disclosure of Information

Any information obtained in connection with this project and that can identify you will remain confidential. It will only be disclosed with your permission, except as required by law. Your name and contact details will not be recorded on any questionnaires and specimens (swabs and slides) - only a code that will not identify you will be used. A listing connecting your name with this code will be stored in a locked filing cabinet, available only to research staff. Your contact details will not be linked with your questionnaire responses. Data will be stored for 15 years after completion of the study and publication. At that stage electronic data will be erased and hard data will be shredded. Only the study investigators and your doctor (if you consent) will have access to your test results.

In any publication, information will be provided in such a way that cannot identify you as an individual.

8. New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

9. Results of Project

A summary of the study results will be available for you at the completion of the study. We can either send this to you by post or email or you can access it through a web site that you will be advised of at completion of the study. Please indicate how you would like to receive this on the Consent Form.

10. Further Information or Any Problems

If you require further information or if you have any problems concerning this project, you can contact the Principal Researcher Dr. Jane Hocking, on any of the numbers below.

Free study phone number: 1800 082 820
Study line phone number: (03) 9341 6265 Email: jhocking@unimelb.edu.au
11. Complaints and Other Issues

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact Ms Rowan Frew, Ethics Manager at the Alfred Hospital Research and Ethics Unit on (03) 9076-3848.

12. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine medical and clinical treatment or your relationship with those treating you.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

13. Ethical Guidelines

This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Alfred Hospital Research and Ethics Unit.
Appendix R
Chlamydia fact sheet

CHLAMYDIA

WHAT IS CHLAMYDIA?
Chlamydia trachomatis is the most common bacterial sexually transmitted infection in our community. It affects both women and men, including men who have sex with men. In women it causes an infection of the cervix and in men it infects the urethra. Less commonly Chlamydia can infect the anus and can also cause conjunctivitis (inflammation of the eye).

HOW IS IT TRANSMITTED?
Chlamydia is most often transmitted by vaginal or anal sex. Condoms prevent its transmission.

WHAT ARE THE SIGNS AND SYMPTOMS?
Most men and women do not have any signs and symptoms. When symptoms are present, the following may be noticed:

Men
• Itching at the opening of the penis
• Slighting or burning when passing urine
• A discharge from the penis
  (which is often clear in colour)
If not treated, Chlamydia may occasionally cause pain and swelling in one or both testicles.

Women
• A change in vaginal discharge
• Irregular bleeding (especially after sex)
• Pelvic pain, including pain during sexual intercourse
• Slighting or burning when passing urine

If not treated, Chlamydia can cause Pelvic Inflammatory Disease (PID) which is infection of the uterus and fallopian tubes. PID may lead to infertility.

HOW DO YOU TEST FOR CHLAMYDIA?
Chlamydia is tested for by taking a swab (a sample of secretion) from the cervix or vagina or by a urine sample. If an anal infection is suspected, a swab is taken from the anus.

HOW IS CHLAMYDIA TREATED?
Very effective treatment is available with antibiotics such as azithromycin or doxycycline. However, if complications of Chlamydia such as PID or testicular infection are suspected, a longer course of treatment is given.

HOW LONG DOES IT TAKE THE SYMPTOMS TO GO AWAY AFTER TREATMENT?
The symptoms will usually start to ease over a few days after treatment. If you are still experiencing problems after a week you should see your doctor again.

WHEN IS IT SAFE TO HAVE SEX AGAIN?
You should use condoms or abstain from sex for one week after treatment. Do I need further tests after I’ve been treated? Yes. To check that you haven’t been re-infected with Chlamydia, it is recommended to have a repeat test in 3 months.

SHOULD MY SEXUAL PARTNERS ALSO BE TREATED?
Yes. If you are treated for Chlamydia but your sexual partner is not, you could be reinfected. It is extremely important to tell all sexual partners during the last three months, that you have been diagnosed with Chlamydia and ask them to be tested and treated.

If you have difficulty telling your partners, we have a website you can visit www.betterhealth.vic.gov.au. As well as general advice and sample conversations it has email, SMSs and letters you can send to your partners either personally or anonymously.

HOW DO I AVOID GETTING INFECTED AGAIN?
Make sure that your current sexual partner(s) are tested and treated. Practising safe sex by always using a new condom for both anal and vaginal sex is the best way to prevent further infections.

This fact sheet is designed to provide you with information on Chlamydia. It is not intended to replace the need for a consultation with your doctor. All clients are strongly advised to check with their doctor about any specific questions or concerns they may have. Every effort has been taken to ensure that the information in this pamphlet is correct at the time of printing.

Last Updated October, 2022

Melbourne Sexual Health Centre
580 Swanston Street
Carlton Vic 3053
Australia
Tel: (03) 9341 6200
Fax: (03) 9347 2230
Phone Call: 1800 032 017
TTY: (03) 9347 0619
Web: www.mshc.org.au
Appendix S  Mycoplasma genitalium fact sheet

Mycoplasma genitalium

WHAT IS MYCOPLASMA GENITALIUM?
Mycoplasma genitalium is a bacterium that infects the mucous membranes of the urethra, cervix, throat and anus.

HOW IS IT TRANSMITTED?
It is transmitted by vaginal, anal and oral sex.

WHAT ARE THE SIGNS AND SYMPTOMS?

Men
Some men will have no symptoms. Those who do may have:
- Inflammation of the urethra (the urine passage);
- Stinging or burning when passing urine;
- A discharge from the penis.

Women
Less is known about Mycoplasma genitalium infection in women. However, Mycoplasma genitalium has been shown to infect the cervix.
Women who do have symptoms may have:
- Pain in the pelvic area and pain during sexual intercourse;
- An abnormal vaginal discharge;
- A red, inflamed cervix (cervicitis) on speculum examination.

HOW LONG UNTIL SYMPTOMS DEVELOP?
Mycoplasma genitalium has recently been identified as an sexual transmitted infection. Symptoms develop in 1 to 3 weeks, although the incubation period has not been established.

HOW DO YOU TEST FOR MYCOPLASMA GENITALIUM?
We test for Mycoplasma genitalium by taking a urine sample or a urethral swab (a sample of secretions) in men. In women a cervical swab of the secretions is taken.

This fact sheet is designed to provide you with information on Mycoplasma genitalium. It is not intended to replace the need for a consultation with your doctor. All clients are strongly advised to check with their doctor about any specific questions or concerns they may have. Every effort has been taken to ensure that the information in this pamphlet is correct at the time of printing.

Last Updated October, 2007

Melbourne Sexual Health Centre
580 Swanson Street
Carlton Vic 3053
Australia

Tel: (03) 9341 6200
Fax: (03) 9347 2230
Free Call: 1800 032 017
TTY: (03) 9347 8619
Web: www.mshc.org.au
Appendix U  CIRIS baseline questionnaire

Chlamydia incidence and re-infection rates:
A longitudinal study of young Australian women

PART A
We would like to ask you a few questions about your age, education and employment.

1) What is your age? _______ years

2) What is your country of birth? ______________________

3) Were you born overseas?
   [ ] Yes. If yes, when did you arrive in Australia? __________
   [ ] No

4) Are you of Aboriginal or Torres Strait Islander origin?
   [ ] Yes
   [ ] No

5) What language do you usually speak at home?
   [ ] English
   [ ] Other (please specify) ______________________

6) What is the postcode of where you usually live? ________

7) What is the highest level of education you have completed?
   [ ] Year 9 or below
   [ ] Year 10 to 12
   [ ] Technical or trade certificate
   [ ] College certificate or diploma
   [ ] Undergraduate university degree
   [ ] Postgraduate university degree

8) Which of the following best describes your current work status?
   [ ] Employed – full time
   [ ] Employed – part time
   [ ] Employed – casual
   [ ] Student
   [ ] Home duties
   [ ] Unemployed
   [ ] Unable to work due to health
   [ ] Other (please specify) ______________________
PART B

As chlamydia is a sexually transmitted disease and this project is about preventing its spread, we would like to ask you some personal questions about your current and previous sexual relationships. All information you provide will be treated as strictly confidential.

