Modelling cost-effective prescribing:

Cost-effective General Practitioner management of genital Chlamydia trachomatis infection in women.

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Abstract

Public expenditure on prescribed pharmaceuticals is increasing in New Zealand and medical practitioners in New Zealand have become aware of the balance between minimisation of health expenditure and maximisation of clinical outcomes. Initiatives to reduce costs of prescribed pharmaceuticals reflect an assumption that cost of prescribing relates to cost-effectiveness. The focus on pharmaceutical overlooks the contribution of laboratory investigations and monitoring to costs of prescribing in General Practice.

This project is a cost-effectiveness analysis based on a model incorporating complexities of prescribing decisions within General Practice in New Zealand. The analysis takes the perspective of the Health Funding Authority. Direct costs to the Health Funding Authority are considered. Many variables have been included in order to demonstrate their impact on the cost-effectiveness of General Practice management from the funder perspective.

Any condition managed by the General Practitioner could have been chosen for modelling. Genital chlamydia infection has been chosen, as recent advances in Chlamydia management have cost and effectiveness implications for New Zealand. Current 7-day treatment with doxycycline or erythromycin is compared to single dose azithromycin, which is not subsidised for prescription in New Zealand. Enzyme-linked immunoassay and micro-immunofluorescence test strategies are compared with the ligase chain reaction a new, more sensitive and specific DNA amplification test.

Data for the model were collected from New Zealand General Practice sources where possible or from the closest available proxy. Best proxy sources have been used where local data was not available. Some evidence relating to behavioural factors in the transmission and treatment of sexually transmitted disease is not available either locally or from overseas. As human behaviour is not totally predictable, and medicine is not an exact science, such variables are simulated from best estimates using risk analysis.

Treatment scenarios are modelled by second order Monte Carlo simulation. The methodology accommodates clinical variability and uncertainty through randomisation of

values from a plausible distribution and range. Results take the form of probability distribution functions, described by measures of variance between their minimum and maximum limits.
A sensitivity analysis and break-even analysis enables decision analysis relating to Chlamydia management options in General Practice. In the setting of this particular model, azithromycin management strategies are more effective than strategies using other current treatments, even though azithromycin is not currently subsidised for prescription in New Zealand. Perverse effects of some funding incentives can be demonstrated.

This modelling project demonstrates that the complexities of health care delivery in the primary care setting can be incorporated into a mathematical model to assess cost, cost-effectiveness and elucidate factors that influence cost-effectiveness of General Practice prescribing. Such a model provides information to assist development of clinical guidelines for cost-effective resource utilisation.

Preface

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1. Introduction

1.0 Why model cost-effective prescribing?

1.0.1 The New Zealand paradigm shift to cost-effectiveness.

Public expenditure on prescribed pharmaceuticals is increasing in New Zealand, as it is overseas. The funders and administrators of health services are challenged to contain costs to ensure that taxpayer money is used to maximum effect (Moore, 1997). Initiatives have been introduced to reduce costs of prescribed pharmaceuticals (Pharmac 1998).

High cost prescribing is, however, not always inappropriate and may be more cost-effective than low cost prescribing, as indicated by the debate on subsidisation of lipid lowering medication in New Zealand (Thomas 1998). In addition, the laboratory investigations and clinical monitoring, an adjunct to pharmaceutical management in General Practice increases costs. For some conditions managed by General Practitioners, the cost of laboratory tests exceeds the cost of pharmacological treatment (A Wiles, 1997). Medical Practitioners in New Zealand have become aware of the balance between minimisation of health expenditure and maximisation of clinical outcomes.

The New Zealand Health Funding Authority has recently signalled a new direction for future funding of General Practice services (NZ Health Funding Authority,1998). The proposal for referred services management and capitation funding takes the emphasis away from prescribing costs alone to address overall patient management costs, including costs of consultation, pharmaceuticals and laboratory utilisation in primary care. In the new paradigm, cost-effective General Practice prescribing is prescribing which achieves greatest efficacy at lowest overall management cost.

1.0.2 General Practice prescribing as a modelling application.

General Practice prescribing is a complex process. Many variables determine the outcome of prescribing in primary care: the nature of the disease, coexisting medical conditions, behavioural characteristics of the prescriber and the patient, the treatment given and cultural setting in which it is prescribed. A clinical investigation into General Practice prescribing

would require large numbers of patients to accommodate all these variables. Such investigation would be not only cumbersome, but also impractical for the small New Zealand population. Modelling with a hypothetical cohort of patients is increasingly applied to clinical questions that would be difficult to adequately address by clinical trial (Briggs 1996), particularly cost-benefit and cost-effectiveness analysis. Modelling brings the additional advantage that comparison of treatments and outcomes can be performed without the considerations of ethical approvals and informed consent.

Many conditions managed by the General Practitioner could have been chosen to model cost- effectiveness. The management of genital chlamydia infection in New Zealand General Practice has been chosen for this project. Recent advances in Chlamydia management have cost and effectiveness implications, but overseas economic analyses use assumptions, probabilities and costs that differ to those in New Zealand.

1.1 Significance of Genital chlamydia in General Practice.

1.1.1 Epidemiology of Genital chlamydia in New Zealand.

Genital chlamydia is the second most common sexually transmitted disease (STD) in New Zealand in all age groups (Lyttle and Preston 1997). In females under twenty-one years of age it is the most common sexually transmitted disease (Dickson et al 1996). Surveillance data indicates that the disease prevalence is rising in New Zealand (ESR-Health 1997). Primary care health service providers deliver the majority of management of uncomplicated chlamydia infections in New Zealand. General Practitioners, Family Planning Clinics, Student Health and Sexual Health Services have a key role in detection and treatment of infections and in containment of the epidemic.

There have been calls for a nation-wide effort to improve infection control with the development of evidence-based management guidelines for primary care providers (Sexual Health Service, 1997).

1.1.2. Chlamydia, the silent epidemic.

The rising incidence of genital Chlamydia infection in New Zealand has recently become newsworthy (*Evening Post* Wellington 7th January 1998). For many that are infected, the disease is silent. International studies have shown that up to 80% of women and 90% of men with the infection have no symptoms. In the absence of symptoms, awareness of infection risk depends upon the infected person acknowledging risk-taking behaviour, or the infected

person receiving notification of exposure to the infection through contact tracing. Asymptomatic screening programmes also detect occult untreated infections.

1.1.3. Disease notification and infection monitoring.

There is no mandatory reporting for genital Chlamydia infections in this country, although this is a legal requirement for syphilis and gonorrhoea under the Venereal Diseases Regulations (New Zealand Government 1982). A small payment is made to General Practitioners on notification of these diseases. Syphilis and gonorrhoea were once prevalent sexually transmitted diseases, but are now less prevalent diseases than genital Chlamydia. All three venereal infections have the potential for significant long-term complications in affected adults and also any offspring.

Chlamydia incidence rates in Sweden have been observed to fall with obligatory infection notification (Mardh 1997). Obligatory notification of cases of chlamydia infection in New Zealand has been proposed (Communicable Diseases Centre 1994). Notifications of laboratory-confirmed cases are more accurate than clinician-based notifications. Clinical notifications are contaminated by non-chlamydia, non-specific genital infections (Ministry of Health a.1997). Variance in clinical presentation confounds criteria for presumptive diagnoses of chlamydia (Denham and Mulhall 1994).

Surveillance data in New Zealand is based on reports from sexual health clinics. Reported cases are an underestimate of incidence. As only infections treated in sexual health clinics are reported, cases seen in general practice and other primary and secondary care health services are not included. There are high prevalence regions in New Zealand such Hawkes Bay and Canterbury (Lyttle 1993) and pockets of high prevalence within regions such as the Porirua basin of the Wellington region (Moriarty and Tamblyn, 1996). There are also ethnic differences, particularly with increasing rates of infection amongst Pacific Island women, and age group differences (ESR-Health 1997).

The women most at risk for genital chlamydia infection are those under twenty-five years old who have had a change of sexual partner within three months (Brunham 1997). Reported infection rates are unreliable as estimates of infection in this young age group as adolescents do not readily present for routine genitourinary examinations and testing.

1.1.4 Disease sequelae in General practice.

The following disease sequelae are associated with chlamydia infection. The strength of that association, and degree to which Chlamydia infection is attributable has not been fully defined. Chlamydia infection is believed to be a major aetiological agent in the following conditions:

- For untreated women the sequelae of infection are menstrual disturbances, cervicitis, acute salpingitis, tubo-ovarian abscess, acute or chronic pelvic inflammatory disease, chronic pelvic pain, and infertility.
- For infected women with preserved fertility, Chlamydia is associated with increased risk of miscarriage, ectopic pregnancy, and premature births.
- For infants of infected women, neonatal sequelae include the hazards of prematurity, chlamydia conjunctivitis and pneumonia.
- For infected male partners the recognised complications are recurrent urethritis, epididymitis, prostatitis, Reiters syndrome (eye inflammation and arthritis with urethritis) and infertility may develop.

The General Practitioner has a pivotal role in the diagnosis, initial management and ongoing community-based care of these complications.

1.1.5 The burden of disease.

The complications listed above carry considerable present and future costs to the health service as well as significant social, personal and intangible costs to the infected person and the community:

- Ectopic pregnancies threaten lives of women and result in foetal loss as well as impairing future fertility.
- Infertility treatment costs could be very high in New Zealand if the best current management is made available to all women who are infertile (Gillett et al 1995).
- Prematurity and neonatal pneumonia are both conditions which may be life-threatening. Neonatal intensive care for premature infants and those with chlamydia pneumonia is a costly service per infant treated.
- Chronic pelvic pain in women, epididymitis, prostatitis and recurrent urethritis in males generate medical management costs for General Practitioner time and expertise in

addition to personal direct and indirect costs to the affected patient. These are not well documented. The costs of these chronic conditions accumulate with time.

- Menstrual disturbances in females and Reiters syndrome in males (Bardin et al 1992) effect predominately personal and intangible costs, which accumulate over time.

The General Practitioner is responsible for ongoing community care after development of these complications, in addition to management of acute uncomplicated infection.

1.2 Management of uncomplicated Genital Chlamydia

1.2.1 Practitioner variability.

The management of any medical condition is subject to practitioner variability. There is considerable scope for variety in approach to clinical presentations, investigation, prescription and ancillary advice, post-treatment follow-up and monitoring, health education, and primary prevention.

The extent of General practice variability and uncertainty in the management of genital chlamydia has been demonstrated by overseas experience. When surveyed, Australian General Practitioners expressed doubts about the sensitivity of available diagnostic tests and half were uncertain of conditions under which tests should be taken (Temple-Smith et al 1997). These General Practitioners treated presumptively without full clinical or epidemiological information; an approach considered inappropriate for asymptomatic infections in low prevalence regions.

Screening for this infection by British General Practitioners was found to be haphazard, sometimes inadequate and only one third of the General practitioners surveyed would prescribe an appropriate antibiotic (Mason et al 1996). As in other countries, the focus in New Zealand to date has been on prescriber variability and cost of General practitioner prescribing. However, the number of General Practitioner visits required, laboratory tests ordered and any other procedures initiated by practitioners also contribute to the overall cost of primary care management. Variability of General Practice management in New Zealand is demonstrated by case studies of the National Preferred Medicines Centre. There have been no case studies specifically on the management of Genital Chlamydia, but a pattern similar to that seen overseas is expected.

1.2.2 Management costs in Primary care.

When General Practitioners are consulted to perform tests, deliver test results or treatment or follow-up, a fee for consultation time is generated. General Medical Services benefits are payable on General Practice consultations by adults eligible for the income-tested Community Services Card and by children under sixteen years of age in New Zealand. Laboratory schedule costs are generated for diagnostic tests requested by General Practitioners, regardless of the patient's Community Services Cardholder status. Laboratory costs also apply to subsequent tests performed to ensure cure. Algorithms for clinical predictors of Chlamydia trachomatis infection have been developed to reduce the cost of consultations and tests and simplify the management. In selected populations, the sensitivity and specificity of clinical indicator algorithms in identification of cases may be almost as good as laboratory tests (Sellors et al 1992).

A single diagnostic test for Chlamydia infection will cost as much or more than the course of treatment, as subsidised chlamydia treatments in New Zealand cost less than the prescription co-payment for a patient who is not a Community Cardholder. The New Zealand Pharmaceutical Advisory Committee sets down subsidised prescription costs and co-payment levels in the New Zealand Pharmaceutical Schedule (1997).

1.2.3 Disease screening

The Australasian College of Sexual Health Physicians currently recommends routine screening for Chlamydia trachomatis during any medical consultations for sexual health examinations such as Papanicolou smears or HIV testing, termination of pregnancy, emergency contraception, oral and intrauterine contraception. Screening is also recommended for women with a new partner, or women presenting with complaints of vaginal discharge, pelvic pain, intractable urinary symptoms and/or clinical findings of cervicitis, pelvic inflammatory disease, proctitis or presence of other sexually transmitted disease (Garland et al 1997). Increased index of suspicion is required by primary care practitioners in order to screen for infection under appropriate circumstances. Disease incidence rates fell in parts of the United States of America with asymptomatic screening programmes (Scholes et al 1996). There is no standard protocol for screening for this disease by General Practitioners in New Zealand.

1.2.4 Detection of infection.

A silent evolution in laboratory diagnosis of Chlamydia infection has begun in New Zealand. Some community-based medical laboratories now offer new generation chlamydia tests, polymerase chain and ligase chain reaction (PCR/LCR) based on DNA hybridisation technology (Clinton Teague, Wellington Medlab, private communication). The older enzyme-linked immunoassays (Elisa) and micro immunofluorescence (MIF) which detect Chlamydia antigens require confirmatory testing, but PCR and LCR do not (Stary 1997). DNA hybridisation tests have become the new gold standard (Sellors 1993). These tests are more sensitive, except in the presence of heavy contamination by blood or discharge. The sensitivity of DNA tests lies between 94%-99% compared to antigen tests at 72%-84%. Urine samples as well as cervical or urethral swabs can be tested by PCR/LCR (Lee et al 1995, Debattista et al 1997, Jensen et al 1997). Urine testing has practical advantages for screening in General Practice since a genital examination is not required.

1.2.5. Treatment regimen.

Preferred treatment practices are also evolving. The Centres for Disease Control guideline (CDC 1993) recommends doxycycline 100mg twice daily for seven days, erythromycin 800mg twice daily in pregnancy. The Australian chapter of the Australasian College of Sexual Health Physicians now recommend directly observed treatment with single dose azithromycin I Gm orally (Garland et al 1997).

Azithromycin is available on the Australian Schedule of Pharmaceutical Benefits but although a registered medicine, it is not subsidised on the New Zealand Pharmaceutical Schedule.

Should azithromycin 1GM orally be prescribed by General Practitioners in New Zealand, extrapolating from the Australian Schedule price the retail cost in this country would be nearly three times that of a standard doxycycline regime (J. McCombie, Pharmac, personal communication). This is similar to the United States of America where the cost of this regime of azithromycin is nearly three times that of a standard doxycycline regime (Magid et al 1996). Since azithromycin is not subsidised in New Zealand, the entire prescription cost would be a cost to the patient.

1.3 Cost-effective chlamydia management.

1.3.1 General practice cost-effectiveness.

Genital Chlamydia management in women has been the subject of many previous economic analyses (Nettleman et al 1986, Sellors et al 1992, Schiotz and Csango 1992, Haddix et al 1995, Nuovo et al 1995, Scholes et al 1996, Magid et al 1996, Howell et al 1997, Marrazzo et al 1997). Only a few of these have included primary care management considerations (Haddix et al 1995, Nuovo et al 1995) and neither of these reflect the cost structures which are appropriate to General Practice in New Zealand. Published analyses from overseas countries consider practices and cost structures that are not applicable to the New Zealand primary care setting. Local factors distinct to General Practice in New Zealand include regional and ethnic influences on disease patterns in the community, local prescriber variability, the socio-economic influence on General Medical Services (GMS) claims and prescription subsidies, local pricing, and the New Zealand Goods and Services tax. The critical factors influencing cost-effective resource utilisation for this infection in New Zealand primary care require identification.

1.3.2 Economics of Chlamydia testing.

The cost effectiveness of testing procedures is of interest as the PCR/LCR tests are more expensive than either Elisa or MIF. In Sweden an economic analysis showed incremental cost-savings with DNA hybridisation tests over older methods for asymptomatic screening when infection prevalence exceeded 6% (Genc and Mardh 1996). Another analysis, modelled on different assumptions, demonstrated cost savings with DNA hybridisation tests when infection prevalence was over 3% (Paavoven1997). Because the sensitivity and specificity of tests affects the numbers treated and complications averted, some economic analyses have started with an assumption that all infections have already been diagnosed using identical technologies (Schiotz and Csango1991, Nuovo et al 1994, Haddix et al 1995, Magid et al 1996).

1.3.3 Integration of management.

In screening programmes, treatment of false positive test results adds to the cost of treatment. However, because DNA hybridisation tests minimise false positives they are cost-effective in a screening programme using the expensive treatment option, azithromycin (Genc and Mardh 1996). In addition, when compliance is ensured by use of direct

observation of treatment, client recall for follow-up visits and tests of cure may not be required. Testing for cure after treatment increases the laboratory cost in Chlamydia management and this aspect alone has been subject to cost-benefit analysis (Schiotz and Csango 1991).

The integration of these management factors in the New Zealand setting is required for cost-effective General Practice treatment. Despite these considerations, no cost-effectiveness studies of chlamydia management have been done in New Zealand or in Australasia (Pfizer pharmaceuticals, personal communication).

1.3.4 Treatment compliance and tolerance.

The simplicity of directly observed treatment has particular appeal to General Practitioners treating adolescent clients. Ensuring adolescent compliance with twice a day treatment for seven days is a difficulty for practitioners.

Gains in compliance achieved with directly observed treatment could potentially be offset by reduced antimicrobial effectiveness, as the susceptibility of Chlamydia trachomatis to macrolides is less than to doxycycline (Welsh et al 1992). Despite this, an economic analysis showed a robust saving in costs of consequences using azithromycin compared to doxycycline in treatment of laboratory proven infection (Magid et al 1996).

Unlike tetracyclines, there is no known teratogenicity concern with either of the macrolides erythromycin or azithromycin.

Since azithromycin is a recent therapeutic drug the side effect profile of single dose treatment is not well established. Long term side effects are still uncertain due to limited experience (Peters et al 1992). The side effect profile of single dose treatment may be quite different to the side effect profile for prolonged courses.

1.3.5 Treatment options.

In New Zealand, marketing by the researched medicines industry has given General Practice prominence to brand named macrolides and tetracyclines that are not the antibiotics recommended by Centres for Disease Control. The evidence for appropriate dose, duration and overall efficacy in Chlamydia treatment is not as rigorous for these alternatives as for the recommended treatments.

The concern about teratogenicity of doxycycline has been recently challenged (Czeizel and Rockenbauer 1997). Any proposal to change treatment strategy for pregnant clients is amenable to exploration by modelling which bypasses the ethical considerations of clinical

trials. Precedent for modelling of treatment policies in pregnancy was set with antenatal acyclovir prophylaxis modelled to prevent perinatal herpes infections (Brocklehurst and Roberts 1997, Randolph et al 1996).

The impact of tetracycline alternatives, required for treatment of Chlamydia in pregnancy, on the cost-effectiveness has not been included in previously published analyses.

1.4 Perverse incentives in infection control.

With the New Zealand Health Reforms of the early 1990s came the introduction of a funder/provider split and the concept of budget holding in primary health care. As a consequence General Practices have moved singly or collectively into fund-holding contracts, with the growth of Independent Practitioner Associations (RNZCGP 1997). Budget holding has introduced a new significance of cost factors to General Practitioners, creating incentives for decisions to be based on cost rather than efficacy considerations alone. The cost-containment ethos has the potential to stimulate the following perverse incentives in the New Zealand epidemic of genital chlamydia infections in adolescents:

- General practitioners who budget-hold for pharmaceutical costs but not for community-based investigations have an incentive to order tests before initiating treatment. Patients may miss treatment if they evade testing, fail to return for results, or return false negative tests, regardless of clinical indications.
- General practitioners who hold pharmaceutical budgets have a disincentive to prescribe double treatments (for the index case and for the sexual partner). There is an additional disincentive if partners live outside the IPA budget-holding region. Re-infection risk and failure to contain the epidemic results from re-exposure to the untreated partner (Stamm 1988).
- Medical practitioners holding a pharmaceutical budget have an incentive to prescribe preferentially to patients who are not eligible for a Community Services Card. These clients contribute a higher prescription co-payment, reducing demand on the pharmaceutical budget. This incentive encourages differential treatment of cardholders and non-card holders. Treatment prescribed on clinical suspicion or epidemiological grounds to non-card-holders would have less impact on the budget than cardholder prescriptions. This could disadvantage cardholders by delaying delivery of effective treatment until return of positive test results, and requiring a return visit for treatment, with risk of loss to follow-up.

- There is a theoretical incentive to prescribe unsubsidised medicines. The only cost to the pharmaceutical budget-holder prescribing unsubsidised medicines is the pharmacy container and dispensing fee for those patients who are exempt from co-payments. The pharmaceutical cost becomes the client burden. To patients with health insurance the higher pharmacy cost of unsubsidised medicine would be no disincentive. Low-income patients might be disadvantaged.
- Pharmaceutical budget-holders carry no extra cost if a prescribed drug is partially subsidised on the NZ Pharmaceutical Schedule since the difference in price is added to the client co-payment, not to the practitioner's budget.
- Aggressive marketing activity, including individual detailing to General Practitioners and preferred supplier deals with IPAs reinforces the incentives for medical practitioners to prescribe familiar agents with real or imagined advantages. Some well-promoted antibiotics have unproven efficacy for Chlamydia infections and some may be inappropriate therapy.
- Practices with a high proportion of Community Services cardholders have an incentive for inefficiency. The more visits to the doctor by eligible patients, the greater the practice income generated from General Medical Services claims.
- A competitive market environment is a disincentive to local and regional networking and co-operation of General Practitioners required for effective contact tracing and treatment.
- Short-term provider contracts are no incentive for contact tracing and treatment. The benefits of contact tracing arise medium to long term. Patient-led contact tracing is time-consuming and fails when the infection contact is unknown, refuse treatment, or are remotely located. Infection control and reduction in complications of untreated disease are at risk if this fails.
- Moral hazard exists. Incentives for General Practitioners to maximise primary prevention and community health are not present. The primary care sector is not a long-term beneficiary of effective General Practice disease management. It is the hospital sector that benefits as a consequence of good primary health care, with cost savings from fewer future complications.

The significance of these incentives will vary across different scenarios, as the modelling project demonstrates.

1.5 The Wellington Modelling Project

1.5.1 Project objective.

The current modelling project is a mathematical modelling initiative designed to understand the factors that influence the cost-effectiveness of General Practitioner prescribing. The objective is to model the complexities of processes and costs of prescribing decisions made within General Practice in New Zealand. Information from the modelling project will assist the development of clinical guidelines for cost-effective resource utilisation and quality assurance in primary care.

1.5.2 The General Practice setting.

In the simulation of management of genital chlamydia in General Practice, lack of New Zealand General Practice data compounds the uncertainty of clinical variables. Academic Departments of General Practice and the New Zealand College of General Practitioners are attempting to address the paucity of General Practice specific research (RNZCGP 1996).

1.5.3 Rationale for Monte Carlo modelling.

Monte Carlo simulation is a special case of Markov modelling which is described in Appendix 1. With increasing use, the limitations of Markov modelling in medical applications have become evident (Briggs 1997). The Markovian assumption restricts the applicability to medical applications without careful modifications including tunnel pathways. A simple spread sheet model uses single values for variables, which at best, represent the observed mean or best estimate. The unpredictability and uncertainty inherent in human medical conditions requires models of human behaviour to be flexible.

Because medicine is not an exact science and human behaviour is not totally predictable, values for variables in medicine are neither black nor white, but various shades of grey. Simple spreadsheet models using extremes of cost and probability give no indication of the probable distribution between these extremes. The Monte Carlo method is one way to incorporate this. Random selection of values for each variable from a plausible range, akin to randomly throwing a dice, gives this methodology its name. In Monte Carlo analysis, values are selected at random from a predetermined plausible range for variables in successive iterations. Re-running the spreadsheet multiple times, using a different randomly selected set of values for variables each iteration, generates not one but a range of possible answers.

Hence, the Monte Carlo simulation process delivers a range within which the true answer will lie. This form of modelling assists analyses of problems with uncertainty in the value of variables. It is useful in problems where the absolute values for the variables are unknown, as in medical applications.

The Monte Carlo method of mathematical modelling has been long understood (Hammersley and Handscomb1964), but the era of personal computers has made this much easier to perform. In first order Monte Carlo simulation, the selection is made randomly from a range. This model applies a second order Monte Carlo cohort simulation. Second order Monte Carlo simulation selects variables according to a pre-determined probability distribution within the range. The estimated mid range and distribution (normal or skew) of a variable between maximum and minimum plausible values are used in the model. In this way, the uncertainties of the data set have been incorporated in a manner that fits expectations for New Zealand conditions. Evidence which lacks the rigour of randomised controlled trials (case-control studies, cohort studies, case reports and anecdotal observations) can be incorporated into a best estimate.

A major advantage in the use of the Monte Carlo cohort simulation is that sensitivity analysis is intrinsic to the Monte Carlo analysis. After several hundred or thousand iterations in which values for a variable are chosen at random from between the plausible minimum and plausible maximum extremes, the variance in the answer across the range is evident. A separate sensitivity analysis is not required.

Factors critical to outcome can be manipulated and weighted differently in simulated trial runs, to represent the extremes of clinical scenario.

1.5.4 Monte Carlo modelling in General Practice.

Monte Carlo analysis has especial appeal for modelling medical conditions in the New Zealand General Practice setting, since specific data are not readily available. Clinical trials not based in General Practice or from countries with different disease prevalence, different lifestyle and behaviour patterns, different public health systems to New Zealand, can be extrapolated for use in the Monte Carlo analysis. In addition, iterations at all randomised decision nodes reveal sensitivity to individual factors in the general practice setting. Despite these advantages the Monte Carlo method is not widely used for cost-effective modelling in medicine. A literature search revealed only one published Monte Carlo analysis of cost-effectiveness of management of Chlamydia infection (Genc and Mardh 1996).

1.5.5 The Genital Chlamydia model.

The size and geographic spread of the New Zealand population precludes large clinical studies such as those which would be required to provide local data on genital chlamydia infection. Mathematical modelling of a theoretical cohort overcomes this problem. A decision tree representing the General Practice management of uncomplicated Chlamydia infection is constructed for the analysis. The number of subjects required in the theoretical cohort depends on input and endpoints. This model is of infection consequences for one hundred thousand women at risk of infection. One hundred thousand subjects were required to model infection consequences in women with laboratory proven chlamydia (Magid et al 1996). Only one thousand subjects were required when microbiological cure alone was an endpoint (Genc and Mardh 1996).

1.5.6 Perspective of the analysis.

For this analysis, the societal perspective from the viewpoint of the New Zealand public health budget, the cost to the Health Funding Authority has been chosen. The results of cost-effectiveness analysis would be of interest if taken from the alternative perspectives of the general practitioner, the patient or the community.

The costs to individual general practitioners vary due to differences in practice organisation, overheads and division of labour. Cost-effectiveness analysis from the perspective of General Practice would require a time and motion study to determine the cost structure, as described to cost management of childhood immunisation (D McLeod, 1998).

A cost-effectiveness analysis from the United Kingdom on treatment options for chlamydia infection in women, showed no savings when assessed only from a primary care perspective (Haddix et al 1995). While the majority of Chlamydia trachomatis infections are treated in primary practice, this sector does not benefit from savings on complications. Most of the complications of infection are treated by specialists and/or at hospital.

The perspective of the patient and/or community would require information on personal direct and indirect costs, and quality of life and life status (see table 2.3.3). Information is lacking on these issues in relation to genital Chlamydia in New Zealand.

The perspective of the New Zealand Health Funding Authority includes both the costs of case management in General practice: consultations, investigation, treatment, contact tracing and the costs of medical management of complications. This is necessary to evade the

influences of cost shifting, between funders and between providers, on the economies of health care provision.

As the perspective is nation-wide, the partner costs and cost of complications can be included even if these are at a different geographic location to the treatment of the index case. This is an important consideration because the young age groups at most risk of Chlamydia trachomatis infection are the most mobile sectors of the population. In addition, results of the analysis are applicable to General Practitioners throughout New Zealand when the analysis is from the perspective of nation-wide funding.

1.5.7 Ethical considerations.

Medical modelling and simulation of clinical scenarios permits testing of permutations and combinations on aspects of management without the practical and ethical considerations of clinical trials. As no primary data collection from patients is needed for this process, there is no requirement for informed consent or ethical committee approval.

1.6 Aim of this project.

The aim of the analysis is to explore the influences on the cost-effectiveness of chlamydia management for women by New Zealand General Practitioners.

This is a cost-effectiveness analysis which compares current management of uncomplicated genital chlamydia in women in general practice settings with that recommended by the Australasian College of Sexual Health Physicians.

The potential applications for such analysis are extensive. Delivery of cost-effective infective disease control is beneficial not only to health service purchasers, budget-holders, and providers but also to consumers and is in the best interests of public health.

The objective of this project is to develop a methodology for decision-making, which considers risk assessment and cost-effectiveness from the viewpoint of a health funder while incorporating some of the clinical uncertainties and variability of General Practice. This project will assist development of evidence-based guidelines for General Practice management genital Chlamydia.

