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Chlamydia trachomatis in Adolescents and Adults

Clinical and Economic Implications

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Summary

The aim of this article is to provide an overview of the epidemiology, diagnosis, screening and pharmacotherapy of *Chlamydia trachomatis* infections in adolescents and adults, together with a critical review of economic studies published on this topic.

C. trachomatis continues to produce enormous social and economic consequences despite advances in prevention, screening and treatment. Both infected men and women are at risk of developing sequelae, although women tend to have more serious complications. Several strategies are available for diagnosis and screening.

In populations with a high prevalence of disease, DNA-amplification assays may be the most cost-effective approach for diagnosis and screening. Empirical treatment of all patients is also cost effective; however, it may not be feasible for all health systems. A single dose of azithromycin is the most cost-effective antimicrobial agent for treatment of *C. trachomatis* infection.

Chlamydia trachomatis is the most commonly reported bacterial sexually transmitted disease in the world and the most frequently reported of all notifiable diseases in North America.[1-3] As a result of its widespread prevalence and significant morbidity, *C. trachomatis* continues to produce enormous social and economic costs. Despite newer therapies, diagnostic and screening techniques, and prevention strategies, *C. trachomatis* remains a significant public health concern.

Although there have been several recent review articles on the diagnosis and treatment of chlamydial infection, a critical review that amalgamates clinical concerns with the economic impact of this disease has not been published. Therefore, the purposes of this article are to provide: (i) an overview of the epidemiology, clinical spectrum, diagnosis, screening, prevention and treatment of urogenital *C. trachomatis* infection in adults; (ii) an overview of the economic impact of this disease; and (iii) a comprehensive review of economic studies on the screening and treatment of *C. trachomatis* infection.

A MEDLINE search was conducted from 1966 to 1997 using key phrases '*Chlamydia trachomatis*', 'sexually transmitted diseases' and 'economics'. Further articles were identified from a manual search of the bibliographies of identified articles. Only landmark (clinical trials that have had a significant impact on treatment and diagnostic decision-making as determined by the authors) peer-reviewed articles and review articles from key sources [peer reviewed medical journals or reviews from organisations such as the World Health Organization (WHO) and the Centers for Disease Control (CDC)] were considered. All identified peer-reviewed economic studies were incorporated into the review.

1. Epidemiology

Over the last decade, the incidence of reported *C. trachomatis* infection has increased dramatically from 3.2 cases per 100 000 population in 1984 to 188 cases per 100 000 population in 1994.[1,2] This trend probably reflects improvements in screening, recognition of asymptomatic infection and reporting, rather than a true rise in the incidence of the disease. Indeed, some reports published after 1994 suggest a slow decline in the incidence of *C. trachomatis* infections, although this is usually in settings where control efforts are clearly in place.[4-7] In the US, the exact number of individuals with reported *C. trachomatis* infection was unknown until 1996 when the CDC reported an annual incidence of 477 638 men and women with this disease.[1,8]

Numerous studies from North America,[9-12] the UK[13-17] and Europe[18-21] have shown that the prevalence of *C. trachomatis* infection in adults and adolescents ranges from 2 to 12%. These studies have also shown that age is the most important

predictive sociodemographic factor, with the highest incidence occurring among sexually active women below the age of 25 years. Prevalence rates in this group of young women may be as high as 10%, since many of these young women are asymptomatic and their infections go untested and untreated. A higher prevalence is also associated with single marital status, nulliparity, lower socioeconomic status, multiple sexual partners and concurrent *Neisseria gonorrhoeae* infection.

Chlamydial control efforts for women are hampered by a number of factors, including underdiagnosis and undertreatment of male sexual partners.[6,7] The exact incidence of chlamydial infection in men is unclear, but a prevalence between 8 and 20% has been shown in asymptomatic men and adolescent boys, or men attending sexually transmitted disease (STD) clinics.[22-26] Similar to predictive factors in women, young age, multiple sexual partners and concurrent *N. gonorrhoeae* infection correlate well with *C. trachomatis* infection.[22,23]

Morbidity and long term consequences of *C. trachomatis* infection are more significant in women then men. Between 10 and 40% of women infected with *C. trachomatis* will experience pelvic inflammatory disease (PID),[27] and current statistics indicate that approximately 1 million cases of PID are diagnosed annually in the US.[27] The importance of the relationship of *C. trachomatis* to PID is underscored by the fact that dramatic reductions in the incidence of *N. gonorrhoeae* and *C. trachomatis* infections in Sweden have correlated with impressive declines in PID morbidity and associated costs.[28,29]