9) Which of the following best describes your current relationship status?
   □ In a relationship and living with partner
   □ In a relationship but not living with partner
   □ Not in a relationship

10) If you are in a relationship, what is the sex of your partner?
    □ Male
    □ Female

11) How long have you been in this relationship? _______ weeks OR _______ months OR _______ years

12) Have you ever had vaginal sex with a man?
    □ Yes
    □ No.
    (If no, please go to question 18)

13) Have you had vaginal sex with a man in the last 12 months?
    □ Yes
    □ No.
    (If no, please go to question 17)

The term ‘sex’ in the following questions refers to vaginal sex with a male partner.

14) In the last 12 months, how many different men (including any current partner(s)) have you had sex with? ______

15) How many of these men were new partners – that is, you had sex with them for the first time in the last 12 months? ______

16) In the last 12 months, how many men have you had sex with where a condom was used every time you had sex? ______

17) In your lifetime, how many different men have you had sex with (including current partner(s))? ______

The following questions refer to any sexual contact you have had with a female partner.

18) Have you had sex with a woman in the last 12 months?
    □ Yes
    □ No.
    (If no, please go to question 22)

19) In the last 12 months, how many different women (including any current partner(s)) have you had sex with? ______

20) How many of those women were new partners – that is, you had sex with them for the first time in the last 12 months? ______

21) In your lifetime, how many different women have you had sex with (including current partner(s))? ______
PART C

The following questions refer to any visits to your GP

29) Have you taken any antibiotics in the last 12 months?
   ☐ Yes.  If yes, how long ago was most recent course? ______ months
   ☐ No
   ☐ Don’t know

29a) Have you seen a doctor (GP) in the last 12 months for any reason?
   ☐ Yes.  If yes, how long ago was most recent visit? ______ months
   ☐ No
   If no, please go to question 29a
   ☐ Don’t know

24) If you answered yes to the above question, were any of those visits related to your sexual health?
   (please tick as many as appropriate)
   ☐ Pap smear
   ☐ Unusual vaginal discharge
   ☐ Pain in lower abdomen or pelvis
   ☐ Check for sexually transmitted infections
   ☐ Other (please specify) ________________________________

25a) Have you ever been tested for chlamydia?
   ☐ Yes
   If yes, how long ago ______ months OR ______ years
   ☐ No
   If no, please go to question 26
   ☐ Don’t know
   If don’t know, please go to question 26

26b) If yes, how did you receive your results?
   ☐ Phone call from your doctor
   ☐ Phone call from clinic
   ☐ Letter from your doctor
   ☐ Letter from clinic
   ☐ During a follow up appointment with your doctor
   ☐ Other (please specify) ________________________________

26) Have you ever been diagnosed with chlamydia before?
   ☐ Yes
   If yes, how long ago ______ months OR ______ years
   ☐ No
   ☐ Don’t know

27) Have you ever been told by a doctor that you have a condition called bacterial vaginosis (also known as BV)?
   ☐ Yes
   If yes, how long ago ______ months OR ______ years
   ☐ No
   ☐ Don’t know

28) Have you ever been treated by a doctor for bacterial vaginosis before?
   ☐ Yes
   If yes, how long ago ______ months OR ______ years
   ☐ No
   ☐ Don’t know

29) In the last month, have you noticed any of the following problems?
   An unusual discharge from your vagina?
   ☐ Yes
   ☐ No
   An unusual smell or odour from your vagina?
   ☐ Yes
   ☐ No
   Burning when passing urine?
   ☐ Yes
   ☐ No
   Pain in the lower abdomen or pelvis?
   ☐ Yes
   ☐ No
   Pain in the lower abdomen or pelvis during sex?
   ☐ Yes
   ☐ No
   Bleeding or spotting from your vagina?
   ☐ Yes
   ☐ No
30) Are you currently using any form of contraception?
   □ Yes □ No

   If yes, please tick the one(s) you use
   □ Condoms
   □ Oral contraceptive pill
   □ Implanon
   □ Depo-provera
   □ IUD (Intrauterine device)
   □ Deplin
   □ Other, please specify ____________________________

21) We will test you for chlamydia several times during this study and want to be able to give you your results. How would you prefer to receive your test results during the study?
   □ Your own doctor – please provide contact details ____________________________
   □ From the doctors on this study:
     □ Yes, email list email ____________________________
     □ Yes, telephone list telephone number ____________________________
     □ Yes, mail list address ____________________________

   (Please note: if you test positive for chlamydia at any stage during the study, someone from the study will contact you)

Thank you very much for your time in completing this survey.
Please place the completed survey in envelope provided and give to research assistant.
Follow-up Questionnaire

Please note your name and contact details do not appear anywhere on this questionnaire. All information is confidential.

Our records show that your last chlamydia test was (insert date) __/__/__.

1a) Have you been tested for chlamydia elsewhere (e.g., GP clinic, hospital) since we last contacted you?
   - Yes please go to question 1b
   - No please go to question 2
   - Don’t know please go to question 2

1b) If you answered yes above, how long ago was the most recent test? ___ weeks ___ months

1c) What was the result of the test?  □ negative for chlamydia □ positive for chlamydia □ don’t know

1d) Would you permit us to contact your doctor to confirm your chlamydia test result? (If yes we will send you a release form for this information)
   - Yes □ No □

2a) Have you taken antibiotics for any other health reason since we last contacted you?
   - Yes please go to question 2b
   - No please go to question 3
   - Don’t know

2b) If yes, how long ago was the most recent course? ___ weeks ___ months

2c) For what reason or health condition did you take antibiotics? ____________________________________________________________

2d) Would you permit us to contact your doctor to find out what antibiotic was used? (If yes, we will send you a release form for this information)
   - Yes □ No □

The next few questions refer to vaginal sex with a male partner.

3) Since we last contacted you, have you had any new sexual partners (men with whom you have had sex for the first time)?
   - Yes If yes, how many □ No □

4) Since we last contacted you, how many men have you had sex with where a condom was used every time you had sex? ______

The next question refers to sex with a female partner.

5) Since we last contacted you, have you had any new sexual partners (women with whom you have had sex for the first time)?
   - Yes If yes, how many □ No □

6a) Have you been to the doctor (GP) for any reason since we last contacted you?
   - Yes - please go to 6b
   - No - please go to 7
   - Don’t know

Version 1.2; Dated: 19/01/2007
6b) If yes, were any of these reasons related to your sexual health? (Please tick where appropriate)
- Pap smear
- Contraception
- Unusual vaginal discharge
- Unusual vaginal odour
- Pain in lower abdomen or pelvis
- Pregnancy
- Check for sexually transmitted infections
- New sexual partner
- Other please specify

7) In the last month, have you noticed any of the following problems?
   - An unusual discharge from your vagina?
     - Yes
     - No
   - An unusual odour from your vagina?
     - Yes
     - No
   - Burning when passing urine?
     - Yes
     - No
   - Pain in your lower abdomen or pelvis?
     - Yes
     - No
   - Pain in the lower abdomen or pelvis when you have sex?
     - Yes
     - No
   - Bleeding or spotting from your vagina?
     - Yes
     - No

8) Have you been treated by a doctor for bacterial vaginosis since we last contacted you?
   - Yes
   - No
   - If yes, how long ago? days OR weeks
   - Don’t know

8a) Are you currently using any form of contraception?
   - Yes please go to question 9b.
   - No please go to question 10

8b) If yes, please tick one or more of the following options
- Condoms
- Oral contraceptive pill
- Implanon
- Depo provera
- IUD (intrauterine device)
- Diaphragm
- Other (please specify)

9a) Have you become pregnant since we last had contact?
   - Yes please go to Question 10b
   - No no more questions - thank you
   - Don't know no more questions - thank you

9b) Are you currently pregnant?
   - Yes no more questions - thank you
   - No please answer Question 10c

10a) Did you have either of the following?
   - Termination (abortion). If yes, did you receive any antibiotics? yes no
   - Miscarriage if yes, did you receive any antibiotics? yes no

Thank you very much for your time in completing this survey.

Please place the completed survey in the reply paid envelope provided and place in mail box.