In taking the perspective of the health funder, this project considers the direct health costs of genital chlamydia infection in women. The intention is not to overlook or understate the true extent of the intangible, indirect personal and social costs of genital Chlamydia infections, but to acknowledge that public health funding covers only the direct costs of health care.

2. Methods: Development of the model

2.0 Overview of model

To perform the decision analysis of cost-effective General Practice management of Chlamydia infection in women, a model of the process was required. The model was based on a decision tree reflecting decisions made by General Practitioners in the management of Chlamydia infection in New Zealand. The data for the model were collected from New Zealand General Practice sources where possible or from the closest available proxy to the appropriate setting.

The current modelling project has included variables deemed by consensus opinion from local experts to be of practical importance in General practitioner management of the infection. The experts consulted are listed in acknowledgements. The model was also tested by consensus opinion against current practice. Inclusion of many variables permits the sensitivity to factors operating in General Practice to be assessed. It is hoped that this will contribute to a better understanding of the significance of such variables in the cost-effectiveness of General Practice management.

2.1 Construction of the decision tree.

2.1.1 General considerations.

The decision tree displayed in figure 2.1.1 was constructed to reflect management of Chlamydia infection in New Zealand General Practice. The flow chart from which it was derived is shown in figure 2.1.3. This flow chart was established in consultation with representatives of the New Zealand Venereology Society.

The decision tree differs from those used in previously published decision analyses on Chlamydia management. The decision tree of Genc and Mardh (1996) which was designed to test for the outcome of short-term cure did not include long term consequences of infection. A simple decision tree used by Nuovo et al (1997) included only the outcomes of cure or not, pelvic inflammatory disease or not, hospitalisation or not. This did not include the complications other than pelvic inflammatory disease, which are of interest to General Practitioners (e.g. chronic pain, infertility, ectopic pregnancy, and other pregnancy outcomes). Magid et al (1996) produced a decision tree with several sub-trees. Their sub-trees represented the risks for adverse drug reaction, sequelae of pelvic inflammatory disease and sequelae in partners of infected index cases and neonates born to infected index cases.

Figure 2.1.1 Decision Tree

As this analysis started with proven Chlamydia trachomatis infection, it bypassed the steps at which the General Practitioner has first input: recognition of risk and testing for infection. The role of the General Practitioner in prescribing appropriate treatment, ensuring compliance, and re-treating where necessary does not fit into their decision tree structure. Howell et al (1997) designed a decision tree to demonstrate the significance of partner tracing and treatment.

To model General Practitioner management of genital Chlamydia a decision tree was required which incorporated from all of these decision trees the elements appropriate to primary care. The resulting decision tree of figure 2.1.1 starts with a community of sexually active women, some with and some without the infection. Sub-trees of figure 2.1.1 represent the probability of women at risk recognising their risk of infection, and then testing for the infection. Other sub-trees reflect the probability of a woman returning a true positive or negative or false positive or negative test result. In the General Practice setting, the probability that an appropriate prescription is given is of interest, as well as determining compliance with treatment. The probability of re-treatment of those non-compliant with primary treatment and compliance with re-treatment is included. The model also includes partner factors; both the probability of the index woman infecting a current partner and the risk of an untreated current partner re-infecting the treated index case. The costs of second generation male infection are included up to one-year post-treatment. Second generation male infections arise when untreated women subsequently infect new partners. Since the focus of this analysis is the management of infections in women, the second generation female infections, which arise when untreated males subsequently infect other women, are not included.

2.1.2 Key decisions.

Six key decisions govern the General Practice management of genital Chlamydia infections. These are listed in table 2.1.1. The woman makes the first key decision, and the General Practitioner makes subsequent decisions. The possible options for the woman and General Practitioner at each of the six key decisions create a complex set of permutations and combinations. The interactions of these six key decision nodes are shown in figure 2.1.2.

These decisions are sequential events, with the exception of nodes #3 and #4, which can occur simultaneously. Sub-trees representing possible events at each of these six key decisions are shown in Figures 2.1.4 to 2.1.9.

Table 2.1.1 Key decisions.

The Key decisions are:
1. Decision (by woman) to seek medical assistance.
2. Decision to test for infection.
3. Decision to treat identified cases.
4. Decision to trace and treat contacts.
5. Decision to test for cure.
6. Decision to retreat treatment failures.

Figure 2.1.2. Key decisions in decision tree

The numbers correspond to the six key decisions.

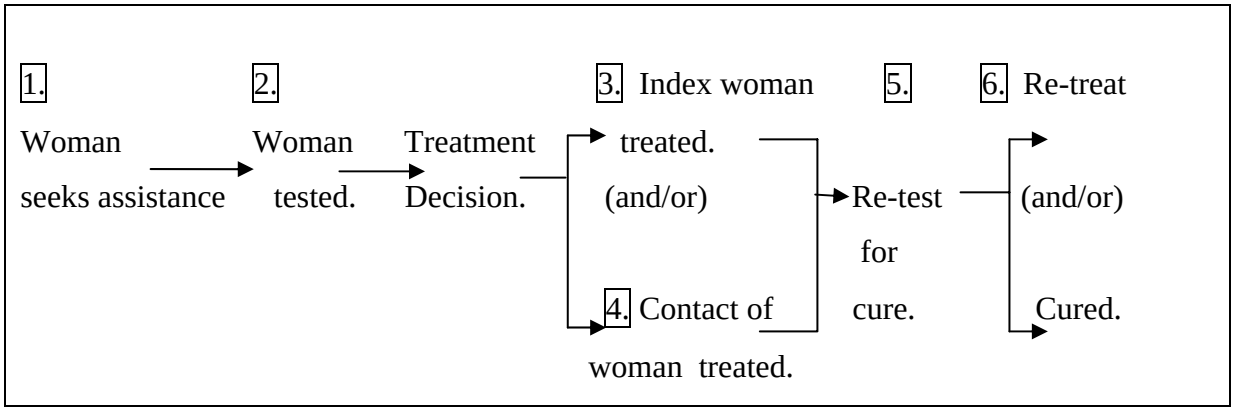
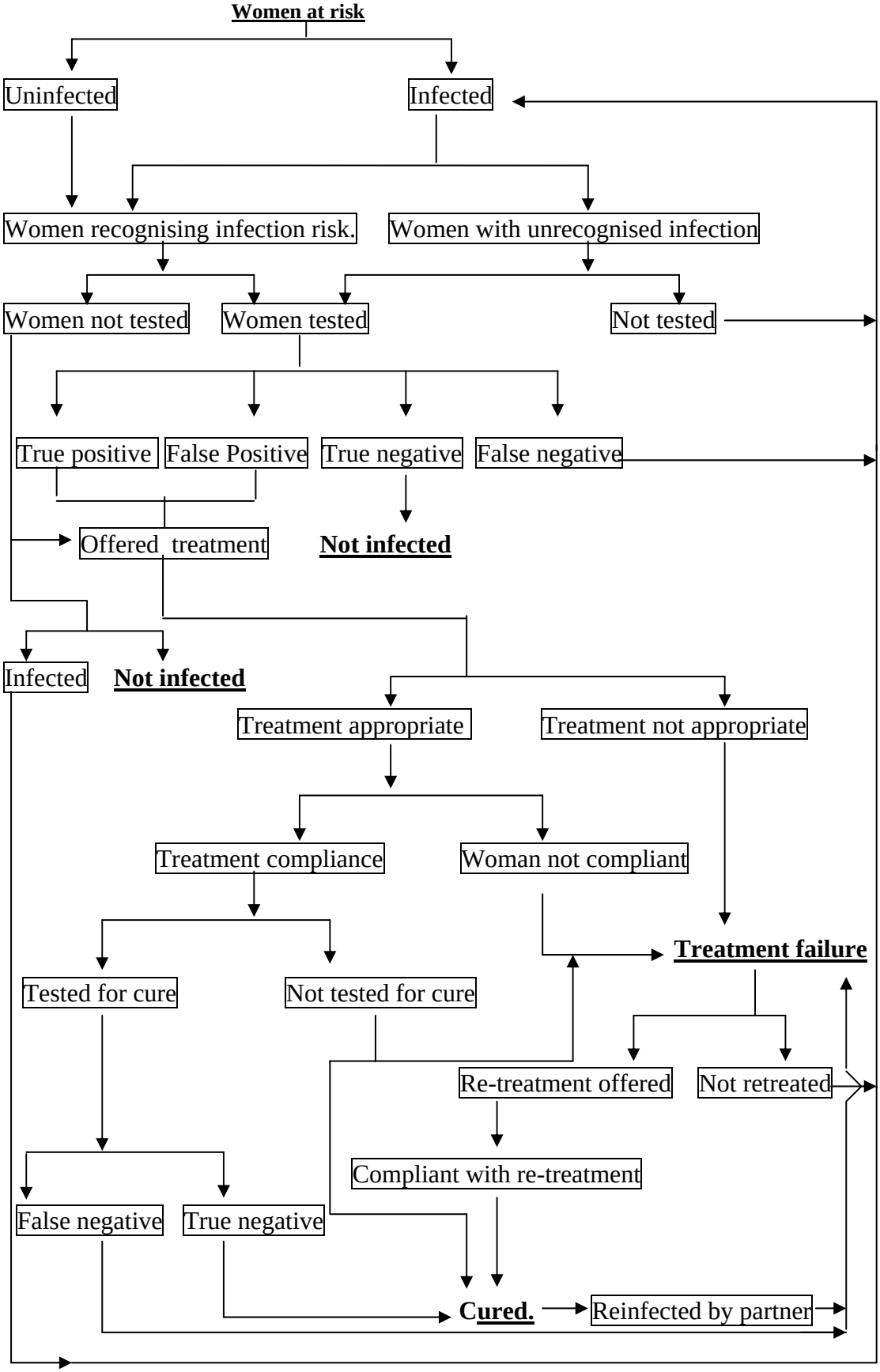


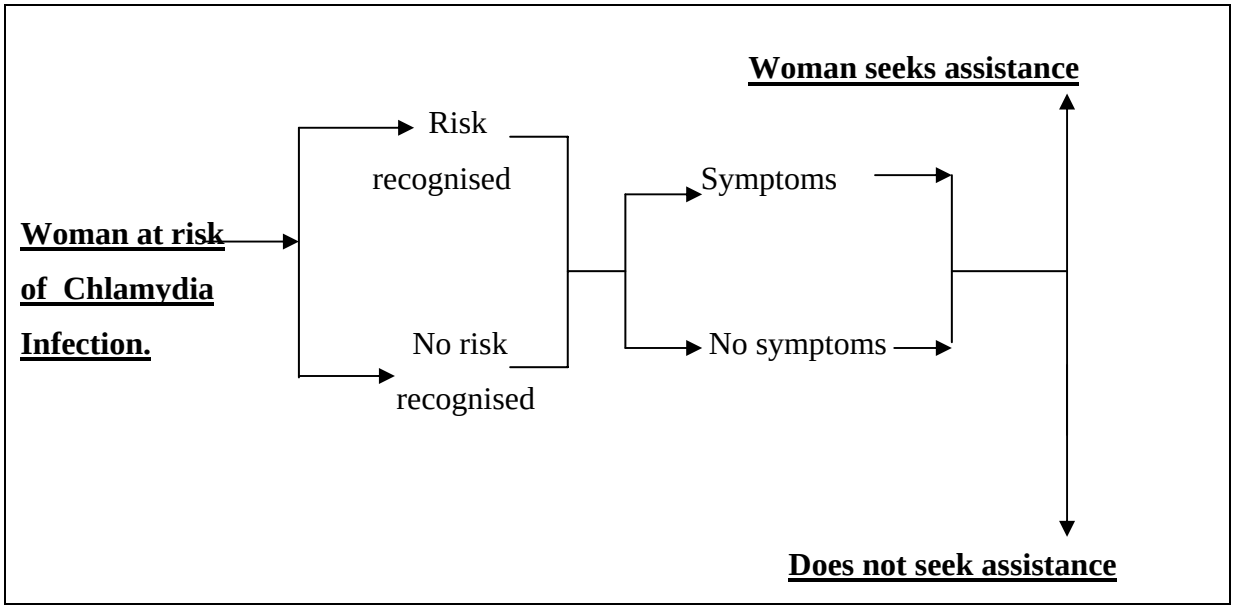
Figure 2.1.3. Flow chart: Chlamydia trachomatis infection in women.



Decision 1: Decision to seek medical assistance.

A proportion of women who are at risk of infection will recognise that risk. A proportion of those who recognise a risk of infection will seek assistance. Some women who are at risk of infection will develop symptoms, but the presence of symptoms is not a guarantee that the woman will recognise the significance of those symptoms and seek assistance for the infection. This is demonstrated in figure 2.1.4. The values for these probabilities are discussed in section 4.1. In addition, because symptoms of infection are non-specific, the presence of symptoms does not imply Chlamydia trachomatis infection. The subsets of women who seek assistance and the subsets that do not, both contain women who are infected and women who are not infected.

Figure 2.1.4 Decision to seek medical assistance.



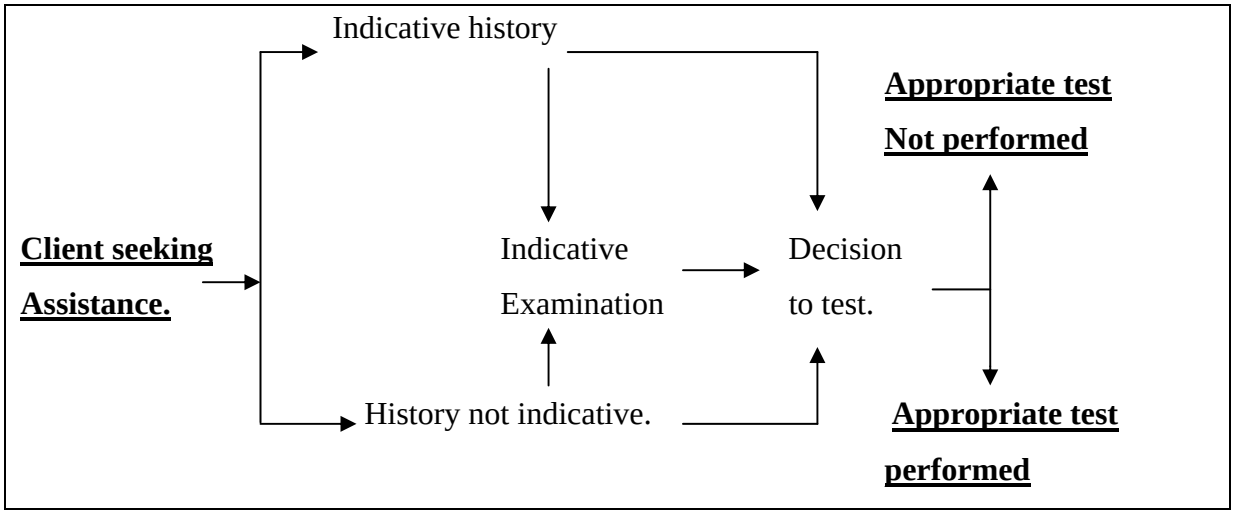
Decision 2: Decision to test for infection.

The decision to test for infection can be made in the presence or absence of indicative history or examination findings. Values for the probability of this are discussed in section 4.2. Disease screening (in the absence of signs or symptoms) is important in the detection of asymptomatic carriers.

The options in decision to test are shown in figure 2.1.5.

In the presence of infection an appropriate specimen for Chlamydia trachomatis must be collected. Chlamydia trachomatis is an obligate intracellular parasite. Specimen collection technique is important and transportation to the laboratory can be critical. An inappropriate specimen or a specimen handled inappropriately will result in failure to detect the organism.

Figure 2.1.5. Decision to test for infection.

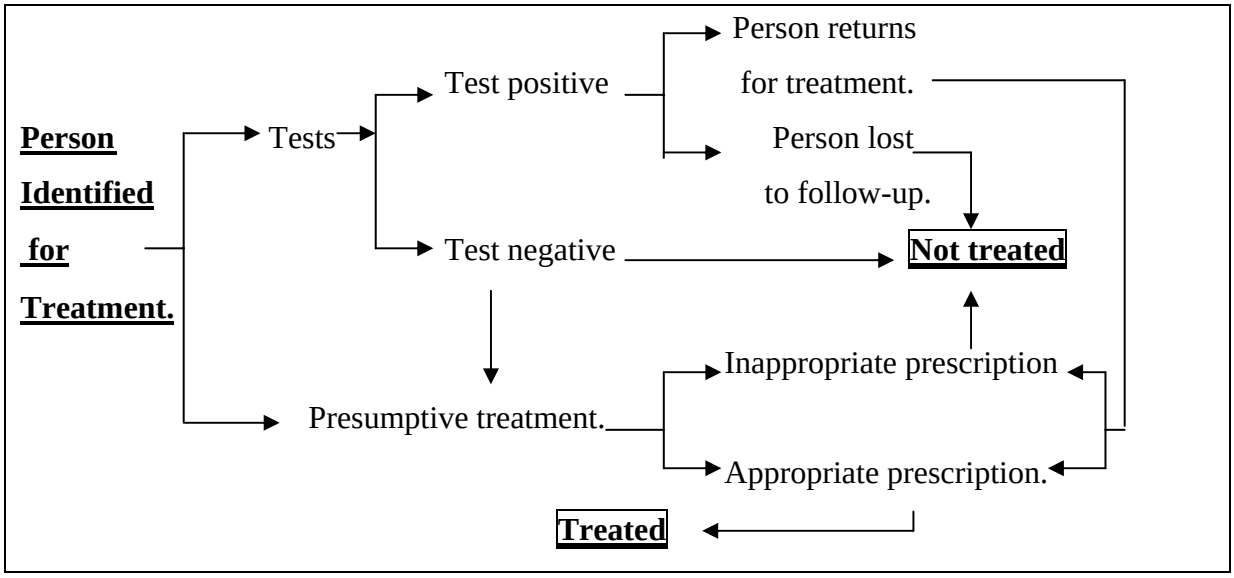


Decision 3: Decision to treat identified cases.

A decision to treat may be made on the basis of a positive test result or on presumptive grounds. The decision to treat on test results may be thwarted if the person to be treated is lost to follow-up.

Figure 2.1.6 demonstrates the options to treat presumptively or to treat on the basis of test results, if the woman returns for a prescription after testing. As successful treatment of Chlamydia requires an appropriate prescription, this is included.

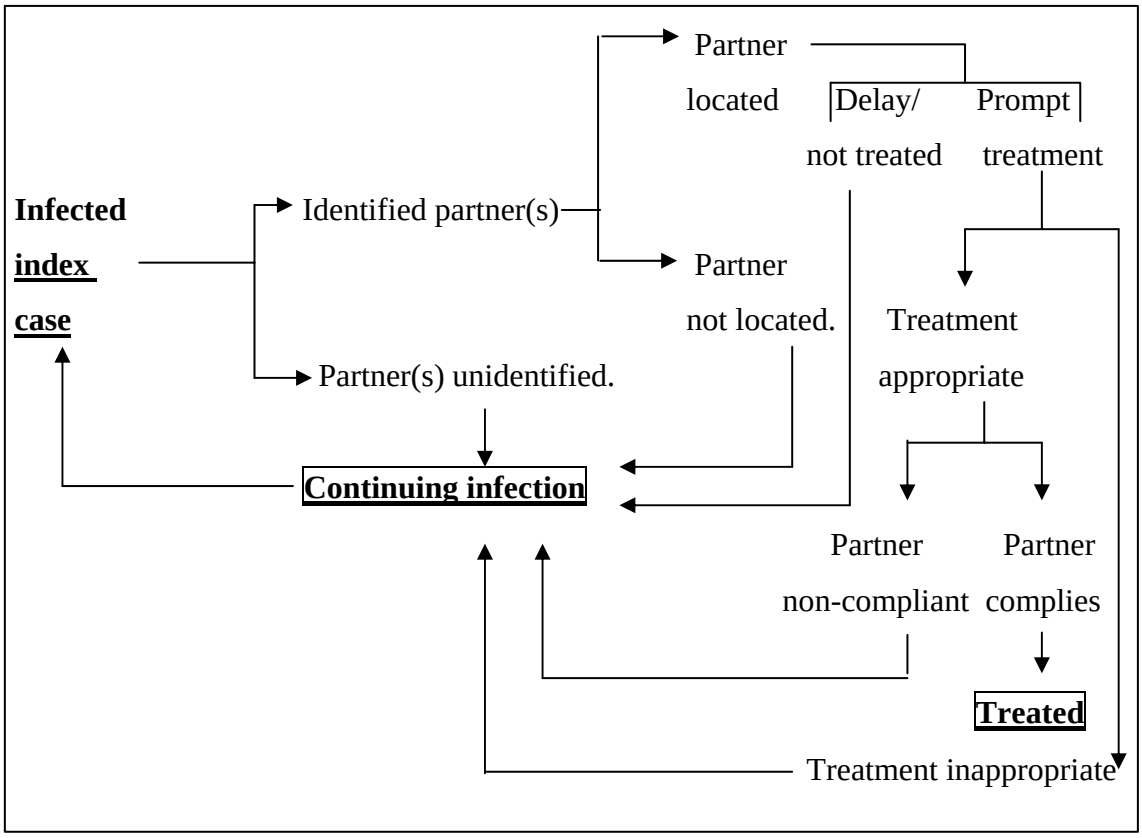
Figure 2.1.6. Decision to treat identified cases.



Decision 4: Decision to trace and treat contacts.

Howell et al (1997) demonstrated that the decision to trace partners has a significant influence on success of treatment. Their decision tree included chance nodes for the male partner to be identified and treated or left untreated and able to re-infect the index case. Their approach acknowledges that contact tracing does not guarantee contact treatment. Partners may be identified but not treated promptly, not treated appropriately, not treated completely or not treated at all. Figure 2.1.7 demonstrates the options in tracing and treating partners. Treatment failures among those partners identified and offered treatment can be due to non-compliance, inappropriate prescription, or timing, which must coincide with that of the index case. Those partners who experience treatment delay or treatment failures or who are untreated are able to perpetuate the infection.

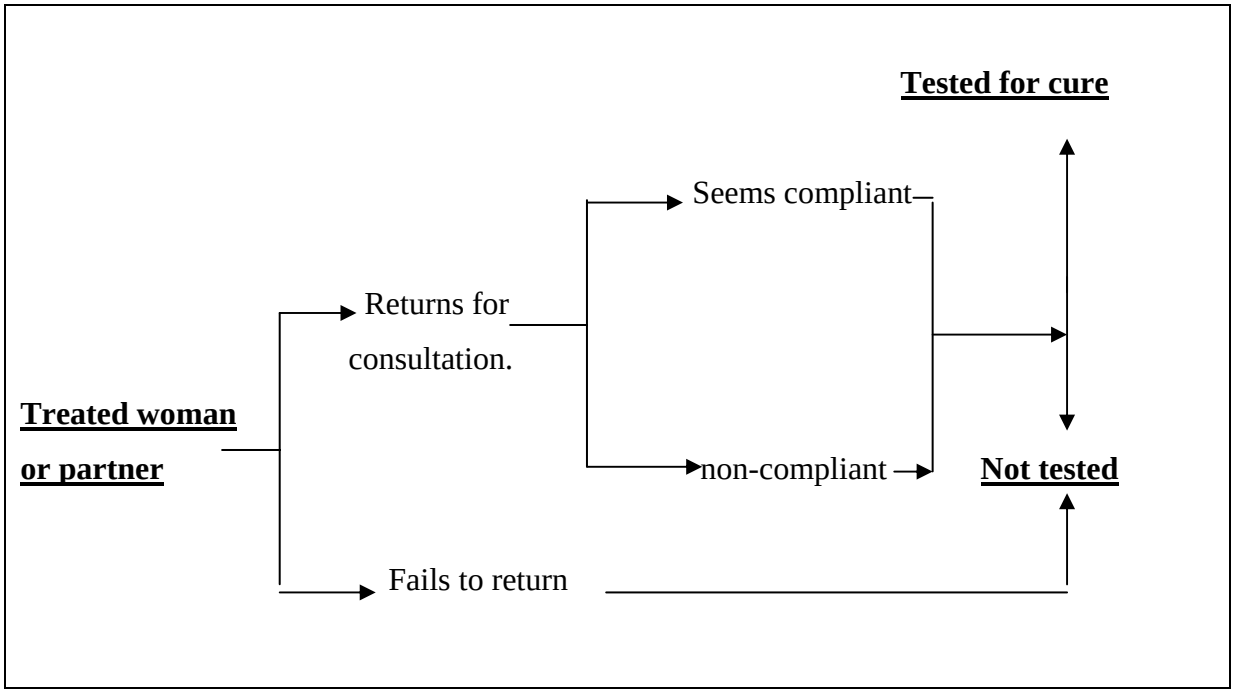
Figure 2.1.7. Decision to trace and treat contacts.



Decision 5: Decision to test for cure.

Cases (both women and their partners) who do not attend for a compliance consultation cannot be re-tested. Some will inevitably be lost to follow-up. This model assumes that all that are treated will attend for a compliance consultation. A test for cure may serve many functions: identification of those requiring re-treatment, and reassurance of the doctor, the treated person and the partner that the infection risk is gone. Figure 2.1.8 demonstrates the options of re-testing or not re-testing those who appear compliant with treatment and/or those who don't.

Figure 2.1.8. Decision to test for cure.

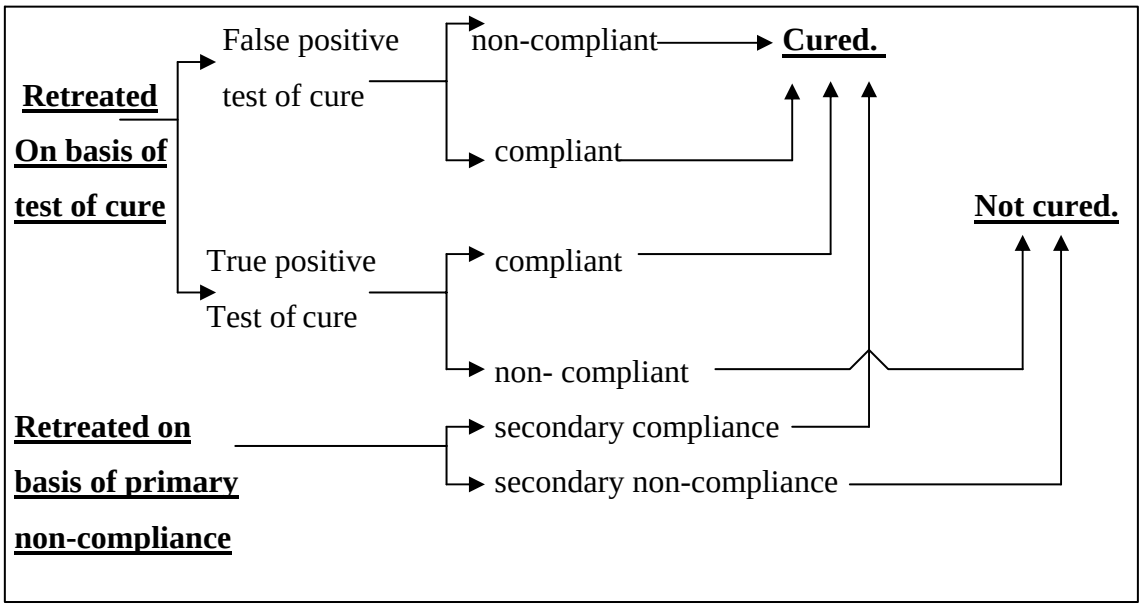


Decision 6: Decision to re-treat.

Decisions to re-treat may be based on clinician estimation of compliance or on results of tests for cure. The choice of test for cure is important, as a test of low negative predictive value may result in unnecessary repeat treatments. Repeated treatment is wasteful of resources if the test of cure was falsely positive, and if the person to be re-treated is non-compliant with re-treatment .

Figure 2.1.9 demonstrates the effect these considerations have on the number cured of infection.

Figure 2.1.9. Decision to re-treat.



2.1.3 Incorporating General Practice processes.

These figures demonstrate that even within each of the key decisions, there exists a range of possible processes that do not readily lend themselves to a single decision tree. The parallel processes, which interact as displayed in the flow charts, do not fit into simple decision trees. The degree of control that is possible over patient behaviour and conditions in everyday General Practice are far different to the control exerted in a clinical trial or in a hospital clinic. The potential exists for considerable variety in outcome due to these processes. To omit these processes would be to fail to demonstrate the complexities that exist in the clinical practice of medicine and in General Practice in particular. The model could be simplified by assumptions that would limit some of these processes, but it would then not

accurately reflect the real issues encountered in the management of chlamydia infection in General Practice.
Simplifying assumptions have been avoided where practical.

2.2. Identification of costs and consequences.

2.2.1 Subsidies in General Practice.

Visits to a General Practitioner in New Zealand generate a subsidy claim against the Health Funding Authority if the patient is a holder of a Community Card or High User card. Additional consultation costs are incurred when the General Practitioner sees patients many times: to initially assess the person, then deliver test results and treatment, then to ascertain compliance after treatment.

Prescriptions generate cost to the Health Funding Authority if the appropriate pharmaceutical subsidy exceeds the patient co-payments. Co-payments are determined by cardholder status with exemptions for high use (see section 3.1.1).
A diagnostic test for Chlamydia infection generates a laboratory cost to the health Funding Authority regardless of the cardholder status of the person tested. A further test to document cure after treatment increases the laboratory cost of managing an infection.

False positive results on initial screening tests or on tests for cure may prompt unnecessary consultations and prescriptions. Non-compliance, if detected, stimulates repeat consultations and re-treatment.