2. Prevention Strategies

Because *C. trachomatis* infections are not commonly associated with overt symptoms and are associated with significant morbidity and mortality, the CDC recommends: (i) promoting behavioural changes that reduce the risk of acquiring or transmitting *C. trachomatis* infection (i.e. delaying age at first intercourse, decreasing the number of sexual partners, careful partner selection and use of barrier contraception); (ii) identifying and treating individuals with chlamydial infection before they can infect sexual partners; (iii) identifying and treating pregnant women before they can transmit the infection to their fetus; and (iv) identifying and treating women before they develop PID and its sequelae.[2]

Table I. Patient groups in whom a *Chlamydia trachomatis* screening test should be performed (derived from Centers for Disease Control and Prevention)[2]

Women with mucopurulent cervicitis
Sexually active women under the age of 20 years
Women between 20 and 24 years of age who display inconsistent use of barrier contraception or have had more than 1 sexual partner during the last 3 months
Women over 24 years of age who display inconsistent use of barrier contraception and have had more than 1 sexual partner during the last 3 months
All women under the age of 20 years who are undergoing a pelvic examination, unless sexual activity since the last test for *C. trachomatis* has been limited to a single, mutually monogamous partner
Women attending sexually transmitted disease clinics
Sexually active adolescents
Pregnant women during their third trimester
Women who undergo an abortion
Women who have been sexually assaulted
Women and children who have been sexually abused

Since *C. trachomatis* infection is especially prevalent among adolescents, and morbidity associated with this infection is far greater in women than men, the CDC recommends screening sexually active female adolescents and adult women, in whom the prevalence rate is 5% or greater.[2] This includes: prison inmates; women attending STD, family-planning and prenatal clinics; and women and children who are sexually assaulted or abused (table I).

There is controversy in the literature over whether *C. trachomatis* testing is necessary in patients with conditions that may be caused by *C. trachomatis* [i.e. mucopurulent cervicitis (MPC), PID and urethral syndrome in women, or urethritis and epididymitis in men], gonococcal infection and partners of individuals known to be positive for *C. trachomatis*. The CDC currently recommends treating these patients presumptively (i.e. without

waiting for test results) in order to relieve symptoms and/or to prevent complications.[2]

3. Clinical Spectrum

3.1 Chlamydial Infections in Women

The most common manifestation of *C. trachomatis* infection in women is MPC. Although the condition is asymptomatic in as many as 50% of women,[30-32] it may be characterised by a yellow endocervical discharge, postcoital vaginal bleeding and a friable, easily bleeding cervix. Other clinical manifestations of lower genital tract chlamydial infections include acute urethral syndrome and proctitis.[2,30]

Approximately 10% of cervical chlamydial infections ascend to the upper genital tract.[33] If not adequately treated, 20 to 40% of women infected with *C. trachomatis* develop PID, which can lead to ectopic pregnancies (10%), infertility (17%) and chronic pelvic pain (17%).[2,34-36] The clinical spectrum of chlamydial PID ranges from subclinical endometritis and salpingitis to overt endometritis, salpingitis, pelvic peritonitis and perihepatitis (FitzHugh-Curtis syndrome).[2,34] The major presenting complaint of symptomatic PID is lower abdominal pain, which often coincides with the onset of menses, mucopurulent cervical discharge, uterine and adnexal tenderness and cervical motion tenderness. Unfortunately, symptomatic PID that produces laparoscopically detectable salpingitis accounts for less than 25% of the total number of cases; more than 50% of infertile women with serological evidence of chlamydial infection have not experienced any symptoms of PID in the past.[2,34-36]

3.2 Chlamydial Infections in Men

In men, *C. trachomatis* is a common cause of nongonococcal urethritis (NGU) [23 to 55%].[2] Compared with gonococcal urethritis, chlamydial urethritis is more likely to be asymptomatic. Clinical symptoms, when present, consist of mild dysuria, and a white, grey or clear discharge.[37] Approximately 1 to 2% of men with symptomatic NGU develop epididymitis, which usually presents with unilateral scrotal pain, scrotal swelling, tenderness and fever.[30,38,39]

Chlamydial infection in men can also cause acute prostatitis and proctitis.[30] Symptoms of acute prostatitis include perineal pain, dysuria, increased urinary frequency and urethral discharge. *C. trachomatis* proctitis occurs in men practising receptive anal intercourse, and is characterised by anorectal pain, tenesmus (rectal sensation of incomplete defaecation), bleeding and rectal discharge. Long term complications of chlamydial infection in men are rare and include Reiter's syndrome, a clinical syndrome consisting of reactive polyarthritis, tenosynovitis, uveitis and urethritis.[30,40]