Version N1.2; Dated 18/01/2007
Appendix W  CIRIS follow up questionnaire after testing positive

Follow-up Questionnaire

PLEASE NOTE YOUR NAME AND CONTACT DETAILS DO NOT APPEAR ANYWHERE ON THIS QUESTIONNAIRE, ALL INFORMATION IS CONFIDENTIAL.

Our records show that your last chlamydia test as part of this study was ___/___/___

If you tested positive for chlamydia at this last test – please answer the following questionnaire.
If you tested negative at this test – please go to question 9a.

1) Did you take all the antibiotics you were given to treat chlamydia?
   □ Yes  □ No  □ Don’t know

2a) Did somebody talk to you about contacting your sexual partner(s)?
   □ Yes  please go to question 2b
   □ No  please go to question 3a
   □ Don’t know  please go to question 3a

2b) If yes – who spoke with you?
   □ My doctor (GP)
   □ Nurse or other staff at my doctor’s clinic
   □ CIRIS study staff
   □ Other (please specify)

2c) If yes, what advice did they give you (please specify)?

2d) Did they give you any information/letter to give to your partner?
   □ Yes  □ No

3a) Did you tell your current sexual partner(s) about this chlamydia diagnosis?
   □ Yes  please go to question 3b
   □ No  please go to question 4a

3b) If so, how did you pass this information on? (you may tick more than one)
   □ Face to face
   □ Over the phone
   □ SMS text message
   □ Doctor gave you a letter to give your partner(s)
   □ Email
   □ Post
   □ Other (please specify)
4a) Were there any other partner(s) you contacted?
   ☐ Yes  please go to question 4b
   ☐ No  please go to question 5a

4b) If yes, how many did you contact? _______

4c) How did you pass this information on? (you may tick more than one)
   ☐ Face to face
   ☐ Over the phone
   ☐ SMS text message
   ☐ Doctor gave you a letter to give your partner(s)
   ☐ Email
   ☐ Post
   ☐ Other (please specify)__________

5a) Were there any partners you did not want to contact?
   ☐ Yes  please go to question 5b
   ☐ No  please go to question 6

5b) If yes, why?________

5c) Did anyone contact them?
   ☐ Yes  please go to question 5d
   ☐ No  please go to question 6

5d) If yes – who contacted them?
   ☐ Your doctor
   ☐ A nurse from the clinic
   ☐ A friend
   ☐ CHRS study staff
   ☐ Other – please specify_________

6) Overall, how many partners did you contact? _______

7) Was your sexual partner(s) treated by a doctor for chlamydia infection?
   ☐ Yes If yes, how many were treated? _______
   ☐ No
   ☐ Don’t know

8) Did you have sex with your sexual partner(s) after you were treated for chlamydia but before they received any treatment for chlamydia?
   ☐ Yes  If yes, with how many partners? ______ and how many times did you use a condom? ______
   ☐ No
   ☐ Don’t know

These questions are to be answered by all participants.

9a) Have you been tested for chlamydia elsewhere (eg: GP clinic, in hospital) since we last contacted you?
   ☐ Yes  please go to question 9b
   ☐ No  please go to question 10a
   ☐ Don’t know  please go to question 10a

9b) If you answered yes above, how long ago was the most recent test? _____ weeks _____ months

9c) What was the result of the test?  ☐ negative for chlamydia  ☐ positive for chlamydia  ☐ Don’t know

9d) Would you permit us to contact your doctor to confirm your chlamydia test result?  ☐ Yes  ☐ No (if yes we will send you a release form for this information).
10a) Have you taken antibiotics for any other health reason since we last contacted you?
   □ Yes  please go to question 10b
   □ No  please go to Question 11

10b) If Yes, how long ago was the most recent course?  _____ weeks  _____ months

10c) For what reason or health condition did you take the antibiotics?

10d) Would you permit us to contact your doctor to find out which antibiotic was used?
   □ Yes
   □ No
   (If yes we will send you a release form for this information)

The next few questions refer to vaginal sex with a male partner.

11) Since we last contacted you, have you had any new sexual partners (men with whom you have had sex for the first time)?
   □ Yes  If yes, how many:__________
   □ No

12) Since we last contacted you, how many men have you had sex with where a condom was used every time you had sex?:__________

The next question refers to sex with a female partner.

13) Since we last contacted you, have you had any new sexual partners (women with whom you have had sex for the first time)?
   □ Yes  If yes, how many:__________
   □ No

14a) Have you been to the doctor (GP) for any reason since we last contacted you?
   □ Yes  please go to question 14b
   □ No  please go to question 15
   □ Don’t know  please go to question 15

14b) If yes, were any of these reasons related to your sexual health (please tick where appropriate)?
   □ Pap smear
   □ Contraception
   □ Vaginal discharge
   □ Unusual vaginal colour
   □ Pain in lower abdomen or pelvis
   □ Pregnancy
   □ Check for sexually transmitted infections
   □ New sexual partner
   □ Other - please specify:__________

19) In the last month, have you noticed any of the following problems?
   An unusual discharge from your vagina?
   □ Yes  □ No
   An unusual odour from your vagina?
   □ Yes  □ No
   Burning when passing urine?
   □ Yes  □ No
   Pain in your lower abdomen or pelvis?
   □ Yes  □ No
   Pain in your lower abdomen or pelvis when you have sex?
   □ Yes  □ No
   Bleeding or spotting from your vagina?
   □ Yes  □ No
16) Have you been treated by a doctor for bacterial vaginosis since we last contacted you?
   ☐ Yes    ☐ If yes, how long ago_________days OR _______weeks
   ☐ No
   ☐ Don't know

17a) Are you currently using any form of contraception
   ☐ Yes     please go question 17b
   ☐ No      please go to question 16

17b) If yes, please tick one or more of the following options
   ☐ Condom
   ☐ Oral contraceptive pill
   ☐ Implanon
   ☐ Depo provera
   ☐ IUD (intrauterine device)
   ☐ Diaphragm
   ☐ Other (please specify)

18a) Have you become pregnant since we last had contact?
   ☐ Yes     please go to question 18b
   ☐ No      no more questions, thank you
   ☐ Don't know no more questions, thank you

18b) If yes, are you currently pregnant?
   ☐ Yes     no further questions thank you
   ☐ No      if no, please answer 18c

18c) If no, did you have either of the following?
   ☐ Termination/abortion, if yes, did you receive any antibiotics? ☐ Yes ☐ No
   ☐ Miscarriage, if yes, did you receive any antibiotics? ☐ Yes ☐ No

Thank you very much for your time in completing this survey.

Please place the completed survey and any specimens in the reply paid padded bag provided and place in mail box as the instructions demonstrate.
Appendix X  CIRIS final psychosocial questionnaire for participants who only tested negative

Final Questionnaire
CHLAMYDIA INCIDENCE AND RE-INFECTION RATES: A LONGITUDINAL STUDY OF YOUNG AUSTRALIAN WOMEN.

The following questions relate to how helpful you found the information we provided, how you felt about participating in the study and what you think about chlamydia testing. Your responses will be most valuable in determining young women’s attitudes to chlamydia. All information you provide is confidential, no reference to your name or contact details will appear anywhere on this questionnaire.

1) Did you access the study website (www.msine.org.au/ciris) at any time during the study?
   - Yes Please go to Question 2
   - No Please go to Question 3
   - I don’t have internet access. Please go to Question 3

Please tick one response for the following questions:

2) Did you find the information on the website helpful?
   - Very Helpful
   - Somewhat Helpful
   - Not Really Helpful
   Please comment

3) Did you find the 1800 number useful?
   - Very Useful
   - Somewhat Useful
   - Not at all Useful
   - Didn’t Use
   Please comment

4) Did you find the information pack given to you at enrolment useful?
   - Very Useful
   - Somewhat Useful
   - Not at all Useful
   - Didn’t Use
   Please comment

5) Did you find the instructions for how to take a vaginal swab useful?
   - Very Useful
   - Somewhat Useful
   - Not at all Useful
   - Didn’t Use
   Please comment

6) Did you feel comfortable collecting a vaginal swab?
   - Very Comfortable
   - Comfortable
   - Neither Comfortable nor Uncomfortable
   - Uncomfortable
   - Very Uncomfortable
   Please comment

Version N FI.09; Dated: 26.01.09
7) Prior to participating in this study, did you know much about chlamydia infection?