Therefore in the General Practice management of genital Chlamydia, the primary care costs are minimised when there are fewest subsidised visits to the doctor, judicious use of laboratory tests and appropriate prescribing to compliant clients who contribute co-payments. These considerations also apply to the management of any identified partner. Treatment of identified partners increases the cost of management of the infected index case, but successful treatment is undermined by short-term re-infection of the woman by an untreated infected partner. Consequences arise in women who are not adequately treated or

who are re-infected by an untreated partner. The untreated partner also suffers consequences of chronic infection.
Hence, General Practitioner management decisions have a significant effect on treatment cost and consequences as shown in tables 2.2.1 to 2.2.3.

2.2.2 Costs for women and partners

Table 2.2.1 demonstrates the possible permutations on costs and consequences when an infected woman consults with an identified partner. The costs are in addition to an initial consultation cost for each person. Some partners are identified and traced but not treated because the partner or doctor has inappropriate information about the diagnosis, the infection risk, or the appropriate treatment. They are at risk of re-infecting the index woman and also of developing infection consequences themselves. Consequences for women and partners arise from delayed treatment or undiagnosed untreated infection.

Complications for women are pelvic inflammatory disease and its sequelae: pelvic pain, infertility, ectopic pregnancy, premature births and neonatal infections. Complications for males are recurrent urethritis, Reiters syndrome, epididymitis, prostatitis and infertility.
Late treatment is included as a complication, as it is more expensive than treatment of early genital Chlamydia infections. Late treatment is treatment of an ascended genital infection: acute pelvic inflammatory disease in the case of women and acute epididymitis or prostatitis in males. In these circumstances a prolonged course of antibiotics is required in an antibiotic mix to cover secondary anaerobic infection, with or without additional tests to secure the diagnosis.

Table 2.2.1.Effects of treatment decisions on consequent cost

Scenario: ***Infected woman attends clinic with infected partner***

Code: Rw/ Rp= reinfection risk short-term (for woman or partner), Cw/Cp=complication risk (for woman or partner); Lw/Lp=late treatment required (for woman or partner).

Test done	**Treatment Offer**	**Outcome**	**Extra costs**	**Cost savings**
Both tested	Both treated	Both cured		
		Woman only cured	Rw, Cp, Lp.	
		Partner only cured	Rp, Cw, Lw.	
	Woman treated, partner not.	Woman cured, Partner spont. Cured.		One treatment
		Woman not cured, partner spont cured.	Rp, Cw, Lw.	One treatment
		Woman cured, partner not cured.	Rw, Cp, Lp.	One treatment
		Neither cured	Cw, Cp, Lw, Lp.	One treatment
Both tested	Woman not treated, Partner treated.	Woman spont. Cured, partner cured.		One treatment
		Woman spont cured, partner not cured.	Rw, Cp, Lp.	One treatment
		Woman not cured, partner cured.	Rp, Cw, Lw.	One treatment
		Neither cured	Cw, Cp, Lw, Lp,	One treatment
Neither tested	Both treated	Both cured		Two Test costs
		Woman only cured	Rw, Cp, Lp	Two Test costs
		Partner only cured	Rp, Cw, Lw	Two Test costs
Neither tested	Woman treated, partner untreated	Woman cured, partner spont. cured.		2 Tests, & 1 treatment cost
		Woman cured, partner not cured.	Rw, Cp, Lp.	2 Tests, & 1 treatment cost
		Woman not cured, partner spont cured.	Rw, Cp,Lp	2 Tests, & 1 treatment cost
		Neither cured	Cw, Cp, Lw, Lp	2 Tests, & 1 treatment cost
	Woman not treated, partner treated.	Woman spont. cured, partner cured.		2 Tests, & 1 treatment cost
		Woman not cured, partner cured.	Rp, Cw. Lw.	2 Tests, & 1 treatment cost
		Woman spont. cure, partner not cured.	Rw, Cp,Lp	2 Tests, & 1 treatment cost
		Neither cured	Cw, Cp, Lw, Lp.	2 Tests, & 1 treatment cost

Table 2.2.1. CONTINUED. Effects of treatment decisions on consequent costs.

Scenario: ***Infected woman attends clinic with infected partner***

Code: Rw/ Rp= reinfection risk short-term (for woman or partner), Cw/Cp=complication risk (for woman or partner); Lw/Lp=late treatment required (for woman or partner). *Similarly if partner only tested.

Test done	**Treatment Offer**	**Outcome**	**Extra costs**	**Cost savings**
*Woman only tested	Both treated	Both cured		One test cost
		Woman only cured	Rw, Cp, Lw	One test cost
		Partner only cured.	Rp,Cw,Lw	One test cost
	Woman treated, Partner not treated	Woman cured, Partner spont. cured.		1 treatment, and 1 test cost
		Woman cured, partner not cured.	Rw, Cp, Lp.	1 treatment, and 1 test cost
		Woman not cured, partner spont. cured.	Rp, Cw, Lw.	1 treatment, and 1 test cost
		Neither cured	Cw, Cp, Lw, Lp.	1 treatment, and 1 test cost
	Woman not treated, partner treated.	Woman spont. cured, partner cured.		1 treatment, and 1 test cost
		Woman spont cured, partner not cured.	Rw, Cp, Lp.	1 treatment, and 1 test cost
		Woman not cured, ptnr cured	Rp, Cw, Lw.	1 treatment, and 1 test cost
		Neither cured	Cw, Cp, Lw, Lp.	1 treatment, and 1 test cost

2.2.3 Costs for women without partners

Table 2.2.2 demonstrates the effects of permutations on costs and consequences when an infected person attends without their partner. The costs are in addition to the consultation cost for the woman. Test and testing or treating only the woman infected can save treatment costs as well as consultation costs. The extent of savings in General Medical Services Benefits and Pharmaceutical Schedule will depend on the Community cardholder status of the partner. The consequences of consulting only with the index woman differ from those in table 2.2.1 if the partner is not treated. In these circumstances there is an increased re-infection risk for the woman and risk of complications for both woman and partner.

Table 2.2.2. Effects of treatment decisions on consequences.

Scenario: ***Infected Woman attends without partner***.

The cost savings listed are additional to the General Medical Benefit saved on partner consultations.

Code: P=partner infected, Rw/Rp=short-term reinfection risk (for woman or partner), Cw/Cp=complications (for woman or partner, Lw/Lp=late treatment required(for woman or partner).CT=contact tracing costs.

Test done	**Treatment Offer**	**Outcome**	**Extra costs**	**Cost savings**
Woman only tested	Woman only treated	Woman cured	P, Rw ,CT, Cp, Lp.	0ne test and treatment
		Woman not cured	P, Cw, Lw, CT, Cp, Lp,	0ne test and treatment
	not treated	Woman spont. cured.	P, Rw, Cp, Lp.	One test and 2 treatments
		Woman remains infected	P, Cw ,Cp, Lw, Lp.	One test and 2 treatments
Woman not tested	Woman treated	Woman cured	P,Rw, CT, Cp, Lp.	Two tests and one treatment
		Not cured	P,Cc,Lc, CT, Cp, Lp.	Two tests and one treatment
	Woman not treated	Woman spont. cured	P,Rw, Cp.Lp.	Two tests, two treatments
		Woman remains infected	P, Cw ,Lw, Cp. Lp.	Two tests, two treatments

2.2.4 Costs for untreated women.

Since genital Chlamydia is commonly asymptomatic, there is a significant group of infected women who remain unaware of the infection and therefore untreated. These people do not generate immediate general practice management costs, but do generate costs for subsequent development of consequences. The predicted outcomes for untreated infected women are represented in table 2.2.3.

Table 2.2.3. Consequences of untreated infection

Code: FL=foetal loss, ND=neonatal deaths, I=infertility tmts, M=multiple births, Pr=prematurity, C=neonatal conjuncivitis, Pn=neonatal pneumonia.

Infection status	Fertility effects	Pregnancy outcome	Maternal & neonatal outcomes
Persistent infection	Fertility preserved	Ectopic pregnancy	FL, I
		Premature labour	FL, ND, Pr, C, Pn.
		Normal delivery	C, Pn,
	Fertility impaired	Assisted conception	FL, M, Pr, C, Pn.
		Ectopic pregnancy	FL, I
		Premature labour	FL, ND, Pr, C, Pn.
		Normal delivery	C, Pn,
	Infertile		I
Spontaneous resolution	Fertility preserved	Ectopic pregnancy	FL, I
		Premature labour	FL, ND, Pr, C, Pn.
		Normal delivery	C, Pn,
	Fertility impaired	Assisted conception	FL, M, Pr, C, Pn
		Ectopic pregnancy	FL, I
		Premature labour	FL, ND, Pr, C, Pn.
		Normal delivery	C, Pn,
	Infertile		I

2.3 Viewpoint on costs and consequences.

2.3.1 Overall perspective

The perspective of the current modelling project is that of the New Zealand-wide purchaser of both community and hospital-based medical services, the Health Funding Authority. Only medical costs of consultations, investigation and treatment have been considered. The costs from the viewpoint of the New Zealand Health Funding Authority do not include the direct patient burden of consultation costs, investigation and treatment, indirect or psychic costs to patient or partner. Social and community indirect and psychic costs are not included.

These other costs are not inconsiderable. Many complications of genital Chlamydia infection carry significant personal direct and indirect and community costs. In other economic analysis, personal costs equal and even outweigh the cost to Health Authorities (Genc and Mardh 1996).

In the instance of an unnecessary treatment given following a false positive test, the costs to the Health Funding Authority are listed in table 2.3.1. However, the costs to the woman and partner of unnecessary treatment include the client burden of doctors consultations and prescription co-payments, travel to appointments and to the pharmacy, opportunity costs (of time, money and health status), psychic costs of false diagnosis, and medication side-effects (if any).

2.3.2. Costs of General Practice management.

The burden of costs of investigation and treatment will depend on the clinical scenario and management plan under consideration, as table 2.2.1 and 2.2.2 previously demonstrated. Only costs to the Health Funding Authority are included.

The initial investigation appropriate for detection of this infection is a genital chlamydia swab. In practice, a General Practitioner performing the initial genital examination will usually request a full panel of screening tests for genital infections and sexually transmitted diseases, this will entail at least two genital swabs including one for chlamydia. The cost of only one genital chlamydia swab has been included in this analysis (see table 3.1.5 for pricing). The cost of any diagnostic swabs in addition to a Chlamydia test was not included, as this is not directly relevant to the current investigation.

The burden of consultation and prescription costs to the New Zealand Health Funding Authority will vary with Community Cardholder status. The patient bears part of the cost of prescribed pharmaceuticals and part of or the entire consultation fee. Community Cardholder status determines how much cost is borne by Health Funding Authority and how much by the patient. For this reason the model includes, as a probability node, a range for the percentage of treated persons who are Community Cardholders in New Zealand general practices. The prescription co-payment contribution has been deducted from the total pharmacy cost to determine burden to the Health Funding Authority. Similarly, the General Medical Services subsidies generated from consultations have been calculated from the proportion of cardholders among those treated.

This model assumes that all people that are treated will be seen at a second consultation to check compliance. In reality, some are lost to follow-up. The size of this effect in General Practice is unknown, therefore this was not taken into account in the model.

The itemised burden of costs incurred by the Health Funding Authority during unnecessary treatment in response to false positive test is listed in table 2.3.1.

Table 2.3.1. Costs of unnecessary treatment.

Costs of unnecessary treatment:
1. General Practitioner consultations. A General Medical Services claim made for each consultation by Community Cardholders.
2. Medications. The Pharmaceutical Schedule price with wholesale and retail pharmacy mark-up and GST added, less any client co-payment.
3. Test of cure. The cost of a test as per laboratory schedule, and a General Medical Services claim, where applicable, for the consultation at which the test is taken.
4. In the event of treatment failure or a false positive test of cure, repeat consultation and medication costs (Steps 1 and 2 again).
5. In the event of non-compliance by woman and/or partner, Repeat consultation and medication costs (Steps 1- 4 again).

2.3.3. Costs of consequences.

Only the Health Funding Authority burden of consequences of untreated infection is included in this analysis. Table 2.3.2 specifies these costs of complications in women in New Zealand. Prices for these complications are discussed in section 3.2.

Table 2.3.2 Health funder burden of consequences in untreated women.

Health funder burden of consequences in untreated women.
1. Pelvic inflammation: Costs of pain investigation and management.
2. Infertility: Direct medical costs of infertility investigation and treatment.
3. Ectopic pregnancy: Cost of investigation and surgical management.
4. Miscarriage: Medical management costs of the event.
5. Premature labour: Medical management of labour and neonatal intensive care.
6. Neonatal pneumonia: initial medical management costs.
7. Neonatal conjunctivitis: Initial medical management.
8. Partner health risks: Health management costs for the partner for recurent urethritis, epididymitis, prostatitis, Reiters syndrome.

Table 2.3.3 lists the direct, indirect and psychic costs to clients, their families and the wider community and future costs. As the New Zealand Health Funding Authority does not carry these costs, they are not considered in this analysis.

Table 2.3.3. Personal and community costs of untreated female infection.

Personal and community costs of untreated female infection.
1. Psychic costs of pelvic pain, quality of life, opportunity costs, including loss of employment and enjoyment of life and indirect costs.
2. Menstrual disturbances. The costs of investigation, quality of life, any effects on fertility, psychic costs, opportunity and intangible costs are considered personal and social costs.
3. Infertility. Personal costs of management of complications of infertility treatments: failure of infertility treatment, loss of or threat-of -loss of life, multiple birth, opportunity costs, indirect and intangible costs including psychic costs, and loss of parental status.
4. Ectopic pregnancy. Loss of life of child, risk of loss of life to mother, future infertility, opportunity cost, psychic costs.
5. Miscarriage. Costs of loss of foetal life, psychic costs, indirect and opportunity costs.
6. Premature labour. Loss of life, indirect psychic costs, future costs of disability and future psychic costs to the child.
7. Neonatal pneumonia. Loss of life, indirect psychic costs and opportunity costs, future costs of disability. Immediate psychic costs to parents and future psychic costs to parents and child.
8. Neonatal conjunctivitis. Opportunity costs, loss of vision, future costs of disability, immediate and late psychic costs to the parents and future psychic costs to child.
9. Partner treatment. Male infertility, loss of future life status, pain, opportunity costs, psychic costs.

2.4. Clinical scenario setting.

2.4.1 The hypothetical cohort

This Chlamydia model considers a hypothetical cohort of one hundred thousand sexually active women of childbearing age.

The size of the cohort was decided by trial and error. Sufficient subjects were required to model infrequent outcome events (neonatal sequelae) in complete integers, representing individual patients. The chosen size is similar to those in a recent Chalmydia models with similar end-points (Magid et al, 1996). The age range of the women is restricted to childbearing age because many of the consequences of infection are complications of

pregnancy. The ideal age range for this model to reflect would be the group most at risk of infection, the under twenty-five year-olds. Data from studies covering a wider age group is taken in recognition of the paucity of age-specific data which compounds the paucity of specific General Practice information, and the lack of information on behavioural aspects of disease management.

2.4.2 The simulation of clinical scenarios.

An EXCEL spreadsheet model, based on the decision tree figure 2.1.1 and sub-trees, was designed to predict the outcomes for the hypothetical women at risk of genital chlamydia. For each of the six clinical scenarios (table 2.4.2), multiple iterations of the spreadsheet were run to produce weighted probabilities for the range of outcomes for these women. Each iteration was a unique random selection of values for each of the variables taken from a plausible range.

The randomisation for this model was achieved with Monte Carlo software @Risk (Windows version, March 1996), which allows multivariate randomisation, producing sensitivity analysis on the randomised variables and probability-weighted outcomes. This is a second order Monte Carlo analysis.

Monte Carlo analysis was chosen because that methodology enables selection of values from a plausible range, hence allowing leeway for clinical uncertainty. Medicine is not an exact science, human behaviour is not totally predictable, and some of the questions asked by the model required answers that cannot be precisely determined. The Monte Carlo method is, as the name suggests, a gamble. As the value for each variable is randomly selected every time, the result of each iteration differs from every other. The result from each iteration represents one gamble outcome from all possible outcomes within the applied range of values.

Second order Monte Carlo analysis is a sophistication of this process, as it permits the random selection to occur within a probability distribution about an estimated mid-range value. The mid-range point can be skewed within the range, and the distribution can take any form: actual data distributions will not always be in normal distibution about the mean. Where the shape of the probability distribution curve within the range is unknown, a triangular distribution about the mean is applied.

The number of iterations was determined by trial and error until sufficient results were obtained to demonstrate statistical convergence. For all scenarios in this model, convergence was consistently achieved within one thousand iterations. Five simulations each of one

thousand iterations were run for every scenario. The results, which are presented in chapter 5, are the cumulated results from these iterations.

2.4.3 The basic management plan.

The basic primary care management plan for genital Chlamydia infection is shown in table 2.4.1. Variations on this reflect clinical scenarios with different management practices in different settings. Six clinical scenarios of topical interest in the management of Chlamydia have been chosen for analysis. Topicality was determined in consultation with the local panel of experts.

Table 2.4.1 Basic management plan

Basic management plan
1. Initial consultation by the woman.
2. Laboratory testing for infection.
3. Short consultation with woman for results.
4. Pharmacological treatment.
5. Short consultation with woman for test of compliance.
6. Laboratory testing for cure.
7. Re-treatment (repeat steps 3, 4 , 5 and/or 6) if indicated.
8. Partner contact tracing process.
9. Partner management (repeat steps 1-8 for the partner(s) of the woman).

2.4.4 Clinical scenarios for testing.

Six variations on the management plan have been selected to demonstrate impact on overall cost-effectiveness, of different primary treatment, and different testing policies are shown in table 2.4.2. Testing options were to test for cure (scenarios numbered 1a or 1d), or not to test for cure (scenarios 2a/2d and 3a/3d). Senarios 1a/1d and 2a/2d used an enzyme-linked immunoassay (Elisa) screening test with micro-immunofluorescence (MIF) to confirm positive results. Scenarios 3a/3d used the DNA amplification technique of polymerase chain reaction (PCR) for the screening test. Treatment options were doxycycline 100mg BD or erythromycin 800mg BD where contraindicated, compared with a stat. dose of azithromycin

1 Gm. The azithromycin scenarios were annotated with “a” following the scenario number, doxycycline/erythromycin scenarios with “d”.

Table 2.4.2 Scenarios tested in the Wellington model.

Scenario number	Test	Treatment
1d.	EIA/MIF with test of cure	Doxycycline
1a.	EIA/MIF with test of cure	Azithromycin
2d.	EIA/MIF /no test of cure	Doxycycline
2a.	EIA/MIF /no test of cure	Azithromycin
3d.	LCR/no test of cure	Doxycycline
3a.	LCR/no test of cure	Azithromycin

Hence scenarios numbered 1d, 2d and 3d use doxycycline with erythromycin as an alternative prescription where tetracycline is contraindicated. Scenarios 1a, 2a and 3a are identical to the scenarios bearing the same number except using azithromycin as the prescription. These latter three scenarios are hypothetical scenarios. Azithromycin is registered, but not subsidised, for prescription in New Zealand. The cost to the patient of unsubsidised medicine discourages prescription of such medicines by New Zealand General Practitioners. As a consequence, it is not in regular use in this country. Azithromycin is compared to standard treatment (doxycycline/erythromycin) because azithromycin is the treatment of choice for genital Chlamydia management according to the Australasian College of Sexual Health Physicians (Garland et al 1997).

Scenarios 1a and 1d are modelled on the steps of the management plan in table 2.4.1. Scenario 1d models the cost and effectiveness of a 7-day prescription of doxycycline for genital Chlamydia (with erythromycin where tetracycline is contraindicated). Scenario 1a models the cost and effectiveness of a single dose of azithromycin. In all other respects, the General Practitioner management of Chlamydia infection in the clinical scenarios 1a and 1d are identical.

Scenarios 2a, 2d, 3a, and 3d model a modification of the management plan of table 2.4.1. All four scenarios omit step 5, testing for cure of the management plan.

Clinical scenarios 2a and 2d differ only in the prescribed treatment option for management of the infection, as do scenarios 3a and 3d. Laboratory testing for infection, step 2 of the management plan in table 2.4.1, is different in scenarios 3a and 3d to all other scenarios.

These two clinical scenarios model the cost and effectiveness of DNA hybridisation tests in the diagnosis of Chlamydia infections by the General Practitioner.
Except for the prescribed drug of choice, the general practitioner management of the infection in scenario 3a is identical to that in scenario 3d. The clinical scenario 3a models the current recommendation for management of Genital Chlamydia from the Australasian College of Sexual Health Physicians. This recommends use of the DNA hybridisation, ligase chain reaction (LCR), to detect infection and use of directly observed single dose azithromycin for treatment (Garland et al 1997). The College does not recommend testing for cure after treatment. The highly sensitive LCR test produces false positive results up to six weeks after treatment by detection of non-viable organisms, and test of cure is not needed to ensure compliance when compliance is ensured with directly observed single dose azithromycin.

2.5 Sensitivity analysis

2.5.1 Sensitivity through randomisation.

Sensitivity analysis is a major focus of this project. Some of the information required for this analysis has not been formally documented or cannot be readily measured in the New Zealand setting. Very little of the information required was available from General Practice sources. Some of the variables require data that are very specific to a particular group of patients or characteristics and/or location.

Monte Carlo analysis is used to both accommodate and to demonstrate the effects of uncertainty in the variables. Variables at probability nodes and decision nodes have been randomised in recognition of the lack of precision of data and application of data not directly related to the New Zealand General Practice setting.

The multivariate Monte Carlo method used in this model demonstrates sensitivity to all randomised variables as it takes values from the extremes of plausible ranges during the randomisation. This assists assessment of the rigour of valuation of uncertain costs and probabilities for immeasurable variables.

Sensitivity to different management scenarios is also of interest. It is predicted that changes in management policy will influence cost-effectiveness of outcome. The effects of changes in management plan such as policies for clinical and laboratory screening, pharmaceutical treatment, follow-up and contact tracing can be tested by sensitivity analysis. Some steps in the management plan are predicted to have a significant influence on costs and consequences, other steps may be less critical to outcomes. Sensitivity analysis on all randomised variables within specific scenarios enables criticality of steps, such as testing for cure and treatment of partners, to be identified. Sensitivity analysis on all randomised variables enables critical steps in management to be identified.

2.5.2 Sensitivity to immeasurable variables

Sensitivity analysis was run on the following variables considered unknown, or not adequately supported by existing evidence. This was derived from the cumulative results of multiple iterations of the model after randomly selecting from the plausible range. Two thousand iterations of each scenario were run for his analysis, the variables to which the results were most sensitive became evident after this number of iterations. The Monte Carlo programme @RISK performs Spearman rank correlation on all randomised variables. An explanation of this correlation is included in appendix C. This function was used to demonstrate the sensitivity of the model to the following randomised variables:

1. Proportion of population infected with Chlamydia. As the prevalence of chlamydia in the New Zealand General Practitioner setting is not known, reported incidence is a used as a proxy measure of prevalence. A survey is underway to gauge incidence from reported primary care practitioner workloads in New Zealand (ESR-Health 1997) but results are not yet to hand. Sensitivity to prevalence is of interest in New Zealand as the prevalence of laboratory proven cases ranges widely throughout the country (Lyttle and Preston 1997).

2. Proportion of population who recognise a risk of infection. The extent to which asymptomatic risk is recognised is uncertain. Sensitivity to this function is of interest in planning health promotion, asymptomatic screening and contact tracing for infectious disease control.

3. Proportion of population who undergo diagnostic testing. There is considerable variance in the use of laboratory services by medical practitioners. Sensitivity to variation in clinical practice is of interest in planning programmes for practitioner variability.

4. Proportion of positive tests that are treated. The sensitivity to women lost to follow-up after General Practice testing is of interest in development of best practice guidelines.

5. Proportion of the population with a contraindication to doxycycline. Doxycycline is not offered to women who are pregnant or likely to be (CDC Atlanta 1993). Sensitivity to alternate treatment regimes for those "likely to be pregnant" offered has not been tested in previous analyses.

6. Proportion of prescriptions at appropriate dose and duration. These functions have been included to test sensitivity to prescriber variation. It is of interest in implementation of best practice guidelines.

7. Proportion of women who are compliant to treatment. Sensitivity to compliance is of particular interest. A single dose regime given under direct observation for chlamydia treatment is an option that ensures compliance. In the absence of local experience with directly observed Clamydia treatment, modelling the regime provides some answers.

8. Proportion withdrawing from treatment with side effects. The influence of treatment withdrawals due to side effect profiles and intolerance is uncertain. Sensitivity is of interest in establishing practice guidelines.

9. Proportion of women and partners who are re-treated. Re-treatment rates for General Practice are not known. Not all that require re-treatment will be given it. Variance in clinical practice and client compliance factors influence re-treatment rates. Sensitivity to this factor is of interest in disease control.

10. Proportion of partners found by contact tracing. Sensitivity to this process is of interest as it is performed with variable success in General Practice settings.

11. Proportion of partners who are given epidemiological treatment. Misinformation, misinterpretation of symptoms and non-compliance contribute to failure to treat all identified partners. Sensitivity to this effect is of interest in development of best practice guidelines.

2.5.3 Sensitivity to General Practice management policy.

There are a number of practical questions in local management which sensitivity analysis in the model helps to answer:

- Which patients is it most cost-effective to screen?
- Which tests should be used?
- Should treatment be given on clinical suspicion without test confirmation?
- How does directly observed treatment compare to standard treatment?
- How do consultation costs affect the overall management cost?
- Should a test of cure be performed?
- How critical is partner tracing?
- Should partners be tested before treatment?

2.6. Time discounting

2.6.1 Discounting and natural history

The prediction of the natural course of this infection and its health outcomes is a difficulty that has been encountered in previous published analyses (Howell et al 1997, Magid et al 1996). The problems arise from an attempt to model natural history of the infection when the natural history is not precisely known.

There are a number of practical considerations in the interpretation of the natural history of Chlamydia infection. These are listed in table 2.6.1.

Table 2.6.1. Natural history considerations in genital Chlamydia infections

Natural history considerations in genital Chlamydia infections
1. Most infections are clinically silent,
2. An acute presentation does not imply a recent infection,
3. Treatment does not ensure reversal of pre-existing damage,
4. Infertility goes unnoticed until, or if, the woman seeks intended pregnancy,
5. More than 10 years may intervene between infection and presentation of some consequences of infection.

2.6.2 Historical discounting approach.

Prior published analyses have made assumptions to overcome some of these unknown time-linked factors. Typically these analyses have made assumptions of comprehensive detection of all infected cases, treatment delivered immediately after infection, hence assumption of evasion of all consequences by appropriate treatment.

An early decision analysis on cost-effectiveness of testing for Chlamydia by culture did not include adjustment for future costs of care for complications, citing as a reason that the duration of infection could not be ascertained (Nettleman et al 1986). Other analyses have assumed a predictable time frame for development of all complications, but the time frame for discounting and the complications discounted differ between analyses. Typically analyses have assumed a fixed timeframe for discounting clinical presentation of all complications, as in Genc and Mardh (1996) who discount over five to ten years. Skjeldestad et al 1988 discounted all complications over 10 years; Phillips et al 1989 assumed all

consequences to be realised within 5 years. Sellors 1992 discounted over 8 years for ectopic pregnancy and infertility only. Others have discounted longer-term complications such as infertility over longer periods and shorter-term complications over shorter periods. Haddix et al (1995) assumed all acute pelvic inflammatory disease to occur in one year, pelvic pain within the second year, ectopic pregnancy by the fifth year and infertility in the tenth year post-infection. Some economic analyses included inconsistencies in the model, such as discounting female complications but not male complications (Magid et al 1996 and Marrazzo et al 1997).

Magid et al (1996) ran the analysis twice: discounted at 5% per annum on all complications manifesting beyond one year post-infection and un-discounted, finding the results to be similar with both methods. Only un-discounted results were reported in their published paper.

2.6.3 Approach of this model.

Practical problems were encountered on consideration of time discounting in this analysis. Following the approach of others, it appears that different discounting rates should apply over different time frames for different complications. Discounting requires assumptions on the natural history of the disease and complications that are not well supported by evidence in New Zealand or elsewhere. Omission of discounting assumes that treatment is sought promptly and implies that all complications occur within one year of infection.

The following problems in discounting for this model were considered:

- The time taken to develop complications in New Zealand is unknown. The time to manifest some complications of the infection is longer than for other complications. If discounting is to be done, different complications will need discounting over different timeframes.
- Many female complications are pregnancy-related and time to future pregnancy is difficult to project. The proxy data in New Zealand are the age-related intended pregnancy rates, which peak in the decade following peak Chlamydia incidence (Lyttle 1994). However, the disease complications of salpingitis, ectopic pregnancy and infertility themselves will themselves reduce future intended pregnancy rates (Sexual Health Service,1997).
- The appropriate discount rates for health are contentious. The standard New Zealand public service discounting rate of 10% may be high for a population aged under twenty-

five years. One Monte Carlo simulation randomised the discounting rate between 5-10% (Genc and Mardh 1996). A rate about 5% or less seems to be more appropriate as women under the age of twenty-five have twenty or more years of reproductive life ahead.