4. Diagnostic and Screening Laboratory Tests

Diagnostic methods for detecting *C. trachomatis* can be subdivided into culture and nonculture techniques. Isolation of *C. trachomatis* from cell culture has been the 'gold standard' for a number of years. However, several tests that do not require culture for detection of *C. trachomatis* have been made commercially available over the last decade. These tests are based on: (i) antigen detection by direct fluorescent antibody (DFA) staining and enzyme immunosorbent assay (EIA); (ii) detection of chlamydial nucleic acid including ribosomal RNA detection by hybridisation with a DNA probe and detection of chlamydial DNA by amplification with polymerase chain reactions (PCRs) or ligase chain reactions (LCRs); (iii) detection of the enzyme leucocyte esterase (LE) in urine; or (iv) serological tests.

Numerous studies have been published, which have compared the culture and nonculture detection methods for *C. trachomatis* and a recent comprehensive review is available.[41] Therefore, we have provided an overview of the tests that are appropriate to use for diagnosis and screening of high- and low-prevalence populations, based on the sensitivity and specificity of the nonculture tests, compared with cell culture (table II).

4.1 Cell Culture

Table II shows the techniques involved, the time to obtain a result, specificity and sensitivity, and advantages and disadvantages of the cell-culture method and various nonculture methods that are used to detect urogenital chlamydial infection in adults. The advantages of the cell-culture method are its high specificity (100%)[42] and its ability to detect only viable chlamydial organisms. The advantage of this technique is that it can be used as a diagnostic tool for low-prevalence populations and in medicolegal issues, such as cases of suspected sexual assault or child abuse.[2]

The cell-culture method has also been evaluated for its sensitivity and specificity with a number of different specimens, and can be used for urethral specimens from women and asymptomatic men, nasopharyngeal specimens from infants, rectal specimens from all patients and vaginal specimens from prepubertal girls.[2]

Although culture continues to play a role in the diagnosis of *C. trachomatis* infection, its use is limited because of many disadvantages, including low sensitivity (70 to 85%), the necessity for a high level of technical expertise, the requirement for cold transportation of specimens, the long time required to obtain results (3 to 7 days) and the high cost required to perform the test.[43]

4.2 Nonculture Tests

A variety of nonculture tests to detect *C. trachomatis* has evolved over the last several years in response to the difficulty in applying cell culture clinically (table II). These tests not only prevent the restrictions that tissue-culture isolation places on the processing of clinical specimens, but also overcome the technical difficulties associated with cold transportation and maintaining a tissue-culture assay. In addition, because nonculture tests do not require strict handling of specimens, they may be easier to perform and are generally less expensive than cell-culture testing.[2]

Antigen-detection methods and non-nucleic acid amplification technologies such as DFA, EIA and DNA hybridisation probe are the most accessible and rapid tests for high volume laboratories. Authors of most studies that have evaluated these tests have reported sensitivities above 70% and specificities of 97 to 99% in individuals from high-prevalence groups (>5% infected), women with endocervical chlamydial infection and men with urethral chlamydial infection. In men and women from groups with a low prevalence of *C. trachomatis* infection (□5%) and in patients with rectal chlamydial infection, a significant proportion of the tests will be falsely positive.[41] For this reason, the most recent guidelines from the CDC recommend that all positive nonculture test results from individuals in low-prevalence populations need to be confirmed.[2] The recommended methods of confirming a nonculture assay include performing a culture test, a second nonculture test that identifies a different target from the one used for the first test, or using a blocking antibody for EIA or competitive probe for the DNA hybridisation probe tests. If the population has a high prevalence of infection, initial positive results do not need to be confirmed.[2]

The guidelines for diagnostic and confirmatory testing in low-prevalence populations do not apply to the recently introduced nucleic acid amplification methods with polymerase chain reaction (PCR) or LCR. Since the specificity of both the PCR and LCR tests is above 99%, the positive predictive value of these tests is high in both low- and high-prevalence populations, and confirmatory testing is currently not recommended.[2] An added advantage of these DNA-amplification tests is that they are very sensitive even when noninvasive specimens are used to screen asymptomatic men and women.[41] DNA-amplification tests using noninvasive sampling have been reported to improve detection rates by as much as 30% compared with current screening tests that use invasive sampling, as a result of increased sensitivity.[41]

The leucocyte esterase (LE) test has limited clinical utility for detecting *C. trachomatis*. The LE test is a rapid dipstick test for use with urine specimens. Studies have shown that the sensitivity