- Never / Hardly Ever
- Rarely
- Sometimes
- Often
- Always / Lot

Please comment

8) How did you feel about being asked to participate in the CPIS study?

- Very Negative
- Somewhat Negative
- Neutral
- Somewhat Positive
- Very Positive

Please comment

9) Did you think that having a chlamydia test was a good or bad idea?

- Very Bad Idea
- Bad Idea
- Neither Bad Nor Good Idea
- Good Idea
- Very Good Idea

Please comment

10) Thinking about young women of your age, how comfortable do you think they would feel about their doctor asking them about the number of people they had sex with over the past year?

- Very Comfortable
- Comfortable
- Neither Comfortable nor Uncomfortable
- Uncomfortable
- Very Uncomfortable

Please comment

10a) What do you think would make young women more comfortable discussing sexual issues with their doctor?

11) There are a number of options that doctors could use for testing for chlamydia. Which option do you think is best?

- Test all young women under 25 who have had sex
- Test all young women who have had more than one recent sexual partner
- Test all young women only when they present to their doctor for a Pap smear and/or contraception advice

Please comment

12) There are a number of different ways chlamydia can be tested. Which way would you prefer?

- A urine test
- A cotton swab that the doctor inserts into the vagina
- A cotton swab that you insert into the vagina (like the one you provided for this study)
- Only do a chlamydia test when presenting for a Pap smear or contraception advice

12a) Why would you prefer the method you selected?

Please indicate how you would feel if you tested positive for chlamydia?

13) I would feel embarrassed about testing positive

- Strongly Agree
- Agree
- Neither Agree nor Disagree
- Disagree
- Strongly Disagree

14) I would feel afraid if my chlamydia test was positive

- Strongly Agree
- Agree
- Neither Agree nor Disagree
- Disagree
- Strongly Disagree

15) I would be worried that some people might treat me differently if they knew I had chlamydia

- Strongly Agree
- Agree
- Neither Agree nor Disagree
- Disagree
- Strongly Disagree

16) Testing positive would make me feel anxious

- Strongly Agree
- Agree
- Neither Agree nor Disagree
- Disagree
- Strongly Disagree

Version N F1.03, Dated: 25.01.08
17) I would worry about how my sexual partner/s might perceive me
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree
18) I would talk to others about the test results
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree
19) I would be concerned about my future health
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree
20) I would feel relieved knowing I had been diagnosed and I could be treated easily
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree

Would any of the following issues prevent you from being tested for chlamydia, if you felt you were at risk IN THE FUTURE?

21) Embarrassment about having a chlamydia test?
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree
22) Concern about testing positive
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree
23) Concern about how my sexual partner/s would perceive me if I was being tested
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree
24) I don’t think I will be at risk so won’t need testing
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree

Do you think any of the following practical issues would prevent you from getting tested for chlamydia IN THE FUTURE?

25) Time to attend an appointment
   - Definitely  - Probably  - Definitely Not  - Don’t Know
26) Knowing where to go to have a chlamydia test?
   - Definitely  - Probably  - Definitely Not  - Don’t Know
27) Unsuitable relationship with a GP
   - Definitely  - Probably  - Definitely Not  - Don’t Know
28) Cost of the test and/or treatment
   - Definitely  - Probably  - Definitely Not  - Don’t Know
   Other, please specify:

The following questions ask about your thoughts on chlamydia testing

29) Would you feel comfortable asking your doctor for a chlamydia test?
   - Very Comfortable  - Somewhat Comfortable  - Not At All Comfortable
30) Would you be willing to have a yearly chlamydia test through a GP?
   - Definitely  - Probably  - Definitely not  - Don’t Know
31) Would you advise your friends to get tested for chlamydia?
   - Definitely  - Probably  - Definitely not  - Don’t Know
32) How would you prefer to get your chlamydia test results?
   - Via the mail  - Via a phone call from my doctor  - Via a phone call from the receptionist at the clinic
   - Via a face to face appointment with my doctor  - Via a face to face appointment with a nurse at the clinic

Who would you talk to if you had questions or concerns about chlamydia?

33) I would talk with friends about chlamydia
   - Strongly Agree  - Agree  - Neither Agree nor Disagree  - Disagree  - Strongly Disagree

Version N F1.03; Dated: 25.01.08
54. I would talk with a sexual health nurse, doctor or counsellor about chlamydia
   [ ] Strongly Agree [ ] Agree [ ] Neither Agree nor Disagree [ ] Disagree [ ] Strongly Disagree
55. I would talk to trained sexual health staff using a 1800 number
   [ ] Strongly Agree [ ] Agree [ ] Neither Agree nor Disagree [ ] Disagree [ ] Strongly Disagree
56. I would talk about chlamydia with my doctor
   [ ] Strongly Agree [ ] Agree [ ] Neither Agree nor Disagree [ ] Disagree [ ] Strongly Disagree
57. I would talk with my partner about chlamydia
   [ ] Strongly Agree [ ] Agree [ ] Neither Agree nor Disagree [ ] Disagree [ ] Strongly Disagree
58. I would not talk to anyone
   [ ] Strongly Agree [ ] Agree [ ] Neither Agree nor Disagree [ ] Disagree [ ] Strongly Disagree
59. Is there anyone else you might talk to? Please list

The following questions ask for your thoughts on the best ways to inform young women about chlamydia

40. [ ] TV ads
   [ ] A story line in a popular soapie such as ‘Neighbours’
   [ ] Nightclubs
   [ ] Sports events
   [ ] School/Tafe/University
   [ ] Workplaces
   [ ] Bus shelters
   [ ] Radio
   [ ] Websites
   [ ] Posters – where would be a good location?
   [ ] Magazines – which ones?
   [ ] Other – please specify:

41. What information do you think would help chlamydia screening become acceptable to young women?
   [ ] Knowing you could set tests in the privacy of your home
   [ ] Knowing it is easily treated
   [ ] Knowing there is support available
   [ ] Knowing there is readily accessible information
   [ ] Knowing more about chlamydia
   [ ] Knowing that many young women are exposed to chlamydia
   [ ] Knowing that chlamydia screening is a part of normal health monitoring
   [ ] Knowing that chlamydia screening was a part of a rational screening program such as the current Pap smear screening program
   [ ] Other – please specify:

42. Do you think women can get chlamydia again after being treated?
   [ ] Yes [ ] No [ ] Don’t know

43. Have you had the HPV (Cervical) vaccine?
   [ ] Yes [ ] No [ ] Don’t know
   If yes, when did you have your last dose? __/____/____ How many doses have you had?

44. Since participating in the study, please indicate how much you agree or disagree with the following statements:
   I am more likely to use condoms with new sexual partners
   [ ] Strongly Agree [ ] Agree [ ] Neither Agree nor Disagree [ ] Disagree [ ] Strongly Disagree
   I will discuss safe sex with my sexual partners
   [ ] Strongly Agree [ ] Agree [ ] Neither Agree nor Disagree [ ] Disagree [ ] Strongly Disagree
   I will talk to my GP about sexually transmitted infections and my sexual health
   [ ] Strongly Agree [ ] Agree [ ] Neither Agree nor Disagree [ ] Disagree [ ] Strongly Disagree

45. Has participating in this study changed your sexual behaviour?
   [ ] Yes [ ] No [ ] Don’t know
   If yes, please explain

Thank you very much for your time in completing this survey.
Please place the completed survey in reply paid envelope provided and place in mail box.

Version N F1.0c; Dated: 25.01.08
Appendix Y CIRIS final psychosocial questionnaire for participants who tested positive during the study

Final Questionnaire
CHLAMYDIA INCIDENCE AND RE-INFECTION RATES: A LONGITUDINAL STUDY OF YOUNG AUSTRALIAN WOMEN.

The following questions relate to how helpful you found the information we provided, how you felt about participating in this study and what you think about chlamydia testing. Your responses will be most valuable in determining young women’s attitudes to chlamydia. All information you provide is confidential, no reference to your name or contact details will appear anywhere on this questionnaire.