- The duration of infection prior to treatment is indeterminate. The infection is silent for variable periods, and the time elapsed prior to detection permits the establishment of some complications regardless of subsequent treatment. Complication rates may not be entirely prevented by treatment (Scholes et al 1996). Estimated future costs should allow for an unknown proportion of inevitable complications. The cost of managing these would not be discountable because the money allocated to management is spent to save future complication expenses prevented by treating reversible disease. Inevitable complications will arise in treated and untreated populations equally, regardless of treatment.
- The appropriate time frame for discounting male complications is not known. The natural history of complications in males is not well understood. This aspect has not been studied in New Zealand.
- Medical developments in management will change projected future cost structures. Advances in the management of infertility have the potential to significantly increase future costs of care (Gillett et al 1995). Recent advances in the conservative management of ectopic pregnancies (Gracycowski and Mishell 1997, Hajenius et al 1997) will reduce management costs for this consequence in the future.
- It is predicted that Monte Carlo randomisation in this analysis will have the effect of producing similar outcomes discounted or un-discounted. This is because the cost and probability range is wider than the 5-10% discounting range.

Precedent for omitting time discounting is set in New Zealand in an analysis of infertility treatments (Gillett et al 1995). The Wellington chlamydia model therefore presents results with health outcomes un-discounted. The potential impact of omission of discounting is softened because costs have been randomised across a range of estimated extremes.

2.7 Handling of decision nodes and probability nodes.

2.7.1 Selection criteria of nodes for randomisation.

The @Risk programme does not restrict the number of variables that could be randomised, but randomisation was not considered necessary at all nodes. Those probability nodes and decision nodes with a significant degree of uncertainty of true value and nodes with a wide

plausible range for the value estimates were selected for Monte Carlo randomisation. At nodes where a sensitivity analysis was required, the values were also randomised.

2.7.2 Randomised probability nodes

The following nodes were selected for randomisation:

1. Probability that women recognise infection risk.
2. Probability that infected women and partners are community cardholders
3. Probability that women have a diagnostic test performed.
4. Probability that doxycycline is not contraindicated.
5. Probabilities that the dose of prescription is appropriate.
6. Probabilities that the duration of prescription is appropriate.
7. Probability that infected women have a current sexual partner.
8. Probability that partners will be traced.
9. Probability that treated women and partners comply with treatment.
10. Probability of treatment side effects.
11. Probability that women and partners needing re-treatment will be re-treated.
12. Probability of development of selected complications: chronic pelvic inflammatory disease, acute symptomatic pelvic inflammatory disease and infertility.
13. Probability of a spontaneous cure with Chlamydia trachomatis
14. Probable rate of a change to new partner
15. Probability of affected males developing symptoms.
16. Probable annual birth rate in affected women.

The values allocated to all these nodes for the purpose of the analysis are displayed in tables of sections 4.4 to 4.6.

2.7.3. Non randomised probability nodes.

The following probability nodes were assigned a fixed value for the purpose of the analysis:

1. The sensitivity and specificity of screening tests.
2. The in-vitro antibiotic susceptibility of the organism.
3. Cross infectivity rates from male to female and female to male.

4. Probability of development of selected complications: chronic pelvic pain rate, ectopic pregnancy, premature delivery, neonatal pneumonia and conjunctivitis.

The values allocated to all these nodes for the purpose of the analysis are displayed in tables of sections 4.2 to 4.6.

2.8. Handling of cost estimates.

2.8.1 Selection of cost estimates for randomisation.

Those cost estimates with a significant degree of uncertainty in the true value, and those with a wide ranging cost estimate were selected for Monte Carlo randomisation.

2.8.2 Randomised cost estimates.

The following cost estimates were selected for randomisation from within an estimated plausible range:

1. Investigation costs of chronic pelvic pain.
2. Cost of neonatal intensive care for premature infants.
3. Cost to treat neonatal pneumonia
4. Cost to treat symptomatic males

The costs that were allocated for the purpose of this analysis are displayed in table 3.2.6.

2.8.3 Non-randomised cost estimates.

The following were allocated a fixed cost price, where that could be established.

1. The General Medical Services payment for cardholders.
2. Costs of screening and confirmatory tests.
3. Cost of pharmaceuticals
4. Cost of outpatient care for PID.
5. Cost of infertility.
6. Cost of managing ectopic pregnancy
7. Cost of management of neonatal conjuctivitis.

The costs allocated to these for the purpose of the analysis are displayed in tables of section 3.1 and 3.2.

2.9 Assumptions.

Limiting assumptions have been avoided wherever possible, and for this reason the decision tree and Markov probability cycles are quite complex. The following assumptions, intrinsic to the model, could have been included as additional randomised probabilities or costs:

- It is assumed that all women with a positive test result will be offered treatment.
- It is assumed that test results and prescription instructions are delivered by telephone, not by further consultation.
- It is assumed that all who require a prescription will collect their treatment from a community pharmacy.
- It is assumed that treatment is only given for positive tests, and no presumptive treatment is offered.
- It is assumed that treatment prevents all future complications.
- It is assumed that complications develop in women with either clinical or subclinical pelvic inflammatory disease.
- It is assumed that contact tracing costs do not require more than a single consultation cost.

2.9.1 Sources of data.

The probability estimates and cost estimates used in this analysis were derived from many sources. Information on an extensive set of epidemiological and clinical variables was derived from both published and unpublished data. All grades of evidence were included, ranging from randomised controlled trials to consensus expert opinion (Sackett et al 1996). Data specific to General Practice in New Zealand were not available for all variables, but New Zealand data were applied wherever available. Information from other countries and other clinical settings was examined in order to establish plausible ranges of approximate values for variables that are not well documented for the New Zealand General Practice setting.

2.9.2 Published databases.

Information was reviewed from the following published sources:
The search was on recent data on epidemiology, natural history and treatment of chlamydia cervicitis and its complications including natural history and management of neonatal sequelae, and clinical trials for treatment efficacy in chlamydia cervicitis.

Medline, Cochrane, Embase, Cinhal,were searched on the topic of Chlamydia infections since 1985 for the following key words: transmission, detection rates, community based screening projects, genital diseases, female, adolescent 13-25 years, infant, new-born, congenital, morbidity, mortality, economics. Erythromycin, doxycycline, and azithromycin, in sexually transmitted diseases, genital diseases in male and female, and cost and cost analysis.

The nursing database (Cinhal) was searched to obtain the nursing perspective on management of infections and complications, and public health aspects of disease control especially community-based STD prevention programmes, behavioural influences on chlamydia spread especially in adolescence. Few articles in this database, 230 in all, dealt with chlamydia. This set overlapped significantly with the findings of other searches, leading to the conclusion that the relevant published literature was well covered.

A search was sought on Markov and Monte Carlo modelling of medical processes, including simulated medical trials and medical economic evaluations limited to infectious diseases and genital infections in particular.

2.9.3 Unpublished industry data.

An approach was made to two companies in the researched medicines industry (Pfizer and Glaxo-Wellcome) for unpublished and in-house data on the pharmacokinetics, side effect profiles and clinical trials of applications of azithromycin and doxycycline in genital chlamydia. There have been no trials comparing the efficacy of azithromycin with standard treatments for genital chlamydia in either Australia or New Zealand (Pfizer, personal communication).

2.9.4. New Zealand Health agencies.

Publications including reports and discussion papers on local public health issues were obtained in discussion with representatives of many New Zealand health agencies:

- New Zealand Guidelines Group, National Health committee.
- Ministry of Health,
- National Preferred Medicines Centre,
- Pharmaceutical Management Agency (Pharmac),
- Royal New Zealand College of General Practitioners,

- New Zealand College of Pharmacists,
- New Zealand College of Midwives,
- Australasian College of Sexual Health Physicians,
- Academic departments of Obstetrics and Gynaecology, General Practice, Medicine and Public Health of the Wellington School of Medicine, University of Otago.
- New Zealand Venereology Society.

2.9.5. Expert opinion.

Local: A multidisciplinary working party was convened to discuss issues in the management of genital Chlamydia in young New Zealanders. Members of this group were consulted for estimates on variables in the New Zealand setting. The membership of this working party is listed in acknowledgements.

Overseas: A personal approach was made to Australian members of the Australasian College of Sexual health Physicians. These colleagues have experience in use of azithromycin as well as doxycycline/erythromycin in Chlamydia management.

Informal discussions on the topic took place with delegates at two international meetings: The 3rd International AIDS Impact Conference (Melbourne, June 1997) and the 1997 Australasian College of Sexual Health Physicians Conference (Melbourne). The latter provided an opportunity to view a demonstration of the model of Magid et al (1996), to present a poster on modelling Sexually Transmitted Diseases in New Zealand and to discuss design of cost-effectiveness analyses.

2.10 Baseline data analysis

The data obtained from sources detailed above was sorted and selected for use in the analysis using the modified Delphi technique. Best estimate values were determined. For the probability nodes and costs subject to randomisation, a plausible range and mid-range value was determined. For nodes not randomised, a best estimate was determined. These values were incorporated into the model.

Each scenario of the model was run 2,000 times, using the Monte Carlo technique at all randomised steps. A single iteration of scenario 1d is included in appendix C as an example to demonstrate the mathematical steps included in the baseline analysis. Multiple iterations of the model generated new data. A cumulative result derived from these iterations produces

a simulated mean value and 95% confidence intervals for each of the randomised variables. The simulated means and confidence intervals are presented in tables 5.1.1 and 5.1.2. The iteration given in appendix C contains the mean simulated data set for scenario 1d at all randomised variables. This particular iteration represents the baseline result for the average case treated under scenario 1d.

2.11 Advanced data analyses

2.11.1 Break-even analysis

At the completion of the analysis of data inputs for the individual scenarios, a breakeven analysis was performed to answer the following questions:

- If azithromycin had a pharmaceutical subsidy on prescription by New Zealand General Practitioners, what would be the effect of the pharmaceutical subsidy on the cost, effectiveness and cost-effectiveness from the perspective of the Health Funding Authority?
- At what level of pharmaceutical subsidy does General practitioner prescription of azithromycin have the same mean cost per treatment as the doxycycline/erythromycin strategy?
- What level of pharmaceutical subsidy is required for General practitioner prescription of azithromycin to achieve the same mean cost per cure as the equivalent doxycycline/erythromycin strategy?
- What level of pharmaceutical subsidy is required for General practitioner prescription of azithromycin to achieve the same mean cost of complications as the doxycycline/erythromycin strategy?
- What is the comparative effectiveness of the strategies under these circumstances?

2.11.2 Decision analysis

The information from the analysis was applied to the six basic steps of the decision tree (figure 2.1.2) to determine the cost, effectiveness and cost-effectiveness of these steps in the General practitioner management of genital Chlamydia. These results enable development of cost-effective clinical guidelines.

Since the information was also applied to determine the influence of the pharmaceutical subsidy on cost of treatment and cure. The decision analysis was extended to evaluate policy for pharmaceutical subsidy on treatment for this condition.

2.12 Conclusion of Chapter 2.

In this chapter the development of the Markov model for analysis is outlined. The rationale for application of a second order Monte Carlo simulation technique for analysis of data is explained. The methods of data collection and data handling are discussed. The approach taken to sensitivity analysis and discounting in the economic analysis is justified. Break-even and decision analysis is introduced for advanced data manipulation.

3. Methods: Valuation of costs

3.0 Burden of costs in General Practice.

The burden of costs of General Practitioner services are shared between the consumer, the third party health payer such as health insurance and the state Health Funding Authority. The costs to the General Practice to supply the service for Chlamydia management and the cost to the woman who is the patient are both perspectives that carry significance and are of interest, but are the subject of another study. For this analysis only the costs to the Health Funding Authority, the funded costs in General Practice, are included.

3.1 Funded costs in General Practice.

3.1.1 Pharmaceutical schedule subsidies.

The cost of subsidised medicines to the New Zealand Health Funding Authority (HFA) was calculated from the New Zealand Pharmaceutical Schedule (Pharmac 1997). The maximum cost to HFA is the subsidised schedule price plus wholesale mark-up, retail mark-up, GST and a dispensing fee. The patient co-payment reduces this maximum cost. Table 3.1.1 shows how the maximum cost to the health funding authority is derived (before the deduction of patient co-payments).

Table 3.1.1 Calculation of maximum prescription costs to HFA in $1997.

Explanation of calculation.	Doxycycline 100mg BD 7days	Erythromycin 800mg BD 7days	Azithromycin 1 Gm stat.
Schedule subsidy	$4.508	$6.241	$0.00 (no subsidy)
+10% wholesale	$4.959	$6.865	$0.00
+11.28% retail	$5.518	$7.639	$0.00
+12.5% GST	$6.207	$8.594	$0.00
+ Dispensing and container fee.	$2.93.	$2.93	$2.93
Pharmacy price (maximum cost to HFA before co-payment)	**$9.14**	**$11.52**	**$2.93**

3.1.2 Patient co-payments.

The patient co-payment adds complexity to the calculation of burden of prescription cost. Co-payments determine the distribution of costs between the HFA and the patient in New Zealand. The levels of patient co-payments differ with community cardholder status.

Community Services Cardholders contribute co-payments of up to $3.00 per prescription item. Non-card-holders contribute up to $15.00 if they are adults and $10 if they are children. Partial or complete exemption from co-payments is earned for families after 20 prescriptions per annum, depending on their card- holder status.
Women and adult contacts who are prescribed doxycycline for genital Chlamydia will pay $9.14 per prescription item if not cardholders, $3 if cardholders and nothing if exempt co-payments. The cost of a doxycycline prescription to the HFA is the cost after deduction of co-payments. This ranges from $0.00 to $9.14 for each doxycycline prescription (as shown in table 3.1.2).

Table 3.1. 2. Cost distribution for doxycycline prescription.

Note: The pharmacy price is for doxycycline 100mg BD 7 days, taken from table 3.1.1

Client co-payment status.	Maximum patient co-payment.	Pharmacy price of medicine.	Patient prescription copayment due	Prescription Subsidy) **Cost to HFA**
Exempt charges	$0.00	$9.14	$0.00	**$9.14**
Card-holder	$3.00	$9.14	$3.00	**$6.14**
Child, no card	$10.00	$9.14	$9.14	**$0.00**
Adult, no card	$15.00	$9.14	$9.14	**$0.00**

Women and contacts who are prescribed erythromycin, will pay $11.52 per adult without a Community card, $10.00 if under 18 years old without a card, and $3.00 with a card, unless exempt co-payments. The cost of an erythromycin prescription to the HFA ranges from $0.00 to $11.52 for each erythromycin prescription as shown in table 3.1.3..

Table 3.1. 3. Cost distribution for erythromycin prescription.

Note: The pharmacy price is for erythromycin 800mg BD 7 days, taken from table3.1.1

Client co-payment status.	Maximum patient co-payment.	Pharmacy price of medicine.	Patient prescription copayment due	Prescription Subsidy) **Cost to HFA**
Exempt charges	$0.00	$11.52	$0.00	**$11.52**
Card-holder	$3.00	$11.52	$3.00	**$8.52**
Child, no card	$10.00	$11.52	$10.00	**$1.52**
Adult, no card	$15.00	$11.52	$11.52	**$0.00**

Azithromycin is registered but not subsidised for prescription in New Zealand. As shown in table 3.1.1, the only cost of an azithromycin prescription to the HFA is the dispensing fee. If prescribed to a woman or contact, there is no cost to HFA after co-payments regardless of community services cardholder status, unless the patient is exempt from co-payments. In this case, depending on cardholder status, the cost to HFA will be either $0.93 or $2.93 per prescription for azithromycin.

It is apparent from these considerations that the mix of cardholders, non-cardholders and exempt persons in a General Practice in New Zealand will influence the cost of prescriptions

to the HFA. The importance of co-payments to cost comparisons in New Zealand has been demonstrated recently (Bishop and Maling 1997).

Co-payments from the adult cardholders have been deducted from the retail pharmacist price. For simplicity all cardholders are assumed to be paying co-payments at adult rates. The influence of reduced co-payments on prescriptions for children and exempt clients is not included in the model.

3.1.3 General Medical Services subsidies.

The full cost of a General Practitioner consultation is borne by the patient in New Zealand unless that patient holds a Community Services Card, a High User Card, or is a child (under 18 years of age). The General Practitioner claims a General Medical Services (GMS) subsidy from Health Benefits Limited for each consultation on behalf of these patients. This is a fixed subsidy paid by Health Benefits Ltd to General Practitioners for medical consultation by eligible patients, shown in table 3.1.4.

Table 3.1.4. New Zealand General Medical Subsidies, 1997.

Age of person	Community cardholder	High User cardholder	Non cardholder.
Adult	$15.00	$15.00	$0.00
Child 6-18 years	$20.00	$20.00	$15.00
Child under 6 years	$32.50	$32.50	$32.50

As with pharmaceutical costs, the cost of consultations to the HFA will vary with the proportion of the population eligible for GMS subsidy. For simplicity all cardholders are assumed to be eligible for the adult GMS subsidy rate. Women under eighteen years of age who are cardholders attract a higher GMS subsidy. When a significant proportion of treated women are in this age group, the consultation costs will increase up to 33% over those included in the Chlamydia model.

3.1.4 Cardholder profiles of practices.

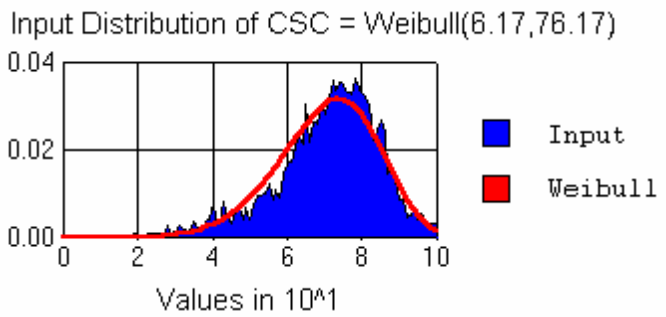
The percentage of community cardholders amongst patients in each practice varies from doctor to doctor. The percentage of cardholders amongst those receiving any prescriptions from General Practitioners has been used as a proxy measure of this variable. The national data for proportion of community cardholders among those receiving prescriptions from General Practitioners was obtained from a General Practice prescribing data warehouse held by the National Preferred Medicines Centre. The proportion of cardholders varies across the country from a minimum of 12% up to 100%. It is heavily skewed toward the higher end of this range. The raw data best fits a Weibull distribution, as shown in figure 3.1.1. This distribution was included in the Monte Carlo analysis at the probability node representing proportion of women or partners with Community Services Cards. This information facilitated the sensitivity analysis on influence of the proportion of Community Cardholders on treatment costs.

Figure3.1.1 Distribution of community cardholders among patients receiving General Practitioner prescriptions.

Key: CSC=community card holders

X is the percentage of community cardholders in any General Practice (0-100%).

Y is the probability that any practice will contain the percentage of cardholding patients (0-.4).



3.1.5. Laboratory subsidies.

When a General Practitioner requests a laboratory test, the community laboratories claim payment from Health Benefits Ltd Christchurch according to a schedule of payments. The

community laboratory price for chlamydia tests is compared with the inter-hospital charging schedule in table 3.1.5. Hospital prices differ from community laboratory prices as they are ex-GST, reflect economies of scale, and in some instances are specially negotiated. This is the case with the hospital price for chlamydia LCR that was especially negotiated to be competitive with community suppliers (H Andrews, personal communication).
Health Benefits LTD schedule prices for reimbursement of community laboratories have been used in this analysis, assuming that practices use community laboratories rather than hospital laboratories for chlamydia testing.

Table 3.1.5 Laboratory prices, Chlamydia testing, 1997.
Key: Elisa= enzyme linked immunoassay, MIF= micro-immunofluorescence, LCR= ligase chain reaction.

Test type.	Community Laboratory	Hospital laboratory
Elisa	$10.25	$9.11
MIF	$9.20	$8.18
LCR	$19.56	$9.11

The Chlamydia model includes the costs of tests for diagnosis of the women, but not for diagnosis of the partners. An assumption is made that the partners who are identified by contact tracing will be assessed and treated on epidemiological grounds. Two different test strategies are compared. When the Elisa test is used for diagnosis, a second test is required to confirm presence of infection in the specimens with positive test results. Bayes theorum is used to calculate the number of true and false positive tests that will require the additional cost of confirmatory testing. The alternative test strategy is the use of LCR, which have recently become available to General Practitioners through community laboratories, and do not require confirmation on positive results.
In the scenarios that apply a test for cure, the cost for both the index case and the case contact is included. The test for cure does not require confirmation, as only one highly specific test is needed to reliably establish absence of infection.
Therefore, the cost of laboratory tests will vary according to the strategy for testing and policy to test for cure. These options are tested in different scenarios.

3.1.5 Practice Nurse subsidies.

These subsidies are paid to General Practitioners as partial reimbursement for the wages of a registered nurse employed as a practice nurse. The contribution of practice nurses to the General Practitioner management of sexually transmitted diseases in New Zealand has not been well defined. Possible nursing roles in Chlamydia infection are patient recalls, asymptomatic screening, notification of results, delivery of medication, reinforcement of instructions, enforcing compliance, case contacting and testing for cure. Utilisation of nurses for these purposes varies from practice to practice. Attributable nursing time is quite unpredictable, depending on the number of cases that requiring nursing input. A time and motion study would provide this information, as for other practice nurse functions in New Zealand (D McLeod et al 1998).

Consultations by a practice nurse are not eligible for General Medical Services Subsidies. The Practice Nurse subsidy is $11.00 an hour, up to 30 hours a week, toward the salary of a full-time practice nurse. Subsidised practice nurse time is not included in this analysis because the amount of nursing time dedicated to management of each case of Chlamydia infection could not be determined.

3.2. Costs of complications.

3.2.1. Cost of specialised care.

Many of the complications of Genital chlamydia require specialist management. Practitioner variability manifests in the management of complications as it does in management of uncomplicated infection. Accepted practices of management of some of the complications may vary with location throughout New Zealand and between individual specialists in any given location.

Local costs for management of complications have been used where they are known. Where local costs are not known, a plausible range of costs has been derived from consideration of data from other locations. Sensitivity to the range of costs is tested by the Monte Carlo method (see section 2.5.2).

Disease related group unit funding formulae (DRG) are now used as indicators of costs in public hospitals in New Zealand. The hospital department derives the funding formulae from consensus opinion on accepted current practice.

The DRG price has been used for cost of complications in the Chlamydia model, where applicable. This approach reflects the cost from the perspective of the Health Funding Authority. An alternative would be to cost the management of complications by specialists

in private practice and private hospitals, but there is no cost to the Health Funding Authority when patients and/or insurers fund private care.

By definition, the DRG price includes all events in the episode of care between admission and discharge from hospital. The cost of ongoing community care, usually provided by the General Practitioner, is not included. This approach therefore underestimates the total cost to the Health Funding Authority.

3.2.2. Obstetric sequelae of Chlamydia trachomatis.

Obstetric complications include threatened and actual miscarriage, ectopic pregnancy, premature delivery, and infertility. As the costs of threatened and complete miscarriages due to Chlamydia are not generally included in analyses, only the latter three are included in this analysis. The costs of management of the selected obstetric gynaecological and neonatal sequelae have been derived from DRG prices. The 1997 prices, obtained from the local Crown Health Enterprise, are included in table 3.2.6.

Ectopic pregnancy is a surgical emergency managed at a hospital. A fixed DRG cost applies. This does not include any post-discharge care (A. Marshall, personal communication). Methods of investigation and treatment of ectopic pregnancy are in evolution (P Stone, personal communication). Conservation of the fallopian tube by medical management with methotrexate and subsequent monitoring of human chorionic gonadotrophin levels promises efficiencies (Gracykowski and Mishell1997 et al, Hajenius1997). These procedures will become outpatient services, costing no more than two outpatient visits, an ultrasound, two or three blood tests and a single oral abortifacient. The cost of this procedure has not been included, as it is not local standard practice.

These conservative approaches to ectopic pregnancies may reduce cost of management of miscarriages and ectopic pregnancies in future and future costs of tubal infertility may be reduced (Crenein et al 1997). Hence the mathematical modelling of medical progress becomes a difficult task.

The management of infertility has been the subject of recent cost-effectiveness analysis in New Zealand (Gillet, et al 1993). The 1993 cost of current practice per live birth has been inflation adjusted to 1997 dollars in the Chlamydia analysis. Costs of management of infertility could increase significantly if the decision is made to fund expanded services in New Zealand (Gillett and Peek 1996).

3.2.3. Gynaecological sequelae of Chlamydia trachomatis

Gynaecological complications include menstrual disorders, cervicitis, acute pelvic inflammatory disease: endometritis, salpingitis, tubo-ovarian abscess and chronic pelvic pain. A wide price range is to be expected for the management of these disparate clinical problems. Following the example of previous analyses, acute pelvic inflammatory conditions are lumped together for costing as a single item, and menstrual disorders, considered personal costs, are not included in this model.

The majority of cases of acute chlamydia pelvic inflammatory disease are treated as an outpatient (Washington 1991). The proportion of acute cases of Chlamydia pelvic inflammatory disease that will require in-patient management is unknown but is considered to be very small in New Zealand (consensus opinion). For this reason, only the outpatient cost for acute pelvic inflammatory disease has been used in this analysis. Outpatient cost is taken as the cost of referral to the local Gynaecology clinic or Sexual Health Clinic. Initial and follow-up consultations, microbiological investigation and treatment are similar cost at both clinics, priced at $193.35 in 1997.

Pelvic pain requires a variable amount of clinical investigation, depending on clinical presentation: acute or chronic, local or referred pain site, presence or absence of associated indicative symptoms. If General Practitioners recognise the pain as gynaecological they are likely to refer to a specialist service. Private Gynaecology specialist referral is of least cost to the Health Funding Authority, for laboratory and radiology subsidies only as GMS does not apply, and co-payments minimise the burden of prescription costs for high-income clients. The cost to the Health Funding Authority of management at the local gynaecological of Sexual Health Clinic is a fixed fee inclusive of microbiological tests and drugs used. The DRG unit cost of Gynaecology outpatient initial and follow-up consultations, microbiological investigation and treatment is similar to the Sexual Health Clinic fee priced at $193.35 in 1997. Should the pain not be initially recognised as gynaecological, any additional prescription, radiology, other investigations, or referral by the general practitioner will inflate this cost. Intensive investigation of pelvic pain by a hospital Gynaecology Department, for initial and follow-up consultation for pelvic symptoms including ultrasound, relevant laboratory tests and laparoscopy has a local DRG unit price of $1,390 in 1997 which is independent of Community Card status. Intractable symptoms with multiple hospital specialist consultations, protracted investigation, invasive procedures and prolonged pharmacological treatment will escalate costs beyond this. The cost for acute inflammatory

disease management has been randomised between these extremes in recognition of the wide plausible range. The price ranges used in this analysis are shown in table 3.2.6.

3.2.4 Male partner complications.

The cost of treating males infected by untreated or partly treated women will vary with the nature of the presentation. Only symptomatic male infections come to medical attention. The clinical presentations of Reiters Syndrome, non-specific urethritis, epididymitis and prostatitis in the male partner can be acute, chronic or relapsing. An acute symptom complex might result in urgent hospital or specialist referral. Chronic symptoms may be investigated and managed either in primary care or by a specialist. A wide range in cost of managing these complications is to be expected. A referral to a private Urologist will generate subsidy costs for any laboratory or radiology investigations and prescription subsidies where applicable. Costs are unpredictable and costing of Urologist referral has not been attempted. A general practitioner consultation, and/or chlamydia test and/or treatment will cost the health funder between $18.18 and $66.42 depending on services given and the patient's community card status.

Referral to the local Sexual Health Service for tests, treatment and a follow-up consultation is charged at $193.35 regardless of card status because this service has a fixed DRG outpatient funding formula. Radiology or hospital specialist referral will add to this cost.

The management of intractable or chronic arthritis or testicular or prostrate pain may trigger referrals to multiple hospital departments for specialist opinion, radiological investigations, biopsies, exploratory surgery, and prolonged antibiotic or anti-inflammatory treatment. The upper cost for chronic or intractable symptoms was set at $1,400 for this analysis (comparable to the maximum gynaecological cost). This could be exceeded in individual circumstances.

The uncertainty and variability of costs of management of male complications has been accommodated by randomising the cost of male complications. As shown in table 3.2.6, the range of costs lies between the minimum of $18.18 and maximum $1,400 with the mid range cost estimated to be $193.35 per person. Since there is little data on severity and management requirements of male complications, and the weighting of costs is unpredictable, a simple triangular distribution of costs about the mid range has been applied to the model.

3.2.5. Neonatal complications.

The costs of neonatal intensive care for prematurity are also included in table 3.2.6. Local costs for neonatal intensive care vary with infant's birth weight, presence or absence of complicating co-morbidity, and hospital providing intensive care. Randomisation was necessary because of the wide range of costs for an affected neonate.

An infected full-term infant with conjunctivitis will usually present after discharge from the birthing unit, and the care will be sought from the GP.

Conjunctivitis managed by the General Practitioner will generate at least two GMS claims (for infant consultation and follow-up) a diagnostic eye swab for chlamydia and/or other pathogens and a prescription. Prescriber variability is expected as this is not a condition frequently encountered by GPs. The prescription cost to health funder will vary with prescription given, community card status, and co-payment. The percentage of cardholders or exempt families is unpredictable for the very small number involved. Systemic erythromycin in a weight-adjusted daily dose is preferred to topical eye treatment, which will not eradicate systemic infection nor prevent progression to pneumonia (Ratelle et al 1997). The total cost of community management will amount to at least $88.00 per case.

Neonatal pneumonia requires in-hospital care, the cost varying with severity, co-morbidity and care setting (either neonatal intensive care or paediatric ward). A full term infant will develop pneumonia in the community at 2-12 weeks of age (Hess 1993) and be admitted to a paediatric ward where the cost structure differs from that in a neonatal intensive care unit. Management costs for a premature infant still in a neonatal intensive care unit at onset of pneumonia is included in cost estimates for neonatal intensive care. The overall cost has therefore been estimated to lie at the lower end of the DRG unit cost range for neonatal intensive care, at $2,433.20 to $4407.20.