1) Did you access the study web site (www.mhec.org.au/ciris) at any time during the study?
   [ ] Yes Please go to Question 2
   [ ] No Please go to Question 3
   [ ] I don’t have internet access Please go to Question 3

Please tick one response for the following questions

2) Did you find the information on the web site helpful?
   [ ] Very Helpful
   [ ] Somewhat Helpful
   [ ] Not Really Helpful

   Please comment

3) Did you find the 1800 number useful?
   [ ] Very Useful
   [ ] Somewhat Useful
   [ ] Not at all Useful
   [ ] Didn’t Use

   Please comment

4) Did you find the information pack given to you at enrolment useful?
   [ ] Very Useful
   [ ] Somewhat Useful
   [ ] Not at all Useful
   [ ] Didn’t Use

   Please comment

5) Did you find the instructions for how to take a vaginal swab useful?
   [ ] Very Useful
   [ ] Somewhat Useful
   [ ] Not at all Useful
   [ ] Didn’t Use

   Please comment

6) Did you feel comfortable collecting a vaginal swab?
   [ ] Very Comfortable
   [ ] Comfortable
   [ ] Neither Comfortable nor Uncomfortable
   [ ] Uncomfortable
   [ ] Very Uncomfortable

   Please comment

7) Prior to participating in this study, did you know much about chlamydia infection?
   [ ] Never Heard Of It
   [ ] Heard Of It But Didn’t Know What It Was
   [ ] Knew A Little About It
   [ ] Knew A Lot About It

   Please comment

Version P.F1.00, Dated: 25.01.08
8) How did you feel about being asked to participate in the CHRS study?
☐ Very Negative ☐ Somewhat Negative ☐ Neutral ☐ Somewhat Positive ☐ Very Positive
Please comment

9) Did you think that having a chlamydia test was a good or bad idea?
☐ Very Bad Idea ☐ Bad Idea ☐ Neither Bad Nor Good Idea ☐ Good Idea ☐ Very Good Idea
Please comment

10) Thinking about young women of your age, how comfortable do you think they would feel about their doctor asking them about the number of people they had sex with over the past year?
☐ Very Comfortable ☐ Comfortable ☐ Neither Comfortable nor Uncomfortable ☐ Uncomfortable ☐ Very Uncomfortable
Please comment

10a) What do you think would make young women more comfortable discussing sexual issues with their doctor?

11) There are a number of options that doctors could use for testing for chlamydia. Which option do you think is best?
Please tick one option only
☐ Test all young women under 25 who have had sex
☐ Test all young women who have had more than one recent sexual partner
☐ Test all young women only when they present to their doctor for a Pap smear and/or contraception advice
Please comment

12) There are a number of different ways chlamydia can be tested. Which way would you prefer?
Please tick one or more options
☐ A urine test
☐ A cotton swab that the doctor inserts into the vagina
☐ A cotton swab that you insert into the vagina (like the one you provided for this study)
☐ A tampon that you insert into the vagina
☐ Only do a chlamydia test when presenting for a Pap smear or contraception advice
12a) Why would you prefer the method you selected?

Would any of the following issues prevent you from being tested for chlamydia, if you felt you were at risk IN THE FUTURE?

13) Embarrassment about having a chlamydia test
☐ Strongly Agree ☐ Agree ☐ Neither Agree nor Disagree ☐ Disagree ☐ Strongly Disagree

14) Concern about testing positive
☐ Strongly Agree ☐ Agree ☐ Neither Agree nor Disagree ☐ Disagree ☐ Strongly Disagree

15) Concern about how my sexual partner's(s) would perceive me if I was being tested
☐ Strongly Agree ☐ Agree ☐ Neither Agree nor Disagree ☐ Disagree ☐ Strongly Disagree

16) I don't think I would be at risk so I wouldn't need testing
☐ Strongly Agree ☐ Agree ☐ Neither Agree nor Disagree ☐ Disagree ☐ Strongly Disagree

Do you think any of the following practical issues would prevent you from getting tested for chlamydia IN THE FUTURE?

17) Time to attend an appointment
☐ Definitely ☐ Probably ☐ Definitely Not ☐ Don't Know

18) Knowing where to go to have a chlamydia test
☐ Definitely ☐ Probably ☐ Definitely Not ☐ Don't Know

19) Unsuitable relationship with GP
☐ Definitely ☐ Probably ☐ Definitely Not ☐ Don't Know

Version: P.F.1.03, Dated: 25.01.08
20) Cost of the test and treatment
☐ Definitely  ☐ Probably  ☐ Definitely Not  ☐ Don’t Know
Other – please specify

The following questions ask about your thoughts on chlamydia testing

21) Would you feel comfortable asking your doctor for a chlamydia test?
☐ Very Comfortable  ☐ Somewhat Comfortable  ☐ Not At All Comfortable  ☐ Don’t Know

22) Would you be willing to have a yearly chlamydia test through a GP?
☐ Definitely  ☐ Probably  ☐ Definitely not  ☐ Don’t Know

23) Would you advise your friends to get tested for chlamydia?
☐ Definitely  ☐ Probably  ☐ Definitely not  ☐ Don’t Know

24) How would you prefer to get your chlamydia test results?
☐ Via the mail  ☐ Via a phone call from my doctor
☐ Via a phone call from the receptionist at the clinic  ☐ Via a face to face appointment with my doctor
☐ Via a phone call from a nurse at the clinic  ☐ Via a face to face appointment with a nurse at the clinic

Who would you talk to if you had questions or concerns about chlamydia?

25) I would talk with friends about chlamydia
☐ Strongly Agree  ☐ Agree  ☐ Neither Agree nor Disagree  ☐ Disagree  ☐ Strongly Disagree

26) I would talk with a sexual health nurse, doctor or counsellor about chlamydia
☐ Strongly Agree  ☐ Agree  ☐ Neither Agree nor Disagree  ☐ Disagree  ☐ Strongly Disagree

27) I would talk to trained sexual health staff using a 1800 number
☐ Strongly Agree  ☐ Agree  ☐ Neither Agree nor Disagree  ☐ Disagree  ☐ Strongly Disagree

28) I would talk about chlamydia with my doctor
☐ Strongly Agree  ☐ Agree  ☐ Neither Agree nor Disagree  ☐ Disagree  ☐ Strongly Disagree

29) I would talk with my partner about chlamydia
☐ Strongly Agree  ☐ Agree  ☐ Neither Agree nor Disagree  ☐ Disagree  ☐ Strongly Disagree

30) I would not talk to anyone
☐ Strongly Agree  ☐ Agree  ☐ Neither Agree nor Disagree  ☐ Disagree  ☐ Strongly Disagree

31) Is there anyone else you might talk to? Please list

The following questions ask for your thoughts on the best ways to inform young women about chlamydia

32) What, in your opinion, are the best ways to advertise for chlamydia screening? You may tick more than one option
☐ TV ads  ☐ A story line in a popular soapie such as ‘Neighbours’
☐ Pubs/night clubs  ☐ School/Title/University
☐ Sports events  ☐ Workplaces
☐ Other – please specify: ________________________________

33) What information would help chlamydia screening become acceptable to young women?
☐ Knowing you could self test in the privacy of your home
☐ Knowing it is easily treated
☐ Knowing there is support available
☐ Knowing more about chlamydia
☐ Knowing that many young women are exposed to chlamydia
☐ Knowing that chlamydia screening is a part of normal health monitoring
☐ Other – please specify: ________________________________

34) Do you think you can get chlamydia again after you have been treated?
☐ Yes  ☐ No  ☐ Don’t Know

Version P Fl.02; Dated: 25.01.08
Questions 35 to 45 are to be answered only by women who tested positive for chlamydia during the study. Please indicate how much you agree with the following statements.