Table 3.2.6. Chlamydia trachomatis obstetric, gynaecological, neonatal and partner complication costs.

Local DRG prices for management of Chlamydia complications are given in 1997 NZ dollars unless stated.

Complication	Service (explanation)	DRG price, $NZ
Acute pelvic inflammatory disease – outpatient care	Outpatient appointment, treatment and microbiological test	193.35
Acute pelvic inflammatory disease –inpatient care	Hospital admission (3days), investigation and non-surgical treatment	1,790
Chronic pelvic pain- outpatient care	Outpatient appointment, treatment and microbiological test	193.35 (less if referred to Private specialist, more if non-gynaecological tests done).
Chronic pelvic pain- inpatient investigation	Outpatient appointment, ultrasound, laparoscopy, laboratory tests.	1,390
Ectopic pregnancy	In-hospital care	2,777.24
Premature delivery	Management of preterm labour	633.43
Premature neonate	Neonatal intensive care (DRG varies for birth weight and complications)	2,433.12 - 8,473.72
Suspected Infertility	Preliminary investigations	567.13
Infertility treatment	Cost per live birth	4,377 in $NZ1993
Partner management	Minimum outpatient management	18.18 - 193.35
Partner management	Intensive investigation	1,400

3.3 Conclusion of Chapter 3.

In this chapter, the cost to the Health Funding Authority for services used in the analysis are priced. There is inconsistency in handling of goods and services tax (GST) by the Health Funding Authority, with services such as general medical services subsidies, laboratory schedules and pharmaceutical schedules inclusive of (GST), but DRG-based hospital services exclusive of GST. Because this analysis represents the perspective of the Health Funding Authority, the GST anomaly between pricing of community based and hospital based services has been maintained.

Where a wide price range exists, the analysis has randomised the cost between the plausible limits in a triangular distribution about the estimated mid-range value.

4. Methods: Valuation of probability estimates

4.0 Determination of probability estimates.

This analysis requires estimates for evidence that is not well documented in New Zealand. Evidence relating to some behavioural factors in the transmission and treatment of sexually transmitted disease is not available either locally or from overseas. Local data have been applied wherever possible. Best estimates from proxy sources have been used where necessary. Considerable emphasis has been given to the determination of the prevalence of genital Chlamydia infection in the New Zealand General Practice population. This is deemed necessary because other economic analyses on this topic have shown sensitivity to the prevalence of genital Chlamydia in the community under study (Magid et al 1996, Genc and Mardh 1996).

4.1 Prevalence of Chlamydia infection.

4.1.1 Significance of prevalence data.

Prevalence of the genital Chlamydia in the community has been shown to be the most important factor determining the cost-effectiveness of management. Previously published analyses on testing, treatment and case contacting for chlamydia infections have all been sensitive to the prevalence of infection in the community under study (Genc and Mardh 1996,Magid et al 1996, Howell et al 1997).

The prevalence of Chlamydia in New Zealand is unknown, so the level of reported Chlamydia infection is a proxy measure of true prevalence in New Zealand. Chlamydia caseloads underestimate true prevalence as they reflect only detected cases. Asymptomatic cases that are not detected go untreated and unreported. In addition, as reports in New Zealand are derived from Sexually Transmitted Disease Clinics, cases diagnosed by General Practitioners, Adolescent Health centres and Family Planning Clinics and Hospital Departments including Obstetrics and Gynaecology are not included.

4.1.2 Reported infection in Australia and New Zealand.

Published reported infection incidence in Australia and New Zealand are shown in table 4.1.1.

While reported figures seem comparable across the two countries there are pockets of high prevalence in both countries, which are not reflected in the cumulative data. A retrospective analysis of attendees at sexually transmitted diseases clinics demonstrated an association with self-reported Maori or Pacific Islands ethnicity (Connor et al 1997). The rate of confirmed infection among these clients appears to be increasing (ESR-Health 1998).

Table 4.1.1. Chlamydia incidence/prevalence in Australia and New Zealand

Key: I=incidence, P-prevalence, STD= sexually transmitted diseases, NZ=New Zealand.

Population Base or clinic type	Description of clients	Location In Australasia	Incidence/ Prevalence (I) or(P)	Test used	Reference
Sexual Health Clinic clients	Both sexes, all ages	Melbourne	3% (I)	Not specified	Pope and Smith 1997
Student Health Clinic clients	Females	Queensland	19.8% (P) 51/258	MIF	Dhupelia and King 1993
Prospective Birth Cohort Study	females 21yrs old sexually active	Dunedin	9% of 421 (P)	Self-report	Dickson et al 1996
STD Clinic clients	New attendees, both sexes	NZ-wide, accumulated years	5.4% (I)	various	Lyttle 1994
STD clinic clients	New female attendees	NZ-wide In 1992	6.9% of 11,804 (I)	various	Lyttle 1993
STD clinic clients	New female clients <15 years of age	NZ-wide in 1997	9.1% of 48 (I)	various	ESR:Health 1997
STD clinic clients	Female clients 15-19years	NZ-wide in 1997	11.6% of 1,240 (I)	various	ESR:Health 1997
STD clinic clients	All ages	Auckland & Christchurch 1991 &1992	11.7% of 8,478 (I)	Case review	Connor et al 1997

4.1.3 Prevalence studies from overseas.

The prevalence of infection in the United Kingdom, derived from screening programmes in a variety of women's clinics are included in appendix table A1. The prevalence range in the United Kingdom (3.6% to 29%) seems similar in range to cases reported in Australia and New Zealand.

Chlamydia infections are ubiquitous, they occur in human populations throughout the world. Reported incidence and prevalence of infection in North America and European countries

are also similar in range (2.5% to 22.7%) to the Australia and New Zealand figures, as shown in appendix table A.2.

4.1.4 Chlamydia infections in General Practice.

Data on who chooses to go to General Practice for treatment of genital Chlamydia, and why, is not available. The services that diagnose and treat genital Chlamydia infections in New Zealand are hospital sexual health clinics, adolescent health, student health, family planning services, and obstetric, gynaecological and other specialist services as well as general practices. The disease surveillance unit of ESR-Health is currently conducting a survey of general practitioners and other services in order to obtain an estimate of the proportion of infections treated in primary care (S Bennett, ESR-Health, personal communication).
Incidence and prevalence data from General Practice in the United Kingdom is shown in appendix table A.3. Because data from diverse countries and diverse clinical settings reveal similar incidence and prevalence data, the prevalence range from this data from general practice in the United Kingdom (2% to 12%) is likely to be a close proxy for prevalence in General Practice in New Zealand.

4.1.5 Chlamydia infections in pregnancy.

Pregnant women attending antenatal clinics form captured populations who are amenable to study. By definition all have been sexually active. Chlamydia prevalence in pregnant women is of particular interest since many of the complications of chlamydia infection manifest as complications of pregnancy.
Appendix table A.4 demonstrates a range of infection prevalence between 3% and 12% in pregnant populations, identifying some sub-populations that are most at risk for infection in pregnancy.

4.1.6 Prevalence for this analysis.

For purposes of the current modelling Project, the estimated prevalence of Chlamydia infection in New Zealand was randomised to enable sensitivity analysis over the range of possible values. The prevalence of genital Chlamydia in women consulting New Zealand General Practitioners was deemed to lie somewhere between 2% and 18%, in a triangular probability distribution about a middle prevalence of 7% derived from consensus opinion in consideration of the available data.

4.2 Laboratory parameters.

4.2.1 Chlamydia tests used.

The use of screening tests that are expensive or technically demanding has been identified as a factor contributing to infection control failure in family practice (Majeroni 1994). The tests in use by local laboratories changed in early 1997, when laboratories stopped using Elisa as a screening test and micro-immunofluorescence as a confirmatory test. The ligase chain reaction test now replaces dual testing in Wellington. The ligase chain reaction is more expensive than either previous test alone. Although this saves confirmatory testing, the cost of screening for Chlamydia is increased in low prevalence populations.

The Chlamydia model has been designed to compare the performance of old and new testing scenarios: dual testing using a screening test with confirmatory test, compared with a single highly sensitive diagnostic test alone.

4.2.2. Test sensitivity and specificity.

Reference laboratories determine sensitivity and specificity by comparison of performance with an accepted gold standard. The apparent sensitivity and specificity of a test can vary with the chosen gold standard, which itself may not be 100% sensitive. Culture of the organism, the old gold standard, has been supplanted by an expanded gold standard. This is a bank of different tests including DNA-based technology to determine true positives and true negatives. As a result of the change, some re-evaluation of test sensitivity and specificity has occurred. Examples of the effect of the gold standard comparison test on apparent sensitivity and specificity of screening tests are given in table 4.2.1.

Some analyses have avoided the dilemma of interpreting reliability of tests by starting with a population with already-proven infection (Magid et al 1996). Some previous economic analyses on the subject of Chlamydia infection have included estimates of test specificity and sensitivity, these are tabulated for comparison in table 4.2.2. The values chosen for the current Chlamydia model is: EIA sensitivity 78% and specificity 97%, MIF sensitivity 85% and specificity 96%, LCR sensitivity 94% and specificity 100%. These are derived from consensus estimate after consideration of available data.

The test sensitivity and specificity is important to overall costs. In this analysis the criteria for offering treatment is a positive cervical swab. Use of tests with low specificity will result in treatments being offered to uninfected women, and reliance on tests of low specificity will cause some infected cases to be overlooked. When infections are missed on testing false negative cost consequences arise in future management of complications. Costs increase when unnecessary treatment is given to non-infected clients on the basis of false positive test results (Haase et al 1995). The costs of unnecessary treatment of women with false positive tests, and cost of complications that are expected in women with false negative tests are included in this model.

Table 4.2.1 Effect of gold standard on apparent test sensitivity and specificity.

Code: DFA= direct flourescent antigen, EIA= enzyme immunoassay, LCR=ligase chain reaction, MIF= microflourescence on antigen, PCR= polymerase chain reaction, DNA primers= amplification technique.

Test and gold standard	Sensitivity	Specificity	Reference
LCR vs DFA/PCR/LCR	86.2%	99.8%	Debatistta et al 1997
LCR vs MIF/DNA primers	87-98%	99.9%	Schachter et al 1994
LCR vsLCR/EIA+DFA	99%	95%	McCarthy et al 1997
Culture vs MIF/DNA primers	52-92%	99.9%	Schachter et al994
PCR vs DFA/PCR/LCR	99.6%	100%	Debatistta et al 1997
EIA vs culture	82.1%	99.3%	Brokenshire et al 1997
EIA vs culture/EIA/MIF	84.4%	100%	Brokenshire et al 1997
DFA vs DFA/PCR/LCR	72.4%	99.8%	Debatistta et al 1997
EIA + DFA vs LCR/EIA+DFA	94%	97%	McCarthy et al 1997

Table 4.2.2 Sensitivity and specificity from published analyses.

Code: EIA=enzyme immunoassay

Test modelled	Chosen sensitivity	Chosen specificity	Justification for choice	Reference
EIA	79	97	Best estimate	Humphreys et al 1992
Culture	50-90%	100%	Literature review	Genc and Mardh 1996
EIA	70-80%	99-100%	Literature review	Genc and Mardh 1996
EIA	80%	98%	Best estimate	Schiotz and Csango 1992

4.2.3 In-vitro organism susceptibility.

Several different serovars of Chlamydia can cause genital infections. Susceptibility to antibiotics differs both within and between the genital serovars D, E, F, G, J and K in-vitro. In a study of susceptibility to tetracycline, azithromycin and erythromycin, one genital

serovar of Chlamydia was consistently sensitive to all three antibiotics but other serovars showed some resistance, and individual isolates of different serovars displayed relative resistance (Welsh et al 1992).

Serovars have been proposed as phenotypic markers for clinical syndromes and antibacterial susceptibility, but this information is not available to the General Practitioner who is making a prescription decision. Chlamydia serovar typing and mean inhibitory concentrations are not routinely assessed prior to treatment of infection.

Microbial resistance does not appear to be clinically significant, perhaps because clinical factors such as compliance and tolerance have greater influence on clinical efficacy.

The extent of variability, in mean inhibitory concentration for doxycycline, tetracycline, erythromycin and azithromycin across four published scientific papers, is demonstrated in Table 4.2.3.

Table 4.2.3 In vitro sensitivities of genital Chlamydia serovars to common treatments.

Key: MIC =mean inhibitory concentration in g/ml.

Antibiotic tested	MIC range	Number of isolates tested	Reference
Doxycycline	0.0008-0.06	45	Rice et al 1995
Doxycycline	0.01-0.02	31	Ossewaarde 1992
Tetracycline	0.0625-1.0	11	Welsh et al 1992
Tetracycline	0.03-0.06	31	Ossewaarde 1992
Erythromycin	0.25-0.10	11	Welsh et al 1992
Erythromycin	0.06	unstated	Ridgway 1996
Azithromycin	0.125	unstated	Ridgway 1996
Azithromycin	0.125-0.5	11	Welsh et al 1992
Azithromycin	0.01-0.06	31	Ossewaarde 1992
Azithromycin	0.125-1.0	45	Rice et al 1995

Overall, Chlamydia trachomatis susceptibility in vitro is greater to doxycycline than to azithromycin or erythromycin. The estimates for sensitivity to the antibiotics used in the current Chlamydia model, derived from consensus opinion are: doxycycline 99%, erythromycin 90%, azithromycin 86%.

4.2.4. Spontaneous cure rate.

Spontaneous cure has been included in prior published analyses. Nettleman et al (1986) modelled a 10% spontaneous cure rate but did not explain the derivation nor supply supporting references. Sellors et al (1992) assumed 10% spontaneous cure rate and Genc and Mardh (1996) a rate between 5-10%. These spontaneous cure rates were based on papers

published in 1989 and 1990. The exact figure for spontaneous cure rate is unknown. Spontaneous cure is now considered to occur uncommonly, if at all. The following problems exist with the concept of spontaneous cure:

- The figures above reflected older and less specific testing technology and persistent infection should now be detectable with more sensitive testing (Workowski and Lampe 1993).
- Loss markers of lower genital tract infection do not imply cure, as chlamydia is an ascending infection.
- Irreversible structural inflammatory damage to fallopian tubes is believed to occur from hypersensitivity reaction to a heat-shock protein, independent of the duration of chlamydia infection. Even if the organism is eradicated, complete cure after infection may not be possible (Scholes 1996).

As a result, the above figures seem unduly optimistic.

The Chlamydia model assumes a consensus estimate of less than one percent of infections that cure spontaneously. The function is randomised between zero and one percent to test sensitivity to spontaneous cure.

4.2.5 Susceptibility of the organism – overview.

Microbiological effectiveness is only one factor in the clinical effectiveness of Chlamydia treatment. Since Chlamydia is an obligate intracellular organism, the tissue concentration and tissue half-life of antibiotics are important factors in therapeutic response (Lode et al 1996). The long serum half-life of azithromycin, high tissue penetration (Ballow and Amsden 1992) and high levels in cervical mucus (Worm and Osterlind 1995) after a single 1 Gm dose are thought to contribute to the efficacy of this regime.

The response of the infection to antibiotics seen in clinical practice is the synthesis of the microbiological factors of drug susceptibility and spontaneous cure rate modified by pharmacokinetic properties, prescribed treatment schedule, and clinical considerations of compliance, limiting side effects and re-exposure to infection. Clinical trials of antibiotic susceptibility report on overall clinical efficacy rate which results from all these factors. The Chlamydia model attempts to separate these factors to determine which factors most influence response.

4.3. Clinical efficacy factors.

4.3.1. Trials of clinical efficacy.

Clinical trials of treatment efficacy of genital chlamydia treatment in women are shown in appendix table B.1. The follow-up period and timing of testing for cure was not identical in these trials. For the purpose of inter-trial comparison, the timing of treatment end-point was chosen to include late treatment responders, reduce losses to follow-up and minimise the opportunity for re-infection. The quoted cure rate is the outcome two weeks after initiation of medication.

Despite differences in microbiological susceptibility, pharmacokinetics, treatment regime compliance and side effects, doxycycline and azithromycin appear to have similar clinical efficacy in the treatment of women with genital Chlamydia when compared at the two-week post-treatment endpoint.

4.3.2. Accounting for clinical efficacy.

Clinical efficacy has been handled in a variety ways in previous published cost-effectiveness analyses. These are shown in appendix table B.2. Some analyses have assumed an overall clinical efficacy rate (Nuovo et al 1995); others have separately modelled the influence of patient compliance and loss to follow-up (Haddix et al 1995), some model patients withdrawn from treatment due to intolerable side effects independently (Marrazzo et al 1997).

In the current chlamydia model, clinical efficacy is considered in a multi-factorial manner in order to determine which efficacy factors are of critical influence. Patient compliance and tolerance, loss to follow-up and short-term re-infection risks from untreated current partners are included as independent variables, distinct from the susceptibility of Chlamydia to the chosen anti-microbial agents and the spontaneous cure rate of the infection. Additional factors in short-term clinical efficacy have also been included. These are estimates of: the percentage of infected women who receive an adequate prescription at an appropriate prescription dose and duration (detailed in section 4.4) the percentage with partners, proportion of those partners given appropriate epidemiological treatment and their compliance (detailed in section 4.6).

The approach to clinical efficacy factors by the current model is more complex than that of other published analyses, as shown in appendix table B.2.

4.4. Prescription factors.

4.4.1. Treatments offered.

Two main treatment strategies are examined; with doxycycline 100mg BD or with azithromycin 1Gm stat. When pregnancy is known or suspected, tetracycline is contraindicated and erythromycin is the recommended substitute (CDC 1993). The proportion requiring a doxycycline substitute is included in the strategy. This consideration applies to sub-groups of women who are pregnant, trying to conceive and those not using effective contraception. The proportion of women who require an alternative to tetracycline is unknown but could be variable.

The effects of tetracycline alternatives have not been modelled in previous studies. The sensitivity of treatment cost to the use of doxycycline alternatives is therefore of interest. This function has been randomised to test sensitivity to between 5% and 50% of women receiving a doxycycline alternative. A skewed triangular probability function about a mid-range value of 15% is used. This approximates the known conception rate in New Zealand women aged twenty to twenty-four years (Midland Health 1997).

There are no teratogenicity concerns with macrolides. No alternative treatment for women who are or might be pregnant is required in the azithromycin treatment strategy (Australian Government Publishing Service, 1994).

Amoxicillin is an effective alternative to tetracyclines in animal models (Beale and Upshorn 1994). It has a well-documented safety profile in pregnancy, and is well tolerated by patients without penicillin allergy. The amoxicillin alternative has not been included in this Chlamydia model as it is not yet recommended practice in New Zealand.

4.4.2. Prescription adequacy.

Evidence for adequacy of prescription in General Practice is anecdotal in New Zealand. The figures used in this model have been determined by consensus estimate, considering available literature and local experience. Consensus opinion is that between 70% and 100% of General Practitioner prescriptions for doxycycline are at an appropriate dose for treatment of Chlamydia (with mid range value of 90% correct). Values have been randomised between these plausible limits in a triangular probability distribution about the mean. Since erythromycin is available in several dose formulations in New Zealand, some dose confusion

is predicted, and the correct dosage mid range value for this has been dropped to 85% of prescriptions. The percentage of prescriptions written for adequate duration to eradicate Chlamydia has been estimated at between 70% and 100%, for both erythromycin and doxycycline with a mid range value of 90%.
There is no literature on prescriber error with single dose azithromycin treatment. Consensus opinion is that prescription error would be eliminated with a single dose regime.

4.4.3. Treatment side effects

Side effects are considered because they incur additional costs for management or, if severe, they impede compliance with treatment. These aspects have been variously dealt with in past analyses. Magid et al (1996) priced the management of minor adverse reactions in 16% of clients on doxycycline and 13% on azithromycin, and major adverse reactions for 1% of patients on either antibiotic. Schiotz and Csango (1992) assumed yeast infections to occur in 15% of clients receiving antibiotics. Phillips et al (1989) assumed a rate of post antimicrobial vaginitis of 15%, and allowed additional cost for prescriptions for pelvic inflammatory disease. Marrazzo et al 1997 included an estimate for extra treatment costs for the 5% of patients considered likely to develop side effects on treatment. Genc and Mardh (1996) predicted that 10-25% of patients would be lost to follow-up and this included treatment withdrawals.

These analyses have adopted side effect profiles which seem high compared to local experience. Side effects with doxycycline are infrequent in New Zealand (consensus opinion), but there is no local experience with single dose azithromycin side effect profile. International experience of the side effect profile of single dose azithromycin is also limited. Hopkins (1991) reported side effects experienced by 3,995 patients. These took various azithromycin regimes for a medley of clinical conditions, only 806 received the single 1G stat dose regime. Hopkins does not comment on tolerance and side effect profile of this single dose regime.

The cost to the Health Funding Authority of any treatments for minor side effects such as diarrhoea or secondary thrush is expected to be quite low, as minor side effects are uncommon, and over-the-counter remedies are available for self medication in New Zealand.

Therefore costs of management of minor treatment side effects have not been included in this model.

Only those side effects resulting in withdrawal from treatment have been included. Women who suffer side effects that cause treatment withdrawal will incur additional costs for an effective alternative treatment. Local consensus opinion determined that between 0-20% of clients on doxycycline and between 20-55% on erythromycin will be subject to side effects that prevent completion of treatment. Few limiting side effects are expected with a single dose of azithromycin. In the absence of definitive data, the rate for side effects applicable to longer courses of azithromycin has been used in this analysis, between 0-20% with mid range value of 10% (Peters et al 1992).

4.4.4. Patient compliance with treatment.

Compliance is an unknown variable in the management of Chlamydia in New Zealand General Practice. The estimates of compliance for this model have been determined by local consensus after considering estimates from other recent analyses. It is assumed that the same compliance rates apply to both the index woman and her partner. The values used in this Chlamydia model are listed in table 4.4.1 for comparison with values from other recent analyses.

Table 4.4.1 Compliance estimates from recent economic analyses.

Analysis authorship	Compliance estimate on Azithromycin 1G stat	Compliance estimate on Doxycycline BD 7days
Haddix et al 1995	1.0	0.8
Magid et al 1996	1.0	0.857
Marrazzo et al 1997	Not applicable	0.7 to 1.0
Genc and Mardh 1996	1.0	0.5 to 1.0 randomised
Wellington Chlamydia model 1998	1.0	0.5 to 0.85 randomised

4.4.5. Re-treatment rates.

Local consensus estimates are that between 0-33% of women who need re-treatment will be successfully retreated. This probability has been randomised in the model using a consensus mid-range estimate of 20%. It reflects the non-detection of primary non-compliance, any repeat prescriptions of inappropriate dose or duration, and inadequate compliance with repeat prescriptions.

It is predicted that re-treatment of partners will be less complete than re-treatment of the index cases. This analysis estimates that between 0-20% of partners needing re-treatment, with a mid range estimate of 10%, will be successfully re-treated. This is because health services follow-up second-generation cases and partners with less rigour than the index cases, and partner compliance with re-treatment is predicted to be lower than for the index women.

Where re-treatment is required, it is assumed that for women on doxycycline this will be due to non-compliance with a 7-day course. If so, women and partners on doxycycline will require an identical re-treatment course (further doxycycline or erythromycin). This is a simplification which does not apply to erythromycin intolerance in women for whom doxycycline is contraindicated. Amoxicillin is an option in this instance but has not been priced (see section 4.4.1).

Those who need re-treatment on directly observed azithromycin will have failed through intolerance of azithromycin, as compliance is ensured. For these patients doxycycline, or erythromycin where contraindicated, is the appropriate re-treatment.

4.5. Complication rates.

4.5.1 Complications for index women.

Handling of probability of pelvic inflammatory disease has differed in prior analyses. As table 4.5.1 shows, some analyses have assumed a single probability for both acute and chronic pelvic inflammation. Women with acute presentations are a subset of women with pelvic inflammatory disease, the remainder have sub-clinical disease until development of complications. In this analysis, acute pelvic inflammatory disease presentations are considered separately from sequelae of chronic pelvic inflammation (infertility, ectopic pregnancy and chronic pelvic pain). Since these complications are features of the natural history of the infection, they are assumed to occur in New Zealand at similar rates to other parts of the world. The probabilities applied in this analysis have been derived from overseas data.

The different probability estimates for pelvic inflammatory complications in previous economic analyses reflect the uncertainty of clinical data in this respect. The probabilities used in recent published cost-effectiveness analyses are listed in table 4.5.1.

Table 4.5.1 Probabilities for female Chlamydia complications from recent analyses.

Publication Source	PID	Acute PID	Infertility	Ectopic pregnancy	Chronic pelvic pain
Nettleman et al 1986	0.10-0.30	Included in above	0.21	0.04	Not given
Sellors et al 1992	0.03-0.11	Not given	0.15	0.055	Not given
Schiotz and Csango 1992	0.20	Not given	0.20	0.025	Not given
Haddix et al 1995	0.20	0.14	0.20	0.06	0.18
Nuovo et al 1995	0.10-0.50 (likely 0.25)	Not given	Not given	Not given	Not given
Scholes et al 1996	Not given	Not given	0.20	0.09	0.18
Magid et al 1996	Not given	0.15	0.17	0.08	0.12
Howell et al 1997	0.20	0.14	0.20	0.06	0.18
Marrazzo et al 1997	0.15-0.40	0.4 of total PID	0.10-0.30	0.05-0.10	0.15-0.20

In the current analysis the probabilities of pelvic inflammatory disease and infertility have been randomised between plausible limits to reflect the extent of uncertainty in their interpretation. The Monte Carlo modelling method is ideally suited to the determination of probabilities in an example such as this, where exact figures are unknown and use of proxy data which may not be a close approximate is necessary. Probabilities for ectopic pregnancy and pelvic pain have not been randomised as data on likely range is scarce.
The rates chosen for use in the current model are presented in table 4.5.2.

Table 4.5.2. Estimates for incidence of complications applied in Chlamydia model

Female Chlamydia Complication	Estimated range (& mid range)
Pelvic inflammatory disease	7-25% , (15%)
Acute PID	1-15%, (7%)
Infertility	15-21% (17%)
Ectopic Pregnancy	8%
Chronic pelvic pain	12%

4.5.2. Neonatal complications

The rate at which women infected with Chlamydia will become pregnant is not readily predictable. The risk of future pregnancy and perinatal complications from Chlamydia infections cannot be readily estimated. The consequences of infection itself can affect future fertility, but also the timing of treatment and safe sex education programmes delivered with treatment could impact on subsequent pregnancy rates. The proxy data are national annual birth rates. Extrapolation from age-specific annual live birth rates may be unreliable since the Chlamydia infection itself will reduce live birth rates through complications of infertility,

miscarriage and ectopic pregnancy. The infertility risk increases with repeated Chlamydia infections, but will become clinically apparent only for those wishing to conceive.

An estimate of the probability of future pregnancies is required for the analysis in order to calculate probability and cost for premature deliveries, neonatal conjunctivitis and pneumonia. The rate of known conceptions (miscarriages and abortions as well as deliveries) in New Zealand women less than twenty years of age, is almost twice the annual live birth rate (Midland Health,1996). National statistics show variation of annual live birth rate in New Zealand rate from year to year, region to region and across age and ethnic groups (Ministry of Health 1997b). A plausible range and mean for the annual birth rate has been derived by consensus opinion from the available data for the purposes of this analysis. This function has been randomised between 1% and 6% about a mean of 3% per annum.

Neonatal complications are infrequent events. Not all infants exposed to infection will develop complications. Premature labour is associated with Chlamydia infection, but the rate attributable to chlamydia is uncertain (Djukic et al 1996). Aberrations of immunity in new-borns to mothers with genitourinary chlamydia (Pirogova et al 1995) and persistence of the organism into childhood raise questions about true neonatal incidence. The number of babies affected by maternal chlamydia might be under-reported.
Not all exposed infants will develop conjunctivitis or pneumonia. Bell et al (1992) documented IgM Chlamydia antibodies in 57% of exposed infants but although Chlamydia was cultured from the tears of 86% of these, only 32% of them had positive cultures from conjunctiva. Topical ocular prophylaxis at birth has been used to reduce conjunctivitis cases in high prevalence areas but it does not prevent treated infants from subsequently developing pneumonia. The available overseas evidence indicates that somewhere between 18% and 50% of exposed infants will develop conjunctivitis and between 11% and 20% will develop pneumonia. (Ratelle and Keno 1997).

The natural history of sequelae for infants exposed to Chlamydia trachomatis is predicted to be similar in New Zealand to that overseas. Infant complication rates available from the international literature have therefore been applied to this analysis. The probabilities of development of neonatal complications are compared from two recent economic evaluations that have considered neonatal complications, and those used in the Wellington chlamydia model, in table 4.5.3. Although neonatal intensive care of premature infants and

management of neonatal pneumonia are the costly services, all the neonatal complications have been considered in this analysis.

Table 4.5.3. Neonatal complication rates

Economic evaluation. authorship	Applied neonatal pneumonia rate	Applied neonatal conjunctivitis rate	Premature delivery rate
Magid et al 1996	0.03-0.16	0.15-0.25	unstated
Marrazzo et al 1977	0.15	0.35	unstated
Wellington Model 1998	0.1	0.17	0.12

4.5.3. Male partner complications.

There is no well-developed evidence base for the rates of male complications after Chlamydia infection. Since male infection is often initially asymptomatic, the prevalence of undetected male infection is not well established and incidence of male complications is not known. The proportion of recurrent urethritis, epididymitis, prostatitis, Reiters syndrome, and infertility that can be attributed to Chlamydia infection is therefore uncertain. As for ascending female Chlamydia infections, aetiological evidence is difficult to obtain. When microbiological evidence is available, the presence of mixed pathogens complicates interpretation 9holmes et al 1990).

As male complications feature infrequently in clinical studies and economic models, there are few information sources to turn to for rates of male complications with a high level of evidence. Best estimates from literature and consensus expert opinions have been used to provide information on complication rates from Chlamydia infection in males. The result is that mixtures of different probabilities for various combinations of male complications have been modelled to date. Marrazzo et al (1997) estimated that 40% of infected men would be treated for symptomatic urethritis and 1% would develop epididymitis. Magid et al (1996) estimated that between 35% and 65% of infected male partners would develop symptomatic urethritis and 2% epididymitis.

The preferred approach in the Wellington Chlamydia Model would have included probabilities and costs for each of the male complications individually. However, because the evidence base in this area was not good, an alternative approach has been taken. Taking the approach used by Genc and Mardh (1996), the Wellington model applies an overall

aggregate rate for probable symptoms in untreated males. This rate represents symptomatic cases of acute and recurrent urethritis, prostatitis or epididymitis and Reiters syndrome. Infertility is not included because it is a problem shared by a couple. Infertility is accounted for only once in this analysis, as a female complication (see section 4.5.1).

The time frame for development of a clinical presentation after infection is unknown. Chronic male infection becomes symptomatic over an unpredictable and extended time frame. As for female disease complications, time discounting would apply if the time frame were known more precisely (see section 2.6.1). The aggregated male complication rate represents the probability that the male complications in the first year after infection by an index case. Infertility is not included, as the clinical presentation is usually considerably delayed beyond one year post-infection.

The rate for development of male complications has been randomised from the consensus estimate of between 0% and 20% in the year post-infection. The estimated mid range value for detection of male complications is 6%. This function randomised has been to allow for clinical uncertainty. Randomisation from a plausible range also softens the impact of time discounting considerations.

4.6 Partner factors.

4.6.1. Partner transmission of Chlamydia.

Mathematical theorums have been developed to describe the spread of infectious disease epidemics (Stigum et al 1994, Hoppensteadt and Peskin 1991, Katz 1992, Brunham 1997). For an infectious disease to spread there must be at least one new person infected, to perpetuate the infection, from each index case.
It has been impractical to include theorums of disease spread in this Chlamydia model. They would have added a significant sub-analysis to the programme. For simplicity, some assumptions have been made on partner transmission factors.

4.6.2. Probability of current relationship.

Precise information on this aspect of human behaviour is not available specifically for New Zealand. The New Zealand census marital status figures could be proxy data for the proportion of women in a current relationship. These have not been used as the census

identifies women who are currently married or in a de facto relationship, but does not identify single women who have a current sexual partner.

The Swedish Health Study revealed that 85% of sexually active women age 15-48 years have a current steady male partner (Genc and Mardh 1996). The age group of participants in the Swedish Health Study was wide, including married women and others in long term relationships. In the Wellington Chlamydia Model women of a younger age group (under twenty-five years) is of interest. A cohort study of adolescents in New Zealand (Dickson et al 1996) revealed 92% to be sexually experienced by the age of 21 years, but the proportion of those who were in a current relationship was not determined. For the Wellington Chlamydia Model a wide plausible range is applied for women in a current relationship, but the mean probability considered appropriate is lower than in either of these two studies (consensus opinion). The Monte Carlo function has been used to randomise the proportion in a current relationship at between 0 and 100% in a triangular probability function about a mean of 50%.

4.6.3. Number of partners infected.

An estimate of the number of partners who are infected is required in order to determine the cost of management of consequential male infections. The number of partners for each woman is an individual behavioural characteristic, which can be quite variable. Magid et al (1996) estimated that between 0.75 and 1.25 males would be newly infected from each woman with untreated chlamydia. Howell et al (1997) modelled the economies of contact tracing between one and ten named partners for every index woman. Men with chlamydia at a Nottingham genitourinary clinic had an average of 1.67 partners within the past 3 months (Carlin and Barton 1996).

Core group theory requires an infected person to average four partners per year to sustain a Chlamydia epidemic (Brunham 1997).

A one-year time frame is considered appropriate to include concurrent relationships and close consecutive relationships (consensus opinion). This carries an implicit assumption that a woman will cease to be infectious after one year. The one-year time frame for partner infections is consistent with the discounting assumption (see section 2.6.3).

The current model applies an estimate of between zero and six male partners per woman per year, within a skewed triangular distribution about an average of one partner for each woman

(consensus opinion). The function has been randomised to accommodate the uncertainty and to assess the sensitivity to the rate of change of partners.

4.6.4 Partner transmission and treatment.

Not all the partners of infected women will become infected on exposure. In the scenarios of this analysis, treatment is offered to current partners without prior testing. Presumptive treatment of partners differs from the approach taken by other analyses. Magid (1996) and Nuovo (1995) included the prescription cost for women, but not their partners. The paper of Genc (1996) addressed the issue of screening asymptomatic women only. Howell et al (1997) estimated a 27% chance of female re-infection if the partner is not also treated.

Presumptive treatment assumes that all partners will carry the infection. This assumption may not hold true for all casual partners. The probability of re-infection of the treated index cases, and the costs of male complications are calculated only from the proportion of male partners who have the infection (those untreated and inadequately treated). The probability of transmission of infection from infected males to treated females and the prevalence of infection in the male partners (after any spontaneous cure) are required for this calculation. Infections in subsequent male partners of women who are either not treated or inadequately treated are considered in this analysis. The probability of transmission from infected females to male partners and the probability of spontaneous cure in infected women are required to calculate this second-generation infection risk.

The probability of transmission of Chlamydia is poorly defined. As many as 45-80% of female partners of infected males become infected (Holmes et al 1990). Transmission rates to discordant partners, based on average coital frequency, are higher for infected males to uninfected females than vice versa. A single or infrequent contact with the infectious case would reduce the partner transmission rate. Cates and Wasserheit (1991) found male to female transmission rates to be 40%, and female to male transmission rates to be 32%. Cofactors to infection increase the transmission rate. In the presence of co-factors such as coexisting infections, or pregnancy the female to male transmission rate is 10% higher (Alary et al 1994).

Genc and Mardh (1996) estimated that 50-70% of the male partners of index females would become infected, incorporating this rate in their Monte Carlo analysis.
For the current model, a fixed local consensus rate of 60% male to female transmission and 45% female to male transmission has been applied.

4.6.5. Partner tracing.

Partner tracing is a key activity in the containment of Chlamydia infection and has itself been the subject of an economic analysis (Howell et al 1997). In that analysis, the contacts of infected index cases were subjected to testing prior to treatment. Between 35% and 75% of named male partners were assumed to present for testing then tested positive, and between 67% and 97% of these were assumed to receive treatment. In a study of infected males, (Carlin and Barton 1996) up to 71.8% of all contacts were traced, and between 36.8% and 66.7% of the partners in heterosexual relationships were traced.
In this model, the probabilities for partner tracing and treatment have been based on local consensus opinion after evaluation of literature. These are shown in table 4.6.1.

Table 4.6.1 Partner tracing factors (consensus values).

Partner tracing factors	Estimated Range	Estimated mid range
Partner contact tracing rate	25-88%	60%
Percentage of partners for epidemiological treated	30-80%	65%

The rates for compliance, tolerance and side effects of medication among partners in this model are assumed to be the same as for the female index clients (see section 4.1).

4.7 Conclusion of Chapter 4.

In this chapter the probability estimates for the analysis have been detailed and the rationale for selection of values has been outlined. A paucity of local data has necessitated the use of overseas data where available. Prior analyses on the economics of Chlamydia infection have handled probability estimates in quite diverse ways. Use of the Monte Carlo method in this analysis has enabled uncertainty to be accommodated by randomisation of many probability variables.

5. Results

5.0 Overview of presentation of results.

This chapter includes the results of generated variable inputs to the model, the results of simulated outputs, the sensitivity of the outputs to the inputs, and the results of a break-even analysis, and decision analysis.

Section 5.1 summarises the variable inputs that have been generated by Monte Carlo simulation for use in the model.

Section 5.2 contains the results of effectiveness of treatment.

Section 5.3 documents cost-of-treatment outputs.

Section 5.4 presents the treatment cost-effectiveness outputs.

Section 5.5 gives measures of sensitivity to inputs of the model.

Section 5.6 discusses break-even analysis.

Section 5.7 is the decision analysis on the General Practitioner management plan.

In sections 5.2 to 5.4, the simulated results are presented in pairs for ease of comparison across similar scenarios. Each scenario of the pair differs only in treatment strategy. Scenarios 1-3 model a variation on General Practitioner management of Chlamydia (section 2.4). Scenarios 1d, 2d, and 3d model the prescription of doxycycline (or erythromycin where contraindicated) for the treatment of genital Chlamydia in women. Scenarios 1a, 2a, and 3a model the prescription of azithromycin under similar conditions of General Practitioner management.

Simulation results in this chapter are presented in summarised form. There are two thousand Monte Carlo iterations of each treatment option for each scenario. The individual iteration results have not been included. In this chapter cumulated simulation outputs are presented, with the mean, 95% confidence interval and/or standard deviation given for the resulting probability distribution function.

5.1 Variable input generation.

This section contains the simulation results on variable inputs. The selection of variable inputs and the use of randomisation to determine them are detailed in sections 2.7.1 to 2.7.3.

5.1.1 Variable inputs common to all scenarios.

The subjects in this Monte Carlo simulation are 100,000 hypothetical women in the care of their General Practitioner in New Zealand. These are sexually active women, aged less than twenty-five years, who are at risk of genital Chlamydia infection. The generated variables listed below are used in each scenario. These variables have been generated by the Monte Carlo method from best estimate values discussed in previous chapters. The appropriate data sections are indicated in brackets.

- Socio-economic status reflected by Community Cardholder status (section 3.1.4).
- Prevalence of genital Chlamydia infection (section 4.1).
- Proportion of women with unrecognised risk of infection (section 4.1).
- Proportion of above women who were subsequently tested for infection (section 4.2.1).
- Proportion of prescriptions of adequate duration for the purpose of successfully treating chlamydia (section 4.4.2).
- Proportion of women with current sexual partner (section 4.6).
- Number of partners per woman per annum (section 4.6).
- Proportion of partners who will be traced (section 4.6).
- Proportion of traced partners who will be offered treatment (section 4.6).
- Compliance of both index women and traced partners (section 4.4.4).
- Proportion of women adequately re-treated when needed (section 4.4.5).
- Proportion of partners adequately re-treated when needed (section 4.4.5).
- Spontaneous cure rate (section 4.2.4).

The simulated mean and 95% confidence intervals generated for these variable inputs are in table 5.1.1.

Table 5.1.1 Input data common to all scenarios

Variable	**Simulated mean**	**95% confidence interval**
Prevalence of Chlamydia infection	9%	4.0%-15.0%
Percentage of infections unrecognised	41.6%	13.6%-65.3%
Percent of women at risk who are tested	76.6%	58.6%-92.9%
Spontaneous cure rate	0.003%	0.0007%-0.007%
Proportion of community cardholders	70.7%	46.9%-90.9%
% Prescription of appropriate duration	86.6%	75.4%-96.1%
Proportion of women with current partner	49.9%	15.7%-84.1%
Average annual new partners per woman	2.3	0.5-4.7
Proportion of partners traced	57.6%	35.4%-75.5%
Proportion of traced partners treated	58.3%	37.3%-73.8%
Proportion of women re-treated	17.6%	5.7%-28.4%
Proportion of partners retreated	10%	0.03%-16.8%

5.1.2 Variable inputs for specific treatment regimes

The following variables are used in either the doxycycline/erythromycin or the azithromycin models:

- Proportion of women to whom doxycycline can be prescribed (section 4.4.1).
- Proportion of doxycycline prescriptions of adequate doses (section 4.4.2).
- Proportion of erythromycin prescriptions of adequate doses (section 4.4.2).
- Proportion fully compliant with seven-day doxycycline (section 4.4.4).
- Proportion fully compliant with seven-day erythromycin (section 4.4.4)
- Proportion with limiting side effects to doxycycline (section 4.4.3).
- Proportion with limiting side effects to erythromycin (section 4.4.3).
- Proportion with limiting side effects to azithromycin (section 4.4.3).

All other azithromycin prescription factors have fixed values, not requiring to be generated. The regime can be offered to all women, as it is not contraindicated in pregnancy and 100% accuracy of single dose prescriptions with full compliance is expected.

The simulated mean and 95% confidence intervals generated for the variable inputs are in table 5.1.2.

Table 5.1.2. Input data common to doxycycline/erythromycin scenarios.

Variable	**Simulated mean**	**95% confidence interval**
Proportion of prescriptions written for doxycycline	77.9%	59.2%-93.1%
% doxycycline prescriptions at appropriate dose	86.6%	75.4%-96.1%
% erythromycin prescriptions at appropriate dose	84.9%	74.7%-96.1%
Compliance on doxycycline	68.3%	55.9%-79.8%
Compliance on erythromycin	68.3%	55.8%-79.8%
Limiting side effects on doxycycline %	10%	0.03%-16.8%
Limiting side effects on erythromycin %	34.9%	24.1%-48.3%
Limiting side effects on azithromycin %	10%	0.03%-16.8%

5.2 Outputs: effectiveness of treatment

Table 5.2.1 shows the prevalence of residual infection among women who have been given the azithromycin treatment regime (in scenarios 1a, 2a and 3a) and doxycycline/erythromycin (in scenarios 1d, 2d, and 3d).

The results of this model demonstrate that the azithromycin treatment regime is more effective than the doxycycline/erythromycin regime in each scenario modelled. Unresolved infection is 2.5 times more likely to remain after treatment with the doxycycline/ erythromycin regime than after the azithromycin treatment regime.

Residual infection in treated women can be a consequence of treatment failure due to poor compliance or side effects, prescription inadequacies or prompt re-infection from a partner.

Table 5.2.1 Residual infection in women after treatment.

Scenario	**Mean prevalence in women after treatment**	**Standard deviation**	**Range of prevalence in women after treatment (95% CI)**
1a	0.24	0.04	0.18-0.30
1d	0.58	0.06	0.48-0.68
2a	0.24	0.04	0.18-0.30
2d	0.58	0.06	0.48-0.68
3a	0.24	0.04	0.17-0.30
3d	0.58	0.06	0.48-0.68

Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

The number of infected male partners left in the community after treatment has been calculated within the analysis from the partner assumptions in the model (section 4.6). Table 5.2.2 gives the sum of male contacts that were inadequately treated, contacts identified but not traced, contacts of women with as yet undetected and untreated infection, and contacts to be infected by inadequately treated women within the year of treatment. This estimation is for the purpose of comparing the effectiveness of the two treatment regimes. Individuals may be counted more than once using this method, as it is possible for any individual male to partner more than one woman with the infection. Due to the transmissible nature of the disease, in order to acquire the organism a transmitting partner must have been in contact with another infected person with either undetected, untreated, under-treated or treated chlamydia in the past.

Table 5.2.2 Infected male partners remaining after treatment.

Scenario	Mean number of infected partners after treatment	Standard deviation	Range of number of infected males after treatment
#1a	9,188	5,558	2,501-20,326
1d	10,191	6,216	2,668-21,855
2a	9,173	5,546	2, 530-20,125
2d	10,210	6,342	2,616-23,017
3a	9,096	5,190	3,665-19,183
3d	10, 476	6,070	3,040-22,347

Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

If the infected women (7,000 of the 100,000) were not treated and had a mean of 2.3 new partners over the coming year, 16,100 males would be exposed to infection. It can be seen from this that treatment has made a small impact on the potential pool of infectious partners.

Under the assumptions of the model, the number of partners with infection after treatment differs by an order of ten, between the minimum and maximum values of the 95% confidence interval in each scenario. There is considerable overlap between scenarios due to the degree of uncertainty in behavioural factors leading to re-infection.
Women and partners with residual infection risk future complications and complication treatment costs. Table 5.2.3 compares the total cost of complications predicted by the model for the 100,000 women and their partners after the two treatments.

There are a large number of women with unmanaged infection in each scenario. This is a consequence of the prevalence of clinically silent infection. Women who are asymptomatic do not present for testing if they do not recognise their risk of acquiring infection. Table 5.2.3 demonstrates that the more effective treatment regime reduces both the overall cost of complications in the community, and the weighting of complications costs predicted for each woman with unmanaged infection.

Table 5.2.3 Cost of complications from the model

Scenario number	Mean complication cost- total for model	Complication cost per woman in model	Complication cost per unmanaged infected woman
1a	$1,905,160	$19.05	$19.58
1d	$2,152,355	$21.52	$22.12
2a	$1,905.160	$19.05	$19.58
2d	$2,152,355	$21.52	$22.12
3a	$1,726,340	$17.26	$17.94
3d	$2,070,891	$20.70	$21.52

Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

5.3. Outputs: cost of treatment.

The costs to the Health Funding Authority for General Practitioner management of uncomplicated infection per woman treated are given in table 5.3.1.

Scenarios 1a, 2a, and 3a represent the azithromycin treatment strategy. The doxycycline (or erythromycin if contraindicated) treatment strategy is represented by corresponding scenarios 1d, 2d and 3d.

Table 5.3.1 Costs per woman treated (uncomplicated infection)

Scenario number	Mean cost/ treatment	Standard deviation	Costs per treatment delivered (95% CI)
1a	$47.64	$4.32	$41.18-$55.05
1d	$55.38	$6.26	$45.37-$65.93
2a	$35.68	$3.79	$29.53-$43.39
2d	$43.39	$5.81	$33.82-$55.81
3a	$35.80	$3.89	$29.50-$42.43
3d	$43.50	$5.74	$34.16-$53.02

Key:

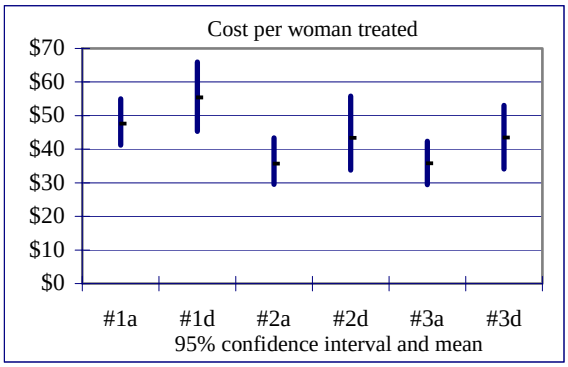
1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

There is approximately $7.70 difference in mean cost between the doxycycline/erythromycin treatment strategy and the equivalent azithromycin treatment strategy in scenarios 1, 2 or 3. This represents the pharmaceutical cost to the Health Funding Authority. It is the Pharmaceutical Schedule subsidy price for each of the doxycycline and erythromycin prescriptions, but not azithromycin prescriptions, modified by patient co-payments. Figure 5.2.1 shows these results in graphic form.

Figure 5.2.1 Cost per women treated in each scenario



Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

The low end of the cost range represents prescribing situations where most patients are not eligible for General Medical Services subsidies, high patient co-payments cover the pharmaceutical subsidy, patients are very compliant, re-treatment is not common and few partners are treated.

At the upper end of the cost range, doxycycline/erythromycin treatment will cost 50-60% more per woman than at the low end. The azithromycin strategy per woman will cost between 30-40% more at the upper end than at the low end of its cost range.

Since there is no pharmaceutical subsidy on azithromycin, the cost of treatment in these scenarios represents the costs of diagnostic tests and consultation costs for treatment and re-treatment of women and partners. The test and consultation costs are responsible for most of the cost of General Practitioner treatment, the cost of pharmaceuticals is a small proportion of the total cost per person treated.

There is a trend towards lower costs with azithromycin treatment compared to doxycycline/erythromycin, although 95% confidence intervals overlap. There is a difference in mean cost of $11.98 between scenarios 1a and scenario 2a or 3a, and between scenario 1d and 2d or 3d. This is the saving from omission of a test of cure (performed in scenarios 1 but not in scenarios 2 and 3).

Two testing strategies have been used in the model. An Elisa screening test, confirmed by MIF, is used in scenarios 1a and 1d and the LCR screening test is used to test for infection in scenarios 2a, 2d, 3a and 3d. The mean cost per woman treated increases slightly (approximately 11 cents per person) with use of LCR compared to Elisa confirmed by MIF. However, the 95% confidence interval is similar using either technology, as shown in figure 5.2.1. The Elisa test confirmed by an MIF test is a cheaper option for screening only in low prevalence communities in which the majority of test results will be negative, and

confirmation tests will not required. In New Zealand the laboratory schedule price of performing the two tests, Elisa plus MIF, is very similar to the schedule price of LCR alone. Since only patients with positive tests have been treated this model, there is no significant difference between treatment costs for scenarios 2a and 3a or between scenarios 2d and 3d.

5.4 Outputs: cost-effectiveness of treatment.

5.4.1 Cost per cure.

The cost per woman cured is taken as the measure of short-term cost-effectiveness of treatment. Table 5.4.1 shows the cost per woman cured after treatment with doxycycline (or erythromyin where contraindicated), derived from scenarios 1d, 2d, and 3d. Scenarios 1a, 2a, and 3a represent the cost per woman cured with azithromycin, under parallel management conditions.

Table 5.4.1 Costs per woman cured

Scenario number	**Mean cost/cure**	**Standard deviation**	**Costs/cure (95% CI)**
1a	$62.63	$7.18	$51.95-$74.97
1d	$136.63	$28.81	$96.10-$188.53
2a	$46.90	$6.13	$37.70-$57.49
2d	$107.06	$24.28	$72.25-$150.48
3a	$47.03	$6.20	$37.29-$58.21
3d	$107.26	$23.97	$72.96-$149.16

Key:

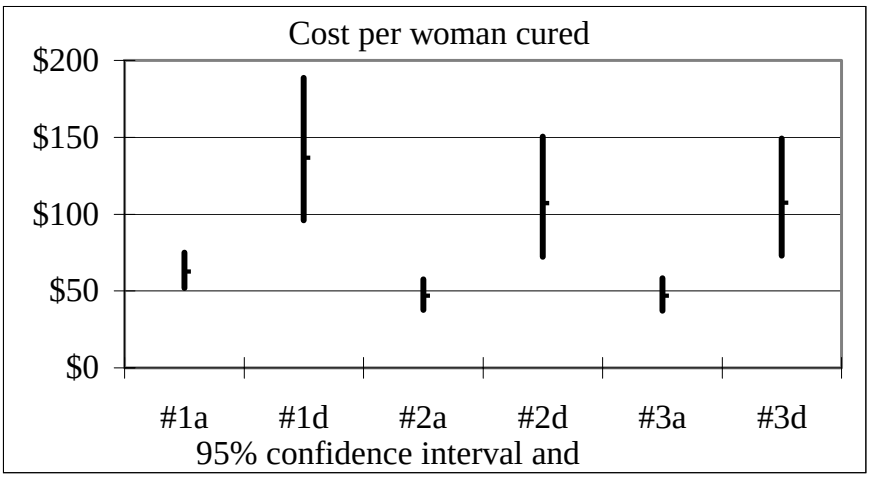
1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

Figure 5.4.1 shows the azithromycin treatment strategy to be significantly more cost-effective than the doxycycline/erythromycin strategy in achieving a short-term cure over all scenarios in this model.

Figure 5.4.1 Cost per woman cured in each scenario.



Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

Omission of a test of cure has saved $29.57 from the mean cost to cure a woman with the doxycycline/erythromycin treatment strategy (scenario 1d compared to 2d) and saves $15.73 with the azithromycin treatment strategy (scenario 1a compared to 2a). The cost of a consultation to determine compliance is included in the cost structure of every scenario, whether a test for cure is included or not. In this model there is no significant difference in short-term cost-effectiveness between the choice of Elisa test confirmed with MIF , or LCR as a diagnostic test.

5.4.2 Cost to prevent complications in women

The number needed to treat successfully in order to prevent complications and hence the cost to prevent complications is the measure of long-term cost-effectiveness of treatment.
Table 5.4.2 documents the costs to prevent complications in the women with the doxycycline/ erythromycin and azithromycin strategies.

Table 5.4.2 Cost to prevent complications in women

Scenario number	**Cost to prevent pelvic inflammatory disease. mean (CI)**	**Cost to prevent chronic pelvic pain. mean (CI)**	**Cost to prevent ectopic pregnancy. mean (CI)**	**Cost to prevent infertility. mean (CI)**
1a	$419.11 ($266.52-$655.73)	$3,493 ($2,221-$5,464)	$5,239 ($3,332-$8,197)	$2,384 ($1,485-$3,775)
1d	$900.24 ($519.00 -$1,501)	$7,502 ($4,519 -$12,508)	$11,253 ($6,488-$18,762)	$5,116 ($2,895-$8,549)
2a	$313.88 ($195.67-$495.34)	$2,616 ($1,630-$4,128)	$3,924 ($2,446-$6,192)	$1,786 ($1,088-$2,855)
2d	$706.87 ($394.84-$1,205)	$5,891 ($3,290-$10,041)	$8,836 ($4,936-$15,061)	$4,023 ($2,212-$7,032)
3a	$315.72 ($201.91-$487.32)	$2,631 ($1,678-$4,061)	$3,947 ($2,518-$6,092)	$1,795 ($1,116-$2,842)
3d	$712.96 ($406.56-$$1,192)	$5,941 ($3,388-$9,930)	$8,912 ($5,082-$14,895)	$4,060 ($2,271-$6,891)

Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

Azithromycin is more cost-effective than doxycycline/erythromycin. The cost to prevent complications such as ectopic pregnancy or infertility with the azithromycin treatment strategy is close to the DRG cost of management of these complications in New Zealand.

5.4.3 Cost to prevent neonatal complications

Cost-effectiveness in preventing infant complications follows intuitively from the cost-effectiveness seen in the prevention of other complications in women. The mean costs to prevent complications in infants under the doxycycline/erythromycin and azithromycin treatment regimes are compared in table 5.4.3. A high degree of imprecision exists in the

variables required to calculate these rare events. This has resulted in a wide range of projected costs and large standard deviations.

Table 5.4.3 Mean cost to prevent complications in infants

Scenario number	Cost to protect infants from exposure to Chlamydia	Cost to prevent neonatal Chlamydia conjunctivitis	Cost to prevent neonatal Chlamydia pneumonia
1a	$1,881 ($1,026-$3,326)	$11,064 ($6,033-$19,566)	$18,809 ($10,256-$33,262)
1d	$3,686 ($1,904-$6,795)	$21,680 ($11,202-$39,759)	$36,856 ($19,043-$67,591)
2a	$1,411 ($767-$2,532)	$8,297 ($4,516-$14,895)	$14,106 ($7,678-$25,322)
2d	$2,875 ($1,448-$5,239)	$16,915 ($8,517-$30,819)	$28,755 ($14,480-$52,392)
3a	$1,462 ($811-$2,564)	$8,601 ($4,768-$15,083)	$14,622 ($8,101-$25,641)
3d	$3,082 ($1,529-$5,757)	$18,132 ($8,993-$33,867)	$30,824 ($15,288-$57,573)

Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

In demonstrating cost-effectiveness, an alternative to considering the cost to prevent neonatal complications is to calculate the predicted savings in neonatal care from treatment of genital Chlamydia. Table 5.6.4 shows the predicted cost savings in neonatal intensive care of premature infants each year from women managed in each of the treatment strategies, over the cost for women receiving no treatment for genital chlamydia. There is overlap between the treatment strategies, but the azithromycin treatment strategy has the greatest potential to achieve savings at the upper extreme of therapeutic response. The potential mean savings in neonatal care projected under the doxycycline treatment strategies are 60% of the potential savings under the azithromycin strategies.

Table 5.4.4 Difference in neonatal intensive care costs between treatment and no treatment.

Treatment regime	**Scenario 1 mean, (95% confidence interval)**	**Scenario 2 mean ,(95% confidence interval)**	**Scenario 3 Mean, (95% confidence interval)**
Doxycycline /erythromycin	$28,136 ($7,753 -$62,027)	$28,084 ($7,967- $61,642)	$36,840 ($10,121-$82,501)
Azithromycin	$47,010 ($13,045-$105,011)	$46,718 ($12,924-$105,061)	$62,749 ($16,853-$144,070)

Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

5.5.4 Overall cost of complications.

An estimate of the overall cost of complications was obtained by adding the costs of all the considered complications for each scenario from the perspective of the Health Funding Authority. As might be predicted in a cohort of 100,000 women, the total complications amount to a large figure, in excess of one million dollars for each scenario. In order to put the total complication costs into perspective, an average complication cost per infected woman was calculated.

Scenarios 1d and 2d, which model treatment of women with doxycycline/erythromycin on a positive Elisa/MIF test and treatment of traced partners with doxycycline, have an average complication cost $21.52 per infected woman in the community. Scenario 3d, which models treatment of women with doxycycline/erythromycin on a positive LCR test and treatment of traced partners with doxycycline, has an average complication cost $20.70 per infected woman in the community.

Scenarios 1a and 2a, which model treatment of women with azithromycin on a positive Elisa/MIF test and treatment of traced partners with azithromycin, have an average complication cost of $19.05 per infected woman in the community.

Scenario 3a, which models treatment of women with azithromycin on a positive LCR test and treatment of traced partners with azithromycin, has an average complication cost $17.26 per infected woman in the community.

From this comparison, the scenario of testing with LCR and treating with azithromycin is estimated to be the most cost-effective in the long term of all options considered, as it produces the lowest overall complication costs per woman with the infection.

5.5 Sensitivity to variable inputs

Spearman ranked correlation coefficients were calculated to determine the sensitivity of the cost per woman cured to the variable inputs. Interpretation of the Spearman rank correlation coefficient is explained in appendix C.