35) I was pleased to have had a chlamydia test so I could get the treatment I needed
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

36) I found it easy to contact my sexual partner(s) and let them know they needed to see a doctor for treatment
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

37) I talked to my friends about my positive result
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

38) Do you think there is anything that could help with contacting sexual partner(s) when a woman is diagnosed with chlamydia? Please tick your response(s).
   □ Your doctor could give you a letter for you to give to your sexual partner(s)
   □ Give details of websites with information about chlamydia infection to pass on to sexual partner(s)
   □ Informant pamphlets about chlamydia given to women to pass on to sexual partner(s)
   □ Your doctor could contact your sexual partner(s) for you
   □ Sending an SMS or email to your partner(s)
   □ Other — please specify: __________________________________________

Please indicate how much you agree or disagree with the following statements about testing positive for chlamydia during the study.

39) I felt embarrassed about testing positive
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

40) I felt afraid when I found out my chlamydia test was positive
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

41) I was worried that some people might treat me differently if they knew I had chlamydia
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

42) The positive test made me feel anxious
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

43) I was worried about how my sexual partner(s) might perceive me
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

44) I was able to talk to others about the test results
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

45) I was concerned about my future health
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

46) Have you had the HPV (Gardasil) vaccine?
   □ Yes  □ No  □ Don’t Know
   If Yes, when did you have your last dose? __/___/20__  How many doses have you had? __________

47) Since participating in the study, please indicate how much you agree or disagree with the following statements.
   I am more likely to use condoms with new sexual partners
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

I will discuss safe sex with my sexual partners
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

I will talk to my GP about sexually transmitted infections and my sexual health
   □ Strongly Agree  □ Agree  □ Neither Agree nor Disagree  □ Disagree  □ Strongly Disagree

48) Has participating in this study changed your sexual behaviour?
   □ Yes  □ No  □ Don’t Know
   If Yes, please explain

Thank you very much for your time in completing this survey.
Please place the completed survey in reply paid envelope provided and place in mail box.

Version: P F1.03; Dated: 25.01.06
Appendix Z  CIRIS introductory letter sent to general practitioners

Dear General Practitioner,

Re: *Chlamydia trachomatis*: An Incidence and Re-Infection Study

Thank you for taking the time to discuss the CIRIS study with me today on the telephone.

I have outlined the important points about the study and included the ‘Patient Information Form’ about the study to give more details about the study for you and your colleagues to read.

If you would like to discuss this more, please do not hesitate to contact me either by phone or email as detailed on the enclosed sheets. There is also a ‘Fax Back’ form if you would like to pursue the study further.

Thank you again,

Regards

Jennifer Walker

T: 03 9341 6265

E: walker@unimelb.edu.au
Appendix AA  CIRIS chlamydia testing schedule
Appendix BB  CIRIS General Practitioner information CD
Appendix CC  Notification of sexually transmissible infections form (Victorian version)

Notification of Sexually Transmissible Infection

Notification of the following sexually transmissible infections is required under the Public Health and Welfare Regulations 2002. Please send completed notification form within the day of diagnosis to Communicable Disease Prevention & Control, Department of Health, Royal Parade, Melbourne VIC 3050 or stamp, seal and post to 1500-00777.

Case Details

Please print clearly. Tick boxes where applicable.

First two letters only:

- Family Name
- First Name
- Postcode of residence

Sex

- Female
- Male
- Transgender

Birth Date

- Month
- Day
- Year

Date of Birth

- Birth date unknown

Date of Death

- Died due to Sex Transmissible Infection
- Died due to other causes

Case History

- Is the person pregnant?
- Yes
- No
- Specify number of weeks gestation

- Is the person HIV positive?
- Yes
- No
- Not tested
- Don't know

- Why was the person tested?
- Blood donation screen
- STI screen requested by doctor
- STI screen requested by patient
- Pre-employment screen
- Patient presented with clinical symptoms or signs of an STI

- Abnormalities on examination
- Patient was an asymptomatic contact of an infected individual
- Pre-employment screen
- Symptoms screening

- Other

- If symptomatic, specify onset of illness:

- Where was the person born?
- Australia
- Overseas
- Don't know

- If overseas, specify country and year of arrival

- What language does the person speak at home?
- English
- Other

- In the person's home?
- Yes
- No

- If yes, state language

- Died due to Sex Transmissible Infection
- Died due to other causes

Case Definition

- Chlamydia trachomatis infection
- Gonorrhea
- Syphilis
- Gonorrhea
- HIV
- HSV
- Syphilis
- Other

- Symptoms (specify)
- Primary
- Secondary
- Tertiary
- Latent

- Syphilis more than 2 years
- Unknown

- Syphilis congenital
- Syphilis post adequately treated
- Syphilis reactivation

Notifying Doctor/Laboratory/Hospital Details

Name of Notifying Doctor, Laboratory or Hospital

Address

City/Suburb/Town

Postcode

Telephone

Signature

Date

Form completed by:

Laboratory:

Clinical comments:

Enhanced STI Notification Form

November 2000 — Page 1 of 1

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Appendix DD  Partner notification letter for *Chlamydia trachomatis*

--

Dear ____________________________

You have been given this letter because you may have been exposed to chlamydia. Chlamydia is a bacterial infection that is passed on through sex and is easily treated with antibiotics. Most people with chlamydia don’t have symptoms and so it is important to see your doctor for testing and treatment. If you are diagnosed with chlamydia you will need to tell your sexual partners that they might be at risk.

Please take this letter to your doctor as soon as possible.

---

Date

Dear Doctor

A partner of your patient has had a positive test for *Chlamydia trachomatis*. We recommend that your patient is treated without delay, and that treatment for chlamydia is completed even if their test is negative. Testing for other STIs such as gonorrhea, syphilis and HIV may also be indicated, particularly in men who have sex with men.

The current recommendations for treatment of uncomplicated *C. trachomatis* are:

- Azithromycin 1 g as a single oral dose^{1,2}

  or

- Doxycycline 100 mg bd for 7 days^{1,2}

Chlamydial infection is often asymptomatic and there may be no abnormality found on examination.

A repeat test to exclude re-infection is recommended 3 months after treatment.


For sexual health physician advice, please visit www.mshc.org.au

---

Melbourne Sexual Health Centre
560 Swanston Street
Carlton, Vic 3053

Phone: (03) 8347 9044
Fax: (03) 8347 2209
Free Call: 1800 932 017
TTY: (03) 9347 8519
web: www.mshc.org.au
Appendix EE  Partner notification letter for *Mycoplasma genitalium*

---

**Sexual Partner Notification Form**

Dear ___________________________

You have been given this letter because you may have been exposed to *Mycoplasma genitalium*, which is a sexually transmitted infection. *Mycoplasma genitalium* can cause inflammation in the genital tract in men and women and is thought to behave in a similar manner to chlamydia. *Mycoplasma genitalium* can be treated with antibiotics.

Please take the information below this line to your doctor.

____________________________________________________

CONFIDENTIAL

Dear Doctor,

A sexual partner of your patient has had a positive test for *Mycoplasma genitalium*. We recommend that your patient is treated without delay, and that the treatment is completed even if their test for *Mycoplasma genitalium* is negative. *Mycoplasma genitalium* is a cause of urethritis in men and of cervicitis in women.

The current recommended treatment for uncomplicated *Mycoplasma genitalium* is azithromycin 1 g as a single dose.

*Mycoplasma genitalium* infection is often asymptomatic and there may be no abnormality found on examination.

In individuals who test positive for *Mycoplasma genitalium* re-testing four weeks after treatment is recommended to ensure that the infection has resolved.

If re-testing indicates persistent infection firstly exclude the possibility of reinfection from a sexual partner. If reinfection has not occurred discuss the management of persistent *Mycoplasma genitalium* infection with a sexual health physician at your nearest Sexual Health Centre.
Appendix FF    Treatment guidelines for chlamydia

CHLAMYDIA

Chlamydia is caused by the bacterium Chlamydia trachomatis. Genital infections are sexually transmitted and usually asymptomatic. They may cause urethritis and epididymitis in men, and cervicitis, pelvic inflammatory disease (PID), ectopic pregnancies and infertility in women. In pregnancy, mother-to-child transmission can lead to neonatal conjunctivitis and pneumonia.

DIAGNOSIS

MSPH uses SDA (a nucleic acid amplification test to detect DNA of C. trachomatis). A first void urine specimen (or urethral swab) is obtained from men. In women, testing can be performed on an endocervical swab, first void urine or vaginal swab. An anogenital swab is used to screen for oral chlamydia in men who have sex with men and women who have anal sex. Annual screening of all sexually active women <25 years is recommended and older women and men with risk factors.