5.5.1 Sensitivity of cost of cure

Table 5.5.1 lists inputs that are positively and negatively correlated with the cost per woman treated. The cost-effectiveness of treatment decreases as cost per cure is increased, and conversely cost-effectiveness increases as cost per cure is decreased.

The cost-effectiveness of treatment, as measured by cost per woman cured in this model, is most sensitive to the proportion of women with current partners to be treated. The model is sensitive to the percentage of community cardholders to be treated. This reflects the extra costs incurred by the Health Funding Authority due to the cost of General Medical Services subsidies for medical consultations and the reduced level of prescription co-payments from this group of patients.

The model is sensitive to the proportion of women for whom a prescription for doxycycline is contraindicated because the pharmaceutical subsidy on erythromycin is higher than that for doxycycline. As expected the model is less sensitive to compliance to erythromycin than to doxycycline, since fewer women require erythromycin prescriptions.

Table 5.5.1 Sensitivity of Cost of Cure.

Positively correlating variable	Spearman Correlation coefficient	Negatively correlating variable	Spearman Correlation coefficient
Percent with current partner	+0.591	Percent of women following instructions for doxycycline	-0.401
Percent community cardholders	+0.435	Doxycycline prescription dose appropriate for women	-0.208
Percent with limiting side effects	+0.137	Percent of women offered doxycycline	-0.2
Percentage of partners traced	+0.103	Doxycycline prescription duration appropriate for women	-0.191
Percentage of partners treated	+0.09	Percent of women receiving retreatment with doxycycline when indicated	-0.114
Percentage spontaneous cure rate	+0.049	Percent of partners following instructions for doxycycline	-0.075
		Doxycycline precription duration appropriate for partners	-0.069
		Percent receiving retreatment with erythromycin when indicated	-0.067
		Erythromycin prescription duration appropriate for women	-0.067
		Percent of women following instructions for erythromycin	-0.06

5.5.2 Sensitivity of cost of complications.

In this analysis, the cost to prevent predicted complications by management of the treated women and their identified partners was calculated. Spearman correlation coefficients on cost to prevent complications show this to be sensitive to the predicted rate for pelvic inflammatory disease, from which all female complications are derived as well as to the factors in figure 5.5.1.

The total cost of all predicted complications in the model was also calculated. This is the cost of complications predicted to develop in all of the 100,000 infected women in the model, including the costs of complications predicted to occur in their untreated male partners. Any women and partners with a treatment failure, or re-infection by an untreated partner shortly after treatment were included as well as those who have not been treated. This total cost of complications is sensitive to both the prevalence of genital Chlamydia in the population, and the proportion of women with unrecognised risk of infection.

5.6 Break-even analysis.

5.6.1 Pharmaceutical subsidy

Since the cost comparisons for General Practice prescription are not made on an equal basis: one treatment strategy is fully subsidised and the other not subsidised, break-even analysis tests the subsidy level required to attain equivalent cost per treatment and cure. The results of the azithromycin treatment scenarios without test of cure (scenarios 2a and 3a) have been manipulated to determine the effect that changes in pharmaceutical subsidy will have on the cost (cost per treatment) and cost-effectiveness (cost per cure) of the azithromycin treatment strategy. Scenario 1a is not included as it is equivalent to scenario 2a with addition of the costs of tests for cure, which, in this model influence cost but not efficacy of Chlamydia management.

Table 5.6.1 summarises the results of this break-even analysis.

For the cost-effectiveness (cost per woman cured) of azithromycin to be reduced to the same level as the equivalent doxycycline/azithromycin treatment strategy, the prescription subsidy for single dose azithromycin treatment must be $31.32 for scenario 2a or $31.41 for scenario 3a. At this level of subsidy, the cost per woman treated becomes $81.73 for scenario 2a and $81.97 for scenario 3a.

If a subsidy were to be applied to azithromycin to bring the cost per woman treated up to the same as for the equivalent doxycycline/erythromycin treatment strategy, that subsidy would be $6.93. The cost per woman cured would then rise to $56.83 for scenario 2a or $56.90 for scenario 3a.

Applying the pharmaceutical subsidy currently paid on either the doxycycline or erythromycin regime results in savings. At a subsidy of $4.50 (the subsidy on the doxycycline regime), azithromycin treatment would save $2.80 per person treated and $53.80 per person cured. At the $6.24 erythromycin subsidy, azithromycin treatment would save $0.80 per person treated but $51.30 per person cured.

Table 5.6.1 Results of break-even analysis: effect of subsidy.

Break-even parameter and Scenario number		**Hypothetical pharmaceutical subsidy**	**Cost per woman treated**	**Cost per woman cured**
doxycycline	2a	**$4.508**	$40.67	$53.28
Subsidy level	3a	**$4.508**	$40.77	$53.35
erythromycin	2a	**$6.241**	$42.62	$55.82
Subsidy level	3a	**$6.241**	$42.72	$55.89
cost-per	2a	$6.93	**$43.39**	$56.83
treatment	3a	$6.93	**$43.50**	$56.90
cost-per-	2a	$31.32	$81.73	**$107.06**
cure	3a	$31.41	$81.97	**$107.26**

Key:

1a/1d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and test of cure.

2a/2d = scenarios of EIA/MIF testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

3a/3d = scenarios of LCR testing, azithromycin or doxycycline/erythromycin treatment, and no test of cure.

5.6.2 Treatment compliance.

The results of scenario 2a and 3a have been manipulated to determine the effect that changes in compliance will have on the cost (cost per treatment) and cost-effectiveness (cost per cure) of the doxycycline treatment strategy.

Table 5.6.2 summarises the results of the break-even analysis, performed only on the doxycycline scenarios without test of cure. When the compliance to doxyycline and to erythromycin is set at the same as the compliance on azithromycin, 100%, the cost per woman treated becomes $42.80 for scenario 2d and $42.90 for scenario 3d. The cost per woman cured is $68.73 for scenario 2d and $68.81 for scenario 3d. The prevalence of residual infection in the women and partners is improved (as would be predicted) and the cost of complications is reduced.

Table 5.6.2 Result of 100% compliance to doxycycline &/or erythromycin.

Scenario number	**Mean cost per woman treated**	**Mean cost per woman cured**	**Mean prevalence in treated women**	**Mean number of infected partners over the model**	**Mean cost of complication over the model**
2d	$42.80	$68.73	38%	9,579	$2,005,388
3d	$42.90	$68.81	38%	9,641	$1,866,041

Key:

2d = scenario of EIA/MIF testing, doxycycline/erythromycin treatment, and no test of cure.

3d = scenario of LCR testing, doxycycline/erythromycin treatment, and no test of cure.

A comparison of table 5.6.2 with tables 5.3.1, 5.4.1, 5.2.2 and 5.2.3 shows that even at 100% compliance the performance of the doxycycline/erythromycin treatment strategy cannot match that of the equivalent azithromycin treatment strategy on cost, effectiveness or cost-effectiveness under baseline assumptions. That is, at 100% compliance with doxycycline/erythromycin regimes, the outcomes of cost per treatment delivered, cost per cure, cost of complications and number of partners infected are not as favourable as the azithromycin outcomes.

5.6.3 Prescription accuracy.

To demonstrate the effect of prescription accuracy on cost-effectiveness, scenarios 2d and 3d were run with the assumption that the dose and duration of all prescriptions for doxycycline and erythromycin would be appropriate to successfully treat genital Chlamydia. Table 5.6.3 gives the results.

Table 5.6.3 Doxycycline/erythromycin outputs at 100% prescription accuracy.

Scenario number, (compliance)	**Mean cost per woman treated**	**Mean cost per woman cured**	**Mean prevalence in treated women**	**Mean number of infected partners over the model**	**Mean cost of complication over the model**
2d at standard compliance	$42.96	$78.43	45%	9,792	$2,058,791
2d at 100% compliance	$42.19	$50.90	17%	8,993	$1,858,624
3d at standard compliance	$43.06	$78.53	45%	9,938	$1,940,477
3d at 100% compliance	$42.29	$50.98	17%	8,993	$1,858.624

Key:

2d = scenario of EIA/MIF testing, doxycycline/erythromycin treatment, and no test of cure.

3d = scenario of LCR testing, doxycycline/erythromycin treatment, and no test of cure.

Under the standard assumptions in this model, if all General Practitioner prescriptions were of adequate dose and duration for the purpose, the mean cost per woman cured with the doxycycline/erythromycin regime can be reduced from $107 to $78.50. A comparison of table 5.6.3 with previous result tables shows that with standard patient compliance, the azithromycin strategy remains superior in cost, effectiveness and cost-effectiveness to the doxycycline/erythromycin strategy even under assumptions that 100% of the latter prescriptions are adequate for purpose.
Similarily, if patient compliance with the appropriate prescriptions could reach 100%, the cost and cost-effectiveness superiority of azithromycin would still be retained.

The results in table 5.6.3 show that the short-term effectiveness (prevalence of infection in treated women) is slightly better for the doxycycline/erythromycin under ideal prescribing assumptions than for the azithromycin strategy under standard assumptions. This is because in the azithromycin strategy, re-treatments were assumed to be due to intolerance, not compliance failure, and doxycycline was the substitute for this purpose (with standard compliance and tolerance assumptions).

The advantages of single dose azithromycin are the assurance of patient compliance and the simplicity of prescription. The price performance of the doxycycline/erythromycin treatment regime should be identical to azithromycin under assumptions of 100% compliance and prescription accuracy. Under such assumptions the treatment cost of each strategy should differ by an amount approximately equal to the difference in pharmaceutical subsidy which applies to doxycycline/erythromycin but not to azithromycin prescriptions.

The proportion of erythromycin prescriptions (which attract a higher subsidy), in the doxycycline/erythromycin strategy, will put the price difference at more than the $4.50 pharmaceutical subsidy for doxycycline prescriptions. The use of fully subsidised doxycycline/erythromycin for re-treatment where necessary in the azithromycin strategy will also modify the price difference. The Monte Carlo randomisation of variables in the model is an unknown and will have an unpredictable influence on the relative performance of the treatment strategies.

The current model predicts that a subsidy of $5.86 per azithromycin prescription would be required to raise the cost per woman treated with azithromycin up to the cost with the doxycycline/erythromycin strategy (under assumptions of 100% compliance and prescription accuracy). This, as expected, is greater than the subsidy for any doxycycline treatment and less than the erythromycin subsidy. It represents that portion of average treatment costs attributable to erythromycin subsidy (where required as a doxycycline alternative), subsidy on partner treatments and all re-treatments. The result of this break-even analysis, which has tested the integrity of the model, is evidence that the use of the Monte Carlo method does not distort predicted results.

5.7 Decision analysis

The information provided in sections 5.2 to 5.5 can be applied to the six key decisions in General Practitioner management of genital Chlamydia (figure 2.1.2).

> Decision 1 (decision by women to seek medical assistance) is not in the control of the General Practitioner, but may be influenced by health promotion messages to raise awareness of risk.

Decision 2 (decision to test for infection). This model shows that although the new tests based on DNA technology are more expensive than either Elisa or MIF alone, the treatment cost and cost-effectiveness using LCR for diagnosis is the same as Elisa with MIF confirmation of positive results, from the perspective of the Health Funding Authority.

Decision 3 (decision to treat identified cases). The results demonstrate that significant complication costs arise from untreated cases. Although treatment is not very efficacious (23% and 58% remaining infected after treatment), effective treatment saves cost of complications. Cost-effectiveness is demonstrated for the all complications, including uncommon events such as neonatal sequelae. The results favour a decision to treat uncomplicated infection with single dose azithromycin. This is a both less expensive to the Health funder and more cost-effective than 7-day doxycycline or erythromycin with current prescription subsidy.

Decision 4(decision to trace and treat contacts). The large number of contacts remaining untreated in the community after treatments in this model are an ongoing re-infection risk to partners. Treatment failure due to re-infection is a risk. The cost of treatment increases with the number of partners treated and the number requiring re-treatment.

Decision 5 (decision to test for cure). Since current treatments for genital chlamydia have high efficacy, the test of cure serves only to confirm the stated compliance. Omission of a laboratory test for cure at the compliance consultation saves almost three times the cost of the test itself in the doxycycline/erythromycin treatment strategy, and almost twice the test cost in the azithromycin strategy. The relative cost and cost-effectiveness of treatment would be predicted to increase if LCR was used for a test for cure.

Decision 6 (decision to re-treat treatment failures). Re-treatment of women and partners increases the cost and reduces cost-effectiveness of treatment. As for decision 4, the decision to re-treat should be made on public health grounds, not on cost to the health funder.

The six options for decision analysis are listed below, with permutations from the break-even analysis. The costs quoted are the simulated mean costs taken from sections 5.2 to 5.4 above.

- A decision to treat women with doxycycline/erythromycin on a positive Elisa/MIF test, trace and treat contacts with doxycycline, re-treat with the same regime if necessary and test women and treated partners for cure with MIF costs (on average) $55.38 per woman treated and $136.63 per woman cured. The prevalence of residual infection among treated women will be 58%. The projected community-wide cost of complications of this approach is $21.52 per woman in the community.
- A decision to treat with azithromycin on a positive Elisa/MIF test, trace and treat contacts with azithromycin, re-treat with doxycycline or erythromycin if intolerant to azithromycin and to test women and treated partners for cure with MIF costs (on average) $47.64 per woman treated and $62.63 per woman cured. The prevalence of residual infection among treated women will be 24%. The projected community-wide cost of complications of this approach is $19.05 per woman in the community.
- A decision to treat women with doxycycline/erythromycin on a positive Elisa/MIF test, trace and treat contacts with doxycycline, re-treat with the same regime if necessary and not to test women or treated partners for cure costs (on average) $43.39 per woman treated and $107.06 per woman cured. The prevalence of residual infection among treated women will be 58%. The projected community-wide cost of complications of this approach is $21.52 per woman in the community.
- The same decision would cost $42.80 per woman treated, $68.73 per woman cured, with 38% prevalence of residual infection among treated women, if women and their partners could be encouraged into 100% compliance with doxycycline and/or erythromycin.
- A decision to treat with azithromycin on a positive Elisa/MIF test, trace and treat contacts with azithromycin, re-treat with doxycycline or erythromycin if intolerent to azithromycin and not to test women or treated partners for cure currently costs (on average) $35.68 per woman treated and $46.90 per woman cured. The prevalence of residual infection among treated women will be 24%. The projected community-wide cost of complications of this approach is $19.05 per woman in the community.
- If azithromycin prescriptions were subsidised at $31.32 per prescription the above decision would cost $81.73 per woman treated, and $107.06 per woman cured, the

same as the cost of cure under the equivalent doxycycline/erythromycin regime with standard compliance assumed.

- If azithromycin were subsidised to $6.93 the above decision would cost $43.39 per woman treated, the same as the equivalent doxycycline/erythromycin regime (at standard compliance)
- A decision to treat women with doxycycline/erythromycin on a positive LCR test, trace and treat contacts with doxycycline, re-treat with the same regime if necessary and not to test women and treated partners for cure costs (on average) $43.50 per woman treated and $107.26 per woman cured. The prevalence of residual infection among treated women will be 58%. The projected community-wide cost of complications of this approach is $ 20.70 per woman in the community.
- If women and their partners were 100% compliant with doxycycline and/or erythromycin, the same decision would cost $42.90 per treatment delivered, $68.81 per cure, and the prevalence of residual infection in treated women would be 38%.
- A decision to treat with azithromycin on a positive LCR test, trace and treat contacts with azithromycin, re-treat with doxycycline or erythromycin if intolerant, without testing women and treated partners for cure, currently costs (on average) $35.80 per woman treated and $47.03 per woman cured. The prevalence of residual infection among treated women will be 24%. The projected community-wide cost of complications of this approach is $17.26 per woman in the community.
- If azithromycin was subsidised at $31.41 per prescription the above decision would cost $81.97 per woman treated, and $107.26 per woman cured. This cost of cure is the same as for the equivalent doxycycline/erythromycin regime (with standard compliance).
- If a subsidy of $6.93 applied on azithromycin prescriptions, the above decision would cost $43.50 per treatment delivered, which is the same cost as the equivalent doxycycline/erythromycin regime (with standard compliance).
- A decision to practice medicine defensively, by testing every patient treated in order to document cure, increases the costs by $11.90 (on average) per woman treated and increases the costs by between $15.00 to $29.00 per woman cured.

6. Discussion

6.0 Main results

This modelling project has demonstrated that the complexities of health care delivery in the primary care setting can be incorporated into a mathematical model to enable assessment of cost, cost-effectiveness and factors that influence cost-effectiveness of General Practice prescribing.

Although this current model has been developed to address economic questions in the management of genital Chlamydia in women, the modelling process could have been applied to any of the conditions managed by General Practitioners in New Zealand.

This model incorporates utilisation of laboratory, pharmaceutical and General Medical Services subsidies in the management of genital Chlamydia by General Practitioners to determine short-term and long-term cost and cost-effectiveness from the perspective of the Health Funding Authority in New Zealand.
Two Chlamydia treatment strategies have been compared: seven-day doxycycline/erythromycin regime, which is subsidised on the New Zealand Pharmaceutical Schedule, and single dose azithromycin, which is not currently a subsidised treatment.
Two Chlamydia test systems have been compared: antigen detection by Elisa confirmed by MIF, and nucleic acid amplification using LCR. The cost-effectiveness of testing for cure has been examined.

In the setting of this model, azithromycin is both the cheapest and the most effective of the two treatment strategies compared. It is cheaper to the Health Funding Authority because it is not currently subsidised for prescription in New Zealand and is also more cost-effective treatment than the doxycycline/eythromycin regime. The model demonstrates that even if full compliance to doxycycline and erythromycin could be ensured, the cost per person treated and cost per person cured with azithromycin would be less than with doxycycline/erythromycin. The simplicity of the single dose azithromyin regime enhances accuracy of General Practitioner prescriptions as well as ensuring patient compliance and minimising side effects. Good compliance with the treatment regime saves repeated

consultation and prescription costs and reduces the need for tests for cure. These savings are relevant in the management of uncomplicated Chlamydia infection, because the cost to the Health Funding Authority of a diagnostic test or a cardholder medical consultation fee exceeds the cost of subsidised prescription medicine. Although this analysis does not help the decision of who to test or when to test, it does explore the cost-effectiveness of DNA amplification testing technology recently introduced to New Zealand, when used with different treatment strategies.

There is considerable overlap between the cost per woman treated by the azithromycin and the doxycycline/erythromycin strategies, although prescriptions for azithromycin carry no pharmaceutical subsidy costs to the Health Funding Authority. At the lower end of the range of costs, the $4.19 - $4.66 difference between treatment strategies is less than the difference due to the doxycycline/erythromycin pharmaceutical subsidies alone.

From the perspective of the Health Funding Authority the superior cost-effectiveness of the azithromycin regime would remain until azithromycin carried a pharmaceutical subsidy up to $31 per prescription. This level of subsidy equates to a dispensing price at a retail pharmacy of $45.61. The retail pricing of azithromycin in New Zealand is a matter of conjecture, as it is not currently available at retail outlets. In Australia the schedule price varies between states but is approximately $NZ15.00 for a 1 Gm dose (Pharmac, personal communication) equating to a New Zealand retail price of $23.58 at this subsidy level. This is well below the break-even price for equivalent cost-effectiveness with the doxycycline/erythromycin treatment strategy.

Although this model differs in structure, costs and assumptions from that of Magid et al (1996), the cost per woman treated under their model with azithromycin ($US39.51) and with doxycycline ($US69.07) confirms that the results of the current model are within the correct order of magnitude.

The sort-term cost of treatment and cost of cure is important information for budget-holding General Practitioners, but it is the cost to prevent complications in the long term which is of significance to the Health Funding Authority as that agency carries future risk. The current analysis therefore addresses both short-term and long-term cost and cost-effectiveness.

The analysis demonstrates that infection remains unresolved in 58% of women in this model treated with a doxycycline/ erythromycin regime and in 23% of women treated with azithromycin. This supports the concept of Nuovo et al (1994) that a substantial number of patients with Chlamydia trachomatis infection fail to respond to therapy. It is consistent with the model of Genc and Mardh (1996) who derived a cure rate from their model of between 42.7% and 62.6% with doxycycline, despite different assumptions. Unresolved infections contribute to the rate of complications long-term.

The current analysis demonstrates that long-term cost-effectiveness, the cost to prevent complications, is sensitive to the prevalence of Chlamydia infection in the population. This is consistent with published economic analyses showing that the cost-effectiveness of population screening and treatment is sensitive to infection prevalence (Magid, 1996, Genc and Mardh 1996).

In the setting of New Zealand primary care, General Practitioners test opportunistically and selectively for disease rather than perform systematic population screening. As a result not all community infections are identified. The current model simulates this approach, by modelling all women at risk, of whom a proportion recognise risk, and a proportion is tested.

The model shows that short-term cost-effectiveness (cost-per-cure) is sensitive to the proportion of women who require an alternative to doxycycline treatment. Inclusion of costs incurred when an alternative treatment to doxycycline is required in pregnancy is a unique feature of this analysis.

The erythromycin regime, which is currently prescribed for this purpose in New Zealand, is more expensive than the doxycycline regime. The complexity of the erythromycin regime, and gastrointestinal intolerance both affect patient compliance. These considerations increase both the cost of treatment and the cost of cure in the regimes using doxycycline and erythromycin.

Literature search failed to find any other economic analyses that consider the cost of tetracycline alternatives for treatment of chlamydia infections in women who may be pregnant. There is, however, some evidence that avoidance of doxycycline in pregnancy may be unnecessarily conservative. In one study, women inadvertently given doxycycline did not produce offspring with typical tetracycline birth defects (Czeizel and Rockenbauer 1997), and infants exposed in the second and third month of gestation had a rate of congenital abnormality no greater than controls.

The analysis is sensitive to the Community Services cardholder status of patients of General Practitioners in New Zealand. General Practitioners in budget-holding practices carry the cost of pharmaceutical expenditure after patient co-payments are deducted. Prescriptions for patients with Community Services Cards cost pharmaceutical budget-holders more than non-card holder prescriptions.
General Practitioners who hold budgets for pharmaceutical costs have an incentive to reduce prescribing costs, but this could be counterproductive to control of the Chlamydia epidemic, since students, the unemployed and those on low-income who are community Card holders are mostly in the high prevalence age-group.

Prescription of unsubsidised medicines saves the pharmaceutical budget-holder, and hence the Health Funding Authority costs of the pharmaceutical subsidy plus margins and pharmacist handling fees. This is saved by cost shifting to the patient, to the disadvantage of low-income patients. The current pharmaceutical budget-holding model of General Practice funding therefore contains perverse incentives to efficient management of the Chlamydia epidemic.

In the current model, long-term cost-effectiveness (cost to prevent complications) is sensitive to the number of women tested for infection. Incentives for General Practitioners to reduce costs of diagnostic tests, such as budget holding for laboratory utilisation, may be perverse to disease detection and infection control.
Tests for cure, in contrast, serve only to confirm clinical information, and could be targeted to cut costs. General Practitioners, who practice medicine defensively, will add between ten and twenty percent to the cost per treatment by re-testing treated patients to document cure for medico-legal purposes.

General Practitioners in New Zealand are reimbursed for eligible consultations, unless they receive capitation-based bulk funding. The Health Funding Authority (1998) has signalled a move toward a population-based funding formula for all General practices. For practices with capitation funding, partner tracing and treatment is not funded if the partner is not a registered patient of the practice. Under population-based funding multiple consultations for any patient, time-consuming activities such as partner tracing, and tracing and treating contacts who are not members of the defined population will carry a financial disincentive

for General Practices. This model shows that treatment cost-effectiveness (cost per cure) is sensitive to patient compliance and to partner factors, both of which increase the number of consultations and prescriptions required to effect cure of the index case.
Prescription to the patient, but not to the partner will reduce pharmaceutical and laboratory and consultation costs, but will waste resources if the index case becomes re-infected, the epidemic is spread, and future complication costs increase.
The decision to treat partners should be made on the basis of public health benefit, not on the cost to the budget holder. A move to population-based funding of primary care is therefore predicted to bring perverse incentives for control of Chlamydia infection.

6.1 Methodological Considerations

As in all models, the limitations of this analysis lie in data imperfections, simplifying assumptions and exclusions.

Data imperfections have been accommodated by the application of Monte Carlo simulation to this model. This technique brings advantages to medical modelling because it permits variables to lie within a range a range of values, rather than assume a fixed value. Genc and Mardh (1996) demonstrated the usefulness of Monte Carlo simulation of chlamydia management, incorporating a plausible range for some of the variables. The current model extends the concept of their model with the application of second order Monte Carlo simulation.

Second order Monte Carlo simulation differs from first order in that values are selected randomly from an estimated range according to a given probability distribution. After multiple iterations (2,000 in this model) both a simulated mean and 95% confidence interval can be derived from second order Monte Carlo simulation. This can be more useful than the simple range of values, which is the output of first order Monte Carlo simulations, in risk analysis.

The practical applications of second order Monte Carlo simulation are the ability to use real data sets as variables in a model, and to accommodate a plausible range of variables even if the distribution is skewed within it. Because it allows real data sets and weighted estimates

to be incorporated, second order Monte Carlo simulation improves the accuracy of inputs to a model. In the current model, the proportion of community cardholders in each practice ranged from 14% to 100% and the distribution was skewed to the upper end of this range. The mathematical best fit to the actual data was a Weibull curve, which was inserted directly into the model as the Monte Carlo distribution function for that variable.

Outputs of second order Monte Carlo simulation are expressed as a probability distribution, with measures of skew and variance about the simulated mean. This enhances the quality of data available from the analysis and improves the accuracy of forecasting from the outputs.

The disadvantage of second order Monte Carlo modelling lies in the requirement for specialised software to independently randomise multiple variables with unique distribution functions within their range. Genc and Mardh (1996) modified an Excel programme for the randomisation of their first order Monte Carlo simulation, but second order additional Monte Carlo require a higher level of software sophistication. An additional disadvantage is that a single figure result as output is not possible with any Monte Carlo method.

The integrity of use of Monte Carlo simulation has been demonstrated by the break-even analysis performed under assumptions of 100% compliance and 100% prescription accuracy. Since the advantages of single dose azithromycin lie in the simplicity of prescription and administration, the difference in treatment cost under these assumptions should equate to the component of pharmaceutical subsidy attracted by doxycyline and erythromycin prescriptions. This model predicts a cost difference per person treated, which lies between the pharmaceutical subsidy of doxycycline and erythromycin.

Simplifying assumptions have been avoided wherever possible by use of an expanded decision tree with Markov cycles at key decision nodes to model clinical complexity. Clinical pathways and outcomes are not always predictable. The behaviour of both doctors and patients can be extremely variable. Modelling with an expanded decision tree and Markov cycles has enabled many clinical variables to be included in the model, but the resulting structure of this model is more complex than spreadsheet models of Chlamydia management such as Genc and Mardh 1996, Magid 1996, and Howell 1997.

The Markovian memory-less assumption requires the probability of a patient moving out of a transition state in the cycle of the model to be independent of any states they have already passed through. This assumption creates difficulties with logic when used in medical modelling (Briggs and Sculpher 1998). The Wellington model has avoided the Markovian assumption with using the decision tree as a tunnel state. The transitions through the decision tree must be visited in the fixed forward sequence. Clinical logic dictates that women at risk of infection are vulnerable to acquiring the infection, not vice versa.

By modelling of a community cohort of 100,000 women at risk, economic issues can be addressed in the context of impact on the community. This model shows the burden of disease remaining in the community after treatment as a result of undetected asymptomatic infection, untreated disease, and short-term re-infection from infected but untreated partners. By analysing subsets of the community, this single model can be used to address economic issues pertaining to treatment of known infections, or asymptomatic screening, or partner management.

This model takes a sole purchaser assumption: that one funder carries all relevant General Practice management costs and complication management costs. Health insurance is a confounding variable on health care costs in New Zealand. Insurance companies provide gap insurance to patients for General Practitioner and Specialist consultations and some referred services. However, the consideration of health insurance has no influence on the costs per woman treated or cured of Chlamydia infection in this model. Costs to the Health Funding Authority of General Medical Services benefits, laboratory service schedules, and prescription subsidies apply regardless of health insurance status in New Zealand. The Health Funding Authority pays as much for insured patients as for uninsured patients with equivalent community cardholder status. Health insurance purchasing activity may have a small influence on the cost of some complications and hence the cost to prevent complications. The service most likely to be purchased by insurance companies is management of infertility, as infertility services are not readily accessible through the New Zealand public hospital system.

This model assumes that a patient will pay the due co-payments to collect their medicine from the pharmacy when given a prescription from their General Practitioner. In practice, the cost of the prescription to the patient at the pharmacy could reduce compliance. Failure to

uplift prescriptions on financial grounds would favour the cheaper subsidised doxycycline or erythromycin prescriptions over unsubsidised prescriptions for azithromycin.

Although the utility of single dose treatments has not been studied in depth in New Zealand, a pilot study of 50 consecutive clients of a Sexual Health Service receiving chlamydia treatment measured utility of single dose treatment by willingness to pay criteria. Clients were willing to pay up to $60.00 for the convenience of a single dose treatment for sexually transmitted disease (H Moriarty, unpublished data). This implies that collection costs of prescriptions may not be important to patient compliance in practice.

General practices in New Zealand are entitled to keep a limited stock of subsidised pharmaceuticals on a Medical Practitioner Supply Order (MPSO) for emergency use and for patients who are unable to collect the prescription at a community pharmacy. Treatment of Chlamydia from MPSO would enable a practice to ensure that their patient has received the doxycycline/erythromycin prescription, but the price of unsubsidised azithromycin discourages practices from supplying this.

If single dose azithromycin were fully subsidised or available on practitioner supply order, general practitioners would be able to ensure compliance with both collection and consumption of the medicine by administering and directly observing ingestion of this treatment.

This model assumes that treatment will be prescribed to all women who test positive for Chlamydia. Failure to treat proven infections due to loss to follow-up after testing is not included. Inclusion of this consideration would increase the cost per person treated and increase the cost per cure in each treatment arm.

The model assumes that all women will be tested before treatment. The possible scenario of presumptive treatment without testing is not included. Clinical algorithms have been developed for presumptive treatment, and its cost-effectiveness debated in papers previously (Humphreys et al 1992, Marrazzo et al 1997). Genc and Mardh (1996) demonstrated that, in the setting of their model, screening of women prior to treatment with azithromycin becomes more cost-effective than presumptive treatment when the prevalence of Chlamydia in the target population exceeds 6%.

The current model is readily adaptable to include the consideration of presumptive treatment. The effect of inclusion would be to reduce the cost per treatment, increasing the cost per cure in low prevalence populations.

The current model assumes that successful treatment will prevent complications.
Haddix (1995) predicted that risk of pelvic inflammatory disease remains in treated women if salpingitis is established by the time of treatment. Their analysis included costs for 6% of women predicted to develop complications of pelvic inflammatory disease despite adequate treatment. Reduction in acute pelvic inflammatory disease does not imply reduction of salpingitis.
A randomised controlled trial (Scholes et al 1996) showed that the incidence of acute pelvic inflammatory disease in 18-34 year old women can be reduced but not entirely prevented by screening and treatment for Chlamydia. Eschenbach et al 1997 showed that clinical signs are poor predictors of laparoscopic salpingitis. An immune mechanism of tissue injury in salpingitis, mediated by cross-reactive heat shock protein is proposed. Thus some adverse consequences may not be prevented by appropriate antibiotic treatment.

The reversible component of disease is a function of disease natural history. If treatment reverses disease, effective management scenarios should prevent all complications. If treatment does not fully reverse disease, the complication rates for treated women will be increased because of inevitable complications. This will impact equally on all treated women regardless of treatment scenarios.

This model assumes that complications may develop all in women with pelvic inflammatory disease, both those who develop acute symptomatic pelvic inflammatory disease and those who do not. The proportion of pelvic inflammatory disease that is attributable to Chlamydia infection is unknown (Cates and Wasserheit 1991). It can be difficult to recover the responsible microorganism from pelvic tissue, and co-infections confound the search for an aetiological agent (Centres for Disease Control 1991).
Evidence of pelvic inflammatory disease is often an incidental finding during gynaecological investigations. Not all women presenting with complications of pelvic inflammation (tubal infertility, ectopic pregnancy and chronic pelvic pain) give a history of previous acute pelvic inflammatory disease. With ectopic pregnancy only 10% of women have a previous history of pelvic inflammatory disease (Brunham et al 1986). The presence

of positive chlamydia antibodies in women with tubal infertility suggests that chlamydia plays a role in pathogenesis of up to 80% of cases (Brunham 1985).
Any estimates of complications of pelvic inflammatory disease that are based on clinical presentation rates will underestimate sub-clinical cases. It is therefore difficult to determine precisely the probability of developing complications from silent pelvic infection, and estimates for sequelae of Chlamydia pelvic inflammatory disease vary in the literature.

Because of these difficulties, some economic analyses of management of Chlamydia infections have not distinguished between the probability of complications arising from all sub-clinical cases of pelvic inflammatory disease and complications from acute pelvic inflammatory disease alone (Nettleman 1986, Sellors 1992, Magid 1996). Since delayed complications can arise in women who have had either acute or sub-clinical pelvic inflammatory disease, the current model bases costs for management of complications on an estimated probability of sub-clinical pelvic inflammatory disease. If the true probability of pelvic inflammation has been underestimated or overestimated in this model, the impact will apply equally to untreated and treated women and across all management strategies.

Women who present with acute symptoms generate immediate costs for investigation and treatment of acute pelvic inflammatory disease in addition to future costs of management of complications. The probability that women with pelvic inflammation will develop acute symptomatic disease is also unknown. Cases of acute Chlamydia pelvic inflammatory disease are frequently managed in outpatient settings because the clinical presentation of acute Chlamydia pelvic inflammatory disease is less dramatic and less severe than gonorrhoea infection. The current model bases costs for management of acute pelvic inflammatory disease on an estimated probability of acute symptomatic disease. Estimates derived from reported cases or hospital admission for acute pelvic inflammatory disease may be underestimates, biased by the most severe cases.

Genc and Mardh (1996) bypassed the uncertainty in predicting probability of acute and chronic Chlamydia complications by estimating an average cost for any patient needing treatment for a complication of chlamydia infection, but this approach does not acknowledge the relative weighting of costs and frequency of individual complications. The second order Monte Carlo method of modelling lends itself well to modelling of such clinical uncertainties.

This model includes an implicit assumption that management of the contacts of index cases does not generate additional costs to the Health Funding Authority, such as health professional time and travel to trace the contacts. Only the costs of prescription, initial and follow-up consultation and test of cure are included for male partners. If a Practice Nurse is required to contact the male partner, the cost to Health Funding Authority is eleven dollars per hour, pro rata.
Contact tracing may require referred services such as the Public Health nurse, District nurse, or Sexual Health Clinic. As a result, the true cost to the Health Funding Authority of tracing partners of infected women may be understated in this model. If such contact tracing costs were to be included, the resulting increase in cost of treatment would apply equally to both doxycycline/erythromycin and azithromycin treatment scenarios.

Use of the Monte Carlo method has also enabled the uncertainty in partner transmission factors for chlamydia trachomatis to be incorporated into the model. The precise rates at which Chlamydia trachomatis will be transmitted to partners are unknown (Howell et al 1997), and some of the factors influencing transmission rates cannot readily be determined. Mathematical models to describe the spread of sexually transmitted disease have been developed over the years (Hyman and Stanley1989, Hoppensteadt and Peskin 1992, Katz 1992, Brunham et al 1994, Kretzschmar et al 1996). Such theorums are complex, but help to understand and predict the infectious epidemic in the absence of definitive data.

The transmission rates of infectious organisms from one person to the next are influenced by many factors. Infectivity of the micro-organism, frequency of exposure, rate of change of partners, degree of risk in exposure behaviours, duration of the transmissible period and presence of cofactors for transmission of infection are all important as well as any herd immunity and removal from infection pool.

The cofactors for Chlamydia infection include co-infections, pregnancy, cervical ectropion, anatomical abnormalities, and use of non-barrier contraception. Prior infection does not confer upon the host any protective immunity to Chlamydia. Removal from the infectious pool by either spontaneous cure or by death of the host is uncommon, and was not included in the model. Chlamydia trachomatis infections contribute to deaths infrequently as a

complication of ectopic pregnancy and neonatal deaths. Infected infants lost to prematurity or pneumonia do not reduce the size of the adult pool of genital infection.

Some decision analyses have bypassed the need to predict future pregnancy, for estimation of ectopic pregnancy and neonatal infections, by omitting perinatal infections from the model (Nettleman et al 1986). The current model makes assumptions about fertility and fecundity of New Zealand women with the infection. The annual birth rate chosen for this analysis is taken from the lower end of the range of pregnancy rates in women attending STD clinics and higher end in Family Planning clinics (Marrazzo et al 1997). A pattern of early and unprotected sexual activity of New Zealand women is confirmed by several studies (Midland Health 1996). Birth rates among young Maori are approximately 2.5 times higher than the average age specific rates. Intended conception among 20-24 year old women increases the birth rate in this age group to almost three times that of the 15-19 year old age group (MOH 1997).

The role of Chlamydia trachomatis in the aetiology of neonatal complications may have been underestimated in the past. Reports of chlamydia inclusions in pulmonary tissue of deceased foetuses, raises speculation of a role for chlamydia in respiratory distress syndromes of premature infants (Djukic et al 1996). This analysis follows the example of prior analyses (Magid et al 1996, Marrazzo et al 1997) including only the neonatal complications of prematurity, neonatal conjunctivitis and pneumonia.

Large numbers of hypothetical patients (100,000) were required to model prevention of uncommon neonatal sequelae. The current model shows that, from the perspective of the Health Funding Authority, the cost to prevent neonatal complications is much higher than the DRG cost of managing any single neonate. Calculation of the potential savings in neonatal care achieved by each management scenario is an alternative approach to demonstrate treatment cost-effectiveness in the long term. This approach, taken in the current model, shows a trend to increased long term financial benefit in the mean costs with use of LCR diagnostic testing and azithromycin treatment.

The current model performs a cost-effectiveness analysis, reflecting the perspective of cost to the Health Funding Authority in New Zealand. Cost-utility, although not included in this model, would demonstrate the importance of Chlamydia infection and management to the

patient and community, and impact on quality of life. This perspective on utility of health services is of paramount importance in General Practice, as uptake and compliance with services is required for successful delivery of health care. If cost-utility from a patient perspective were included, it would be expected to favour the most acceptable, convenient and effective management regime (azithromycin treatment combined with DNA testing technology).

Only direct medical costs are included in this model. Indirect costs, such as loss of productivity due to illness, constitute a substantial proportion of overall costs of Chlamydia infection (Washington and Katz 1991, Marrazzo 1997). Exclusion from the current analysis is considered justified because indirect costs are not costs to the Health Funding Authority.

Private costs have not been included, as these are also not costs to the Health Funding Authority. Inclusion of private costs would have increased short-term costs of infection management, favouring the treatment giving most rapid cure (azithromycin). Inclusion of the private costs of complications such as ectopic pregnancy infertility and prematurity would significantly increase long-term costs, favouring the most effective management (DNA test technology and azithromycin treatment).

The cost of loss of life is not included in this analysis as it is not a cost to the Health Funding Authority. Chlamydia infections contribute to loss of life through miscarriage, ectopic pregnancies, prematurity and neonatal death, and loss of potential to generate life through infertility. Only the costs to the Health Funding Authority of medical management of these complications in $NZ1997 have been included in this model.
Although loss of life from Chlamydia infection is an uncommon event, inclusion of the cost of even one death would increase complication costs significantly, favouring the most effective treatment regime (azithromycin). The cost of a life in New Zealand for economic purposes was 2.15 million dollars in $NZ1997, when inflation adjusted from the value of two million dollars derived in 1990 (Miller and Guria 1991).
The perverse view on loss of life is that, since patient death spares the Health Funding Authority from future medical care, the resulting medical savings could favour delivery of the least effective treatment.

Potential cost savings from the control of Chlamydia trachomatis in its cofactor role in transmission of other sexually transmitted diseases (including HIV) have not been included. Savings in the prevention of second-generation Chlamydia infection in women (women infected by the male partners of the women in this model) have not been included. If included, these considerations would increase the cost-effectiveness of treatment, favouring the most effective treatment (azithromycin) and the management plan with best long-term cost-effectiveness (use of LCR screening test followed by azithromycin treatment).

This model does not include the cost to deliver test results and treatment instructions to women who require it. Since consultations with a General Practitioner generate a cost to the patient in New Zealand, many practices permit follow-up by telephone, or use Practice Nurses to deliver treatment instructions. Telephone consultations by General Practitioners do not qualify for claims on the General Medical Services benefit. Five or ten minutes of nurse time, at the Practice Nurse salary subsidy of eleven dollars per hour, would increase treatment costs by less than ten percent.
As doxycyline/erythromycin is a more complex regime, involving more doses and longer duration than azithromycin, women given doxycycline/erythromycin may require more nurse instruction time than azithromycin. Inclusion of nurse practitioner time would therefore increase treatment costs of the doxycycline/erythromycin regime above the azithromycin regime.

Amoxicillin has recently been proposed as an acceptable alternative to erythromycin in pregnancy and for gastrointestinal intolerence. The analogue ampicillin is judged inappropriate for Chlamydia from treatment trials, but adequate clinical efficacy to amoxicillin has been demonstrated in double blind randomised trial in pregnancy (Alary et al 1994). The amoxicillin alternative has not included in this analysis as it is not yet recommended treatment for chlamydia.

The results of this particular model apply to sexually active New Zealand women, under the age of 25 years, in the care of General Practitioners. The results do not directly apply to women treated in hospital outpatient clinics, family planning clinics, where health services are funded differently. The results of this model do not apply to males treated in General Practice in New Zealand. However, the model can readily adapted to be transferable to any of these groups of patients and clinical settings.

6.2 Implications for clinical guideline development.

Within the limitations of the methodological considerations discussed above, the following findings from the analysis should be included in any guidelines for the management of genital chlamydia in New Zealand General Practice:

- In the management of this infection in General Practice, the cost of consultations and investigations are greater than the cost of the prescription.
- Single dose Azithromycin (1 Gm stat) is more effective than a 7 day course of doxycycline (100mg BD) for the treatment of genital Chlamydia in women.
- Azithromycin is more cost-effective to the HFA than doxycycline if it carries no prescription subsidy or a subsidy less than $31. Consideration should be given to the cost of this prescription to the patient and the effect this might have on compliance.
- Compliance is a major factor in the cost-effectiveness of treatment in this infection. Cost-effectiveness is greatest when compliance is high. Costs increase when treatment must be repeated. Costly long-term complications result from treatment failure.
- The possibility of pregnancy should be considered for any women not on reliable contraception. Doxycycline is a tetracycline and is still contraindicated in pregnancy. Erythromycin and azithromycin are considered safe bue effective alternatives in pregnancy.
- Erythromycin (800mg BD, 7 days) is less cost-effective than doxycyline. The cost-effectiveness of treatment is sensitive to the percentage of women requiring treatment with erythromycin. Gastrointestinal intolerance, which limits compliance, is common with erythromycin.
- Partners identified through contact tracing should be treated simultaneously with the index case on the strength of the epidemiological evidence. It is not necessary to test them first. Testing partners can delay delivery of effective treatment, risking loss to follow-up, and increasing management costs of the infection.
- A follow-up consultation is advised to determine compliance, reinforce contact tracing, assess risks of re-infection from untreated partners and deliver health education messages.
- There is no difference in cost and little in cost-effectiveness between the new DNA technology-based LCR test or the Elisa test (confirmed by MIF) to detect infection

except in very low prevalence populations. In these circumstances, Elisa/MIF testing is cheaper.

- Testing for cure at the follow-up consultation should not be done routinely. It adds to the cost and reduces cost-effectiveness of treatment. LCR in particular is contraindicated as a test for cure after treatment due to the high false positive return in that setting.

6.3 Implications for pharmaceutical funding policy.

The evidence from this analysis provides arguments for the promotion of prescription of azithromycin by General Practitioners in New Zealand for treatment of genital Chlamydia in women and their sexual partners. This is on the basis of greater cost-effectiveness of azithromycin than the treatments that are currently fully subsidised on the New Zealand Pharmaceutical Schedule.

The recommendation to Pharmac should include the following advice:

- Single dose azithromycin is a more effective General Practitioner prescription for genital chlamydia than the doxycycline or erythromycin regimes, which are currently fully funded on the New Zealand Pharmaceutical Schedule.
- Single dose azithromycin is more cost-effective than doxycycline or erythromycin for General Practitioner treatment of uncomplicated genital Chlamydia in women in New Zealand.
- The cost-effectiveness superiority of azithromycin over doxycycline or erythromycin is rigorous. Azithromycin would remain more cost-effective if it was subsidised up to $31 for a single 1 Gm prescription on the New Zealand Pharmaceutical Schedule.
- Promotion of evidence-based prescribing guidelines for management of Genital Chlamydia in the New Zealand Pharmaceutical Schedule is recommended to ensure cost-effective General Practitioner management, including the non-pharmacological aspects of infection control.

7. Conclusion

Economic evaluation is increasingly used to support decision-making in health (Nuitjen and Starzewski, 1998). Mathematical modelling is emerging as a method to address issues in Medicine that are difficult to apply in the traditional manner by clinical trials (Briggs 1996). It is now recognised that many questions in clinical practice are unanswered by organised research, which is often presented in ways that make it difficult to apply directly into practice (Godlee, 1998).
Traditional clinical trials are too short to demonstrate cost-effectiveness by prevention of those Chlamydia complications, which manifest over a decade or more after infection. Ethical and practical considerations arise in randomised double-blind trials of infectious disease treatment and follow-up. These can be by-passed with modelling. Genital chlamydia is an ideal subject for modelling for these reasons.

Application of Monte Carlo simulation to this particular model has enabled the cost-effectiveness of General Practice management of a particular clinical application, genital Chlamydia, to be determined from the perspective of the Health Funding Authority. This has been possible despite the paucity of research data specific to both General Practice and chlamydia infections in New Zealand.

The Monte Carlo method has enabled generation, from best available published data, of a simulated mean data in the absence of definitive local data. For genital Chlamydia infection in New Zealand women under 25 years of age, treated by general practitioners, a prevalence and 95% confidence interval was able to be generated. The prevalence of Chlamydia infection in New Zealand is unknown although most common among women aged less than 20 years (Connor et al 1997) with incidence declining over 25 years of age, and 82% of reported chlamydia infections occuring in women under 24 years old (Lyttle and Preston 1997). Incidence data underestimate infection in the young age group who are less likely to present to health services. In addition, the population consulting General Practitioners about a possible sexually transmitted infection may differ from the population seen by hospital-based specialist clinics (Johnson et al 1996) as patient selection criteria will differ.

Incompletely studied variables such as behavioural characteristics of this age-group have also been accommodated in this model by use of Monte Carlo simulation.

The implications of Chlamydia infection for the age group modelled are significant, and young people may be more susceptible to complications (Simms et al 1997). Lyttle (1994) suggests that the recent apparent increase in Chlamydia infections in New Zealand is due to increased detection as a result of service development, improved sensitivity of tests and increased screening of cases of non-specific urethritis. If this is the case, it is important to ensure that when the infections are detected the management is both effective and cost-effective.

A number of endpoints have been calculated in this model to measure long term effectiveness, including cost to prevent complications, cost saving from complications averted, mean complication cost per infected person in the community and the total cost of predicted complications has been calculated for each scenario.
The size of the complication cost reflects the burden of unrecognised and untreated infection in the community. The wide confidence intervals in this analysis reflect the influence of the Monte Carlo method at work in the presence of clinical and statistical uncertainty.

The Monte Carlo method could have applications for modelling cost and cost-effectiveness of prescription for other conditions treated by General Practitioners, especially where data on risk is scarce. The potential uses of the methodology also extend to health resource allocation problems in New Zealand. Applications of modelling methodologies with Monte Carlo simulation to assess risk may assist decision-making not only for prescribers but also for health service planners and funders.

This model was designed to examine the influence of utilisation of laboratory tests, pharmaceuticals and General medical Services on the cost and cost-effectiveness of prescribing in General Practice in New Zealand. The construction of this model has provided insight into the many information gaps in the understanding of this infection. Aspects of sexual health behaviours in New Zealand, natural history of the disease, including the health-care seeking behaviours of people at risk and the responses of health service provider, are not well documented. These are arenas for future research to provide assist provide relevant

information to New Zealand policy makers. In addition, an understanding of the cost-effectiveness of General Practitioner management decisions such as testing, treatment and contact tracing provides information to assist development of evidence-based guidelines for management of Genital chlamydia in New Zealand General Practice.

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Appendix

Appendix A. Tables of prevalence and incidence of Chlamydia infection.

Table A1. Chlamydia Prevalence in non-pregnant females: United Kingdom (UK) specialised clinics.

Key: EIA=Elisa test, DFA=immunofluorescence,

Population or clinic	Numbers tested	Location	Prevalence	Test used	Reference
Gynaecology clinic	1267	London	3.6%	culture	Fish et al 1989
Gynaecology clinic	1611	Kent	6.3%	EIA	Edet 1993
Genitourinary Medicine clinic	284	London	20.4%	culture	Oriel et al 1978
Family planning clinic	452	Manchester	7.3%	Culture & some EIA	Macaulay et al 1990
Cervical smear candidates	458	Liverpool	13.3%	EIA & DFA	Hopwood and Mallinson 1995
Family planning clinic	252	Wirral	9.1%	EIA,DFA, Culture	Hopwood et al 1990
Genitourinary Medicine clinic	182	London	29%	DFA	Hay et al 1994
Genitourinary Medicine clinic	796	Bristol	19%	culture	Richmond et al 1980
Colposcopy clinic	101	Glascow	6%	culture	Smith et al 1991

Table A2. Chlamydia prevalence in non-pregnant females- America/Europe.

Key: STD=sexually transmitted diseases, LCR=ligase chain reaction, PCR=polymerase chain reaction, and EIA=Elisa tests,

Population	Described	Location	Prevalence	Test used	Reference
STD clinic attenders	261 consecutive clients	Amsterdam	10%	cervical swabs, PCR and EIA	Ossewaarde et al 1997
STD clinic attenders	544	Vienna	2.5%-2.6%	cervical swabs, various	Ossewaarde et al 1997
Family Planning & Student health		Finland	5.6%	PCR urine	Poukku 1997 (in Paavonen 1997)
Family planning	3,000 women asymptomatic	14 european countries	Varies between 0%-7.6%	PCR urine	Mardh 1997.
Family Planning	1,002	Canada	7%	Culture and EIA	Sellors et al 1992
Student health	191	Canada	4.2%	Culture and EIA	Sellors et al 1992
Family Planning		USA	3.9% - 9.3%		Nelson 1992
Family planning	unstated	USA	8%-40%	Meta-analysis	Cates and Wasserheit 1991
Adolescent Health	1,264 Adolecsents	USA clinics	18.5%-22.7%	culture	Hammer-schlag et al 1993
Disease reports	Cases/head of population	USA- all states	197.5 per 100,000	Mandatory reports	Webster et al 1993
Gynaecol-ogical exam	222 aged 18-25yrs	Denmark	11.2%	LCR	Ostergaard et al 1996
STD clinic	404 patients	Denmark	9.2%	PCR	Ostergaard et al 1997
STD/Family Planning clinic	Cross-section study, 31,025	USA	6.6%	various	Marrazzo et al 1997
In vitro Fertilisation	450 clients prospective	Finland	10%	culture	Van Schouwenberg et al 1992

Table A3. Chlamydia incidence /prevalence in females from general practice in the United Kingdom.

Key: I=incidence, P=prevalence, TOP=termination of pregnancy, GU=genitourinary

EIA=elisa test, DFA=immunofluorescence

Study Population	Description of sample	Location	Prevalence or incidence (P/I)	Test used	Reference
Laboratory specimen	4,028 tests submitted	Lothian	3.5% (I)	EIA	Ross et al 1996
pre-menopausal women	169 women examined by speculum	1 London practice	10.7% (P)	DFA, culture	Longhurst et al 1987
Women for TOP	103 women ages 16-44	4 East London practices	12% (P)	DFA	Southgate et al 1989
Women with GU symptoms	386 women to 65yrs	1 Cardiff practice	6% (P)	DFA	Owen et al 1991
Pre-menopausal women	409 women examined	2 practices SE London	9% (P)	DFA	Oakeshott et al 1992
Cervical smears	197 women up to age 58 yrs	1 Glascow practice	12% (P)	culture	Smith et al 1991
Cervical smears	1255 attending for smear	28 London practices.	3% (P)	EIA	Oakeshott 1995
Cervical smears	287 ages 15-40 for smear	10 Fife practices	2% (P)	DFA	Thompson and Wallace 1994

Table A4. Prevalence of Genital Chlamydia in pregnancy.

Key: EIA=elisa test, MIF=immunofluorescence,

Population studied	Description of sample.	Location	Prevalence	Test used	Reference
Perinatal women	Prospective	San Francisco	2-37%	culture	Schachter et al 1986
Antenatal Clinic clients	Retrospect. case review	Ohio USA	5.75%	MIF	Cohen 1992
Mothers of 264 babies with neonatal problems	Retrospective maternal testing, case-controlled study.	Finland	15%	IgM MIF serology	Gencay et al 1995
Antenatal clinic clients	gestation 10-22 weeks, 178 women	Japan	17.4%	EIA serology	Numazaki et al 1996
Pregnancy Termination clinic	400 women	Swansea England	9%	EIA	Blackwell 1993
Pregnancy Termination clinic	89 women	London England	7.8%	culture	Ridgway et al 1983
Pregnancy Termination clinic	167 women	Liverpool England	11%	culture	Duthie et al 1987
General Practice & Antenatal Clinic	284 women	London	8%	culture	Southgate et al 1983
Caesarian section candidates	52 women	Belgrade	15.4%	culture	Djukic et al 1996
Genitourinary, & Antenatal clinics	252 women	throughout United Kingdom	7%	culture	Wood et al 1984

Appendix B. Treatment efficacy of genital Chlamydia infection.

Table B1 Selected trials of treatment of Chlamydia treatments in women.

Key: r= randomised, c= controlled, db= double blind, nb= not blinded, mc= multicentre, wd= subjects withdrew, LTF= lost to follow-up.

Drug in trial	Dose and duration	Trial type	No.Cured to treated	Test for cure used	Reference
Roxythromycin	300mg daily, 10days	r. c. nb	23/23	culture	van Schouwenberg et al 1992
Doxycycline	100mg BD 10 days	R, c, nb	22/22	culture	van Schouwen-berg 1992
Minocycline	100mg nocte 7days	Db, c,	18/19 (1wd)	culture	Romanowski et al 1993
Doxycycline	100mg BD 7 days	Db, c	20/21 (1wd)	culture	Romanowski et al 1993
Azithromycin	1GM stat	R, c. mc	14/17 (PCR) and 17/17 (culture)	Pcr & culture	Ossewaarde 1992
Doxycycline	200mg daily, 7days	R, c, mc	14/14	Pcr & culture	Ossewaarde 1992
Azithromycin	1GM stat	R, mc, nb	87/89	culture	Martin et al 1992
Doxycycline	100mg BD 7 days	R, mc, nb	76/77 (1 wd)	Culture	Martin et al 1992
Doxycycline	100mg BD 7 days	Mc, nb	6/6	unstated	Johnson and Raymond 1991
Doxycycline	200mg, then 100mg 6/7	Mc,nb	27/38 10 LTF	unstated	Johnson and Raymond 1991
Azithromycin	1Gm stat	MC, nb	34/35	unstated	Johnson and Raymond 1991
Azithromycin	1Gm stat	nb	68/73 3 LTF	‘’	Johnson and Raymond 1991
Azithromycin	500mg BD	nb	22/22	‘’	Johnson and Raymond 1991
Azithromycin	500mg then 250mg2/7	nb	20/20	‘’	Johnson and Raymond 1991
Doxycycline	100mg BD 7 days	nb	59/64 5 LTF	‘’	Johnson and Raymond 1991
Azithromycin	500mg then 250mg2/7	Mc, nb	30/43 12 LTF	unstated	Johnson and Raymond 1991
Doxycycline	100mg BD 7 days	Mc, nb	36/39 1 LTF	varied	Johnson and Raymond 1991
Azithromycin	1Gm stat	Mc, nb	49/66 17 LTF	varied	Johnson and Raymond 1991
Azithromycin	1Gm stat		32		Lassus 1990
Azithromycin	500mg then 250mg2/7		31		Lassus 1990
Doxycycline	100mg BD 7 days		32		Lassus 1990
Erythromycin	500mg QID	R, db	87/99, 12wd	culture	Alary et al 1994
Amoxycillin	500mg TDS	R, db	98/100, 1wd	culture	Alary et al 1994

Table B2 Approach to clinical efficacy in prior cost-effectiveness analyses.

Key:

C= estimated client compliance rates,

F= clinical follow-up assessment,

S= side effects limiting complience,

P= prescription appropriateness,

R= re-infection risk from untreated partners,

*= compliance adjustment included in estimate of efficacy.

Authors	Drug used	Treatment efficacy range	Other factors modelled
Nuovo et al 1995	Azithromycin Doxycycline Erythromycin	0.88-0.99* 0.82-0.99* 0.77-0.91*	Unstated .. ..
Haddix et al 1995	Azithromycin Doxycycline	0.965 0.965	C, F.
Magid et al 1996	Azithromycin Doxycycline	0.94-0.98 0.8-0.9	C, F, S.
Genc and Mardh 1996	Azithromycin Doxycycline	0.95-1.0 0.95-1.0	C, F,
Marrazzo et al 1997	Doxycycline	0.95	C,S
Wellington Chalmydia Model 1998.	Doxycycline Erythromycin Azithromycin	0.99 0.90 0.86	C, F,S,P,R

Appendix C. Processes of the analysis.

C.1 Example of baseline analysis.

The following five pages are a printout of the mathematical steps of scenario 1d. This scenario entails testing with Elisa/MIF, treatment with doxycycline (or erythromycin where contraindicated) and testing for cure with MIF.

C.2 Explanation of use of Spearman rank correlation coefficients.

In this modelling project the factors which influence the cost-effectiveness of prescribing, and the relationship of those variables to the cost-effectiveness of prescribing are of integral importance.

It is the correlation, the degree of the relationship between variables and outcomes, which is of especial interest in the interpretation of the results of this analysis.

It becomes necessary to measure the correlation in order to determine in a quantitative manner how these results inter-relate.

When precise values for variables are not available, the data may be ranked in order of size of effect or importance. To compare results from a Monte Carlo simulation ranking is necessary, as there is no single figure output value from this methodology.

Spearmans formula for rank correlation between two variables X and Y relates differences between ranks of corresponding values of X and Y to the number of pairs of values (X,Y) in the data.

Values of the correlation coefficient vary between –1 and +1. The signs +/- are used for positive and negative linear correlation.

In the context of this analysis a high correlation coefficient, either –1 or +1, implies direct dependence of the variables which are being compared.