If a Chlamydia result is equivocal or inhibitors are present the test should be repeated. It is recommended that the repeat test should be a swab, if the initial test was a urine sample.

TREATMENT

Uncomplicated infection:

- Azithromycin 1g single dose OR
- Doxycycline 100mg BD for 7 days Single-dose azithromycin and seven days of doxycycline have similar efficacy.

Positive Anal Chlamydia:

- Refer to LGV guidelines

Treatment in pregnancy:

Recommended:
- Azithromycin 1gm single dose

Alternative:
- Erythromycin ethylsuccinate (EES) 800mg QID for 7 days OR
- Erythromycin ethylsuccinate (EES) 400mg QID for 14 days
- Amoxicillin 500mg TDS for 7 days

Epididymitis:
- Doxycycline 100mg BD for 14 days OR
- Roxithromycin 300mg daily for 14 days

Pelvic Inflammatory Disease (PID):

Women with PID may only of mild or subtle symptoms and signs. In cases of moderate or severe PID consider admission to hospital. Consider other causes of abdominal pain, including pregnancy complications.

For the woman presenting with mild PID use:
- Azithromycin 1gm stat PLUS
- Doxycycline 100mg BD for two weeks PLUS
- Metronidazole 400mg BD for two weeks

If the patient is pregnant or breastfeeding, substitute doxycycline with roxithromycin 300 mg orally, daily for 14 days (category B1). Where adherence to 2 weeks of doxycycline (or roxithromycin in pregnant or breastfeeding women) is unlikely, there are data to indicate they may

Disclaimer

The content of these treatment guidelines is for information purposes only. The treatment guidelines are generic in character and should be applied to individuals only on the advice of a treating practitioner on a case-by-case basis. GaySave Health, through MSPH, does not accept liability to any person for the information or advice (or the use of such information or advice) which is provided through these treatment guidelines. The information contained within these treatment guidelines is provided on the basis that all persons accessing the treatment guidelines undertake responsibility for assessing the relevance and accuracy of the content and its suitability for a particular patient. Responsible use of these guidelines requires that the prescriber is familiar with contraindications and precautions relevant to the various pharmaceutical agents recommended herein.
CHLAMYDIA

March 2010

be replaced by adding a second dose of azithromycin 1g orally on day 6. Review as soon as results for urgent chlamydia and gonorrhoea tests are available (about 3 days). If there is a history of recent sex with a partner from overseas or any other reason to suspect gonorrhoea, add:

- Cotrimoxazole 500mg IMI. For mild pelvic pain or tenderness in a woman with recent instrumentation of the upper genital tract use.
- Metronidazole 400mg BD for two weeks WITH
- Doxycycline 100mg BD for two weeks.

REVIEW
A repeat test to exclude reinfection is recommended at three months. Test-of-cure for chlamydia is no longer routinely recommended at MSHC as treatment is highly effective. However, it should be performed at least 3 weeks after completion of treatment if symptoms persist or if there is concern regarding adherence or reinfection from an inadequately treated partner.

CONTACTS
Partners of individuals with Chlamydia should be contacted, treated and tested. A detailed sexual history will direct the clinician to how far back contact tracing is feasible. Sexual partners should be offered treatment without waiting for their test results. They should be tested as this may guide further contact-tracing and subsequent test-of-cure. Contacts of contacts are generally tested rather than treated, but treatment may be more practical for some. Individuals should abstain from sex with their partners till 7 days after both have received treatment.
Appendix GG  Treatment guidelines for *Mycoplasma genitalium*

**MYCOPLASMA GENITALIUM**

**MELBOURNE SEXUAL HEALTH CENTRE**
**TREATMENT GUIDELINES**  
**JUNE 2006**

*Mycoplasma genitalium* (MG) is a fastidious aerobic bacterium without a cell wall, which is sensitive to antibiotics of the macrolide group and the tetracyclines. MG is sexually transmitted and infects the mucous membranes of the urogenital, conjunctival, pharyngeal and rectal. In men, it can cause urethritis and prostatitis, and in women, it may cause cervicitis, endometritis and salpingitis. MG infection in males can cause prostatitis and epididymitis, and in females, it can cause cervicitis and pelvic inflammatory disease, but in both genders, it may be asymptomatic.

**DIAGNOSIS**

In men with MG, a test for *Mycoplasma* can detect MG in the semen. In women, a test for *Mycoplasma* can detect MG in the endocervical or endometrial fluid.

**TREATMENT AND FOLLOW-UP**

- **Ampicillin** 1g single dose.
- **Erythromycin** 2g single dose.
- **Azithromycin** 1g single dose.

If re-infection has been excluded with:
- Moxifloxacin 400mg daily for 10 days.

Explain that this is an off-label use. Discuss quinolone risk of achalasia in patients and the risk of side effects.

**CONTACTS**

Contacts of MG should be treated empirically with 1g of *Azithromycin* and screening undertaken.

**Male contacts require:**
- Information and explanation of MG.
- STI screening in keeping with standard practice at MSHC.
- A repeat test after 7 days.

**Female contacts require:**
- Women with symptoms suggestive of PID should be treated with moxifloxacin 400mg daily for 10 days and anti-microbial cover such as metronidazole, rather than waiting to see if azithromycin will be effective.
- Information and explanation of MG.
- STI screening in keeping with standard practice at MSHC.
- A cervical swab for PCR.

 DISCLAIMER

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The information contained within these treatment guidelines is provided on the basis that all persons screening the treatment guidelines undertake responsibility for assessing the relevance and accuracy of the content and its suitability for a particular patient. Responsible use of these guidelines requires that the prescriber is familiar with concomitant medications and precautions relevant to the various pharmaceutical agents recommended here.
Appendix HH  Instructions for how to take a self collected vaginal swab and how to send it back to the research team

Directions for taking your own vaginal swab

1. Take the cotton-tipped swab out of its plastic case, just twist and pull to remove it.

2. Gently separate the lips of your vulva and insert the cotton-tipped swab into the vagina gently pushing the swab upwards and slightly angled towards the base of the spine. This is similar to the way that you would insert a tampon. Insert the swab to approximately half the length of a finger and rotate it gently several times. There should be no pain or discomfort.

3. Replace the cotton-tipped swab into the original holder.

4. You should now have:
   - a cotton tipped swab back in the original case
   - a questionnaire to return in the prepaid envelope.

Please place both items in the prepaid envelope, sign the front of the envelope and place in the regular red postbox as addressed to the Department of Molecular Microbiology at the Royal Women’s Hospital in Melbourne.
What to do with your swab

1. The swab:
   Following the instruction sheet, take a sample from your vagina, using the swab.

2. Pack the swab away into the ziplock bag enclosed, pack this into the cardboard tube and put the stopper on.

3. Pack both tube and the completed questionnaire into the padded envelope.

4. Seal and post in a regular red post box.
Appendix II  Prompts sent via email or mobile phone text message a week prior to sending out the follow up kit

1. Email prompt reminding participants to expect a follow up kit in the post.

Hi

Soon you will receive follow up information in the post for the CIRIS project. If your contact details have changed could you please let us know either by SMS on 0417 539 739 or email ciris@mshc.org.au.

Thank you for your assistance with this important research.

Regards

Jenny Walker

And the CIRIS team

2. SMS prompt reminding participants to expect a follow up kit in the post.

CIRIS reminder: Soon u will receive follow up info in post. If contact details changed pls txt 0417 539 739 or email ciris@mshc.org.au. Thx
Appendix JJ  Reminders sent by email or via mobile phone text message 2 weeks after sending out the follow up kit if it had not yet been received.

1. Reminders sent by email:

Hi

You should have received your follow up for the CIRIS project in the post recently; please don’t forget to return it to us as soon as possible, or call us if you need a copy to be resent.

If your contact details have changed could you please let us know either by SMS on 0417 539 739 or email ciris@mshc.org.au.

Thank you for your assistance with this important research.

Please ignore this if you have already sent your questionnaire back.

Regards

Jenny Walker

And the CIRIS team

2. Reminders sent via mobile phone text message

CIRIS reminder: Hi, please don’t forget to send back your CIRIS questionnaire and if contact details changed pls txt 0417 539 739 or email ciris@mshc.org.au. Thx
Appendix KK  Log forms used by the research assistants to record (anonymously) all women who attended the clinic within the age group on the day of recruiting.

Clinic: | Research Assistant: | Date: | Session: |
---|---|---|---|

<table>
<thead>
<tr>
<th>Participant code</th>
<th>Date of birth</th>
<th>UR number</th>
<th>Triage (Y/N)</th>
<th>Consent (Y/N)</th>
<th>Refused: (reason)</th>
<th>Ineligible:</th>
<th>Swab (tick)</th>
<th>Slide (tick)</th>
<th>Q’airre (tick)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A: not in age range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B: no vaginal sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C: transient</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>D: won’t do swabs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E: unable to consent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F: pregnant</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G: other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOTAL
Appendix LL  Management of positive results phone check list

*Chlamydia trachomatis or Mycoplasma genitalium* phone checklist for CIRIS

Please record consultation details in the patient file stored at MSHC

**UR number:**

**Date:** ___ / ___ / ______

1. Does the client have any of the following symptoms? (answer yes or no)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Dyspareunia</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Abnormal vaginal discharge</td>
<td></td>
</tr>
<tr>
<td>Abnormal vaginal bleeding</td>
<td></td>
</tr>
</tbody>
</table>

Please record that the following have been discussed with the client:

(Tick if discussed with client)

1. Does the client has any known **ALLERGIES** to antibiotics  Yes/No

If yes, please specify: _____________________________

2. Correct administration procedures for azithromycin:

<table>
<thead>
<tr>
<th>Tick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose</td>
</tr>
<tr>
<td>Two tablets at once</td>
</tr>
<tr>
<td>Will be posted to patient</td>
</tr>
</tbody>
</table>

If you vomit up the azithromycin within 2 hours of taking it please contact us (1800 082 820)
3. Possible side-effects of azithromycin:

<table>
<thead>
<tr>
<th>Possible side-effects</th>
<th>Tick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication generally well tolerated</td>
<td></td>
</tr>
<tr>
<td>Occasionally some experience transient headaches, flushing, nausea, or abdominal discomfort</td>
<td></td>
</tr>
<tr>
<td>Azithromycin is used with caution in severe renal failure</td>
<td></td>
</tr>
</tbody>
</table>

4. Effects of azithromycin on oral contraceptive pills:

<table>
<thead>
<tr>
<th>Effects of azithromycin on oral contraceptive pills</th>
<th>Tick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue to take pills as per normal and use additional contraceptive method while taking antibiotics and for 7 days post treatment</td>
<td></td>
</tr>
<tr>
<td>Safe sex practices for 7 days post treatment</td>
<td></td>
</tr>
</tbody>
</table>

**Partner notification:**

Attempt to notify and treat all partners in the last 3 months, up to 6 months may be appropriate and if client has an RSP ideally trace back to prior partner before this relationship.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the participant have a regular sexual partner</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Number of SPs in last 3 months</td>
<td></td>
</tr>
<tr>
<td>Number of SPs (last 3 months) contactable</td>
<td></td>
</tr>
<tr>
<td>Number of SPs last 6 months</td>
<td></td>
</tr>
<tr>
<td>Number of SPs (last 6 months) contactable</td>
<td></td>
</tr>
<tr>
<td>Number of contact letters sent to client</td>
<td></td>
</tr>
</tbody>
</table>

*I have discussed all the above with the client.*

RA Signature: _____________________________ Date: ___ / ___ / _____

Prescribing Dr’s Signature: ___________________________ Date: ___ / ___ / _____
Appendix MM  Negative test result letter – *Mycoplasma genitalium* and/or chlamydia

Date

Hi Name,

Thank you very much for agreeing to participate in our CIRIS Study. We really appreciate your help in enabling us to conduct this important study.

The [*Mycoplasma genitalium* (MG) and/or chlamydia] test result for Study ID number: XXXXXX is negative, which means that [*Mycoplasma genitalium* (MG) and/or chlamydia] was NOT DETECTED in the swab provided.

Your involvement in this study will take 12 months and we will be in contact in a couple of months for more follow up. Please feel free to telephone (1800 082 820) or email me (ciris@mshc.org.au), if you would like to talk about the study and learn more about the results, or if you have any comments, questions or suggestions about MG or chlamydia and this study. There will be regular updates posted on the study web-page on [www.mshc.org.au/ciris](http://www.mshc.org.au/ciris).

Once again, thank you very much for your help in this important study!

Regards

Jenny Walker & the CIRIS team
Appendix NN  *Mycoplasma genitalium* test-of-cure questionnaire

We notified you of your MG results and if you tested positive you would have received treatment with an antibiotic called azithromycin.

*If you tested positive, it is important that we ensure that this medication has worked properly, so we are asking you to collect another vaginal swab.*

Please follow the instructions provided in this pack for collecting the swab and mail it back to us in the post as per the instructions. Once we have tested this sample for MG we will let you know if the treatment has cured this infection. If the swab tests are still positive for MG we will be in touch with you to discuss further treatment.

It would help if you would answer the following questions please.

1. Did you take the two tablets of the antibiotic (azithromycin) prescribed by your doctor to treat this infection? **Please tick**
   - ☐ Yes
   - ☐ No

   *To ensure you have not been re-exposed to MG since you took the antibiotic*

2. Were your sexual partner(s) also treated?  
   **Please tick**
   - ☐ Yes
   - ☐ No

3. Have you had unprotected sex since you took the treatment with any previous* partners who have not been treated for MG?  
   **Please tick**
   - ☐ Yes
   - ☐ No

*previous partner means a person you were having sex with in the 3 months before you were diagnosed with MG*

Please return this with the swab in the postal pack provided.

Thank you for completing this.

The CIRIS team. 1800 082 820
Appendix OO    Antibiotic and test result requests

CONSENT FOR RELEASE OF INFORMATION

I, ____________________________________________ (Name of participant)
of ____________________________________________
_____________________________________________ (Address)

DOB: ___ / ___ / __________ hereby give permission to Dr Jane Hocking, or her delegate at the Sexual Health Unit at the University of Melbourne, to obtain medical information and/or copies of the medical records from:

_________________________________________________ (Name of clinic/doctor)
of ____________________________________________
_____________________________________________ (Address)

that relate to any recent test result and/or treatment (as detailed on reverse side).

I understand this information will be used only in relation to the CIRIS project in which I am a participant.

Signed ___________________________________________

Name ____________________________________________ (Participant)

Date ___ / ___ / __________

Witnessed by:

Signed ___________________________________________

Name ____________________________________________

Date___ / ___ / __________
Dear Dr __________________________,

Please provide Dr Jane Hocking or her delegate at the Sexual Health Unit at the University of Melbourne with the following details:

**Antibiotics prescribed in the last 6 months to:**

Patient: (Name) ___________________________(DOB) ___ / ___ / _________

of _______________________________________________

__________________________________________________ (Address)

Antibiotics prescribed: _______________________________

Date(s) Prescribed: __________________________________

**Chlamydia test result(s) in the last 6 months for:**

Patient: (Name) ___________________________(DOB) ___ / ___ / _________

of _______________________________________________

__________________________________________________ (Address)

Chlamydia test result: _______________________________

Date(s) of test(s): __________________________________

Signed: __________________________________________

Name (of doctor): __________________________________

Date: ___ / ___ / _________

Yours sincerely,

Dr Jane Hocking
School of Population Health
The University of Melbourne
Victoria, Australia 3010
Ph: 61 3 8344 0762
Email: j.hocking@unimelb.edu.au
Author/s: WALKER, JENNIFER

Title: The epidemiology of Chlamydia trachomatis and Mycoplasma genitalium in young Australian women

Date: 2011


Persistent Link: http://hdl.handle.net/11343/36274

File Description: The epidemiology of Chlamydia trachomatis and Mycoplasma genitalium in young Australian women

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