Table II. Laboratory diagnosis of *Chlamydia trachomatis*

Laboratory test	Technique	Time	Spec. (%)	Sens. (%)	Disadvantages	Advantages
Cell culture						
Culture	1. Specimens inoculated onto cell culture monolayers 2. Chlamydial elementary bodies infect cells and form cytoplasmic inclusions 3. These are visualised following incubation (48-72 hours) either by staining with fluorescein-labelled antibody, which binds to chlamydial LPS layer or major outer membrane protein (MOMP), or by species-specific anti-MOMP fluorescein-labelled monoclonal antibody	3-7 days	100	70-85	1. Specimens need to be refrigerated (2-8°C) for transport and storage 2. Freezing specimens (–70°C) until processing results in 20% loss of viable organisms 3. Processing of specimens should be within 48 hours of collection 4. Decreased sensitivity 5. High level of expertise needed 6. Increased time required to obtain results	1. Preserves organism for genotyping or antimicrobial susceptibility testing 2. Detects only viable infectious chlamydial elementary body 3. Minimal potential for contamination 4. Specimens collected from endocervix, vagina, rectum, urethra and nasopharynx have all given good sensitivity/specificity results
Antigen detection methods						
Direct fluorescent antibody (DFA)	Direct visualisation of C. trachomatis by staining with fluorescein-labelled specific antibody	30 min.	98-99[a]	89-90[b]	1. Highly trained personnel required 2. Microscopic evaluation of each specimen is intensive and laborious 3. Used primarily for endocervical smears	1. Rapid 2. No refrigeration of specimens required during transport 3. Not dependent on viable organisms
Enzyme immuno-sorbent assay (EIA)	1. Immunohistochemical detection of genus-specific LPS antigen (direct EIA) followed by a secondary enzyme-linked IgG antibody 2. The conjugated enzyme either converts a colourless substrate to a coloured product, which is read by a spectrophotometer, or a fluorescence-generating substrate to a signal detected by a fluorescence reader	3-4 hours	97[c]	85[d]	1. Specificity without the blocking assay is low as a result of antibodies to LPS cross-reacting with other Gram-negative bacteria (false positives); thus, EIA cannot be used without the blocking assay for low-prevalence populations 2. Not useful for urine specimens because of lack of sensitivity	1. Rapid 2. Refrigeration of specimens not required during transport 3. Not dependent on viable organisms
Rapid tests	1. Employ EIA technology 2. Detection of genus-specific LPS antigen	30 min.	95	70	1. Specificity is low as a result of antibodies against LPS cross-reacting with other Gram-negative bacteria (false positives) 2. Less sensitive and specific then laboratory-performed EIA	1. Rapid 2. Performed in physician's office 3. Refrigeration of specimens not required during transport 4. Not dependent on viable organisms 5. Highly trained personnel not required

Nucleic acid detection methods						
DNA hybridisation probe	1. Uses chemiluminescent DNA probe 2. Probe hybridises to a species-specific sequence of chlamydial 16s ribosomal RNA (rRNA) 3. A DNA-RNA hybrid is formed, absorbed onto a magnetic bead and the chemiluminescent response is detected with a luminometer	2-3 hours	98-99[e]	85	1. Highly trained personnel required 2. Less sensitive than DNA amplification tests 3. Positive results in low prevalence populations need to be confirmed by the probe competition assay	1. Can be used in conjunction with a probe for detection of *N. gonorrhoeae* so that only 1 sample is required 2. No refrigeration of specimens required during transport 3. Not dependent on viable organisms
Nucleic acid amplification by polymerase chain reaction (PCR)	1. Two oligonucleotide primers with sequences complementary to a specific segment of *C. trachomatis* DNA are added to specimens 2. The primers are hybridised to the DNA template and extended with the use of DNA polymerase 3. Multiple cycles of this process results in logarithmic amplification of *C. trachomatis* DNA 4. PCR products detected by electrophoresis/colorimetric probe assay, and staining with DNA-intercalating fluorescent dye	3-4 hours	98	94	1. False negatives are a problem because of substances present in clinical specimens, which inhibit the polymerase reaction 2. Not useful for female urine specimens because of lack of sensitivity 3. Test not dependent on viable organisms; thus, it is vulnerable to contamination with persisting nucleic acid residues	1. Refrigeration of specimens not required during transport 2. Approved for cervical, male urethral, male urine specimens
Nucleic acid amplification by ligase chain reaction (LCR)	1. Four oligonucleotide probes recognise and then adhere to *C. trachomatis* DNA at specific target sites 2. Each pair of probes hybridise close together on the DNA 3. The gap is filled by DNA polymerase and closed by the ligase enzyme 4. Multiple cycles of this process result in logarithmic amplification of *C. trachomatis* DNA 5. LCR is detected by an immunocolorimetric-based bead-capture system	30 min	99	94	See PCR	See PCR (the 2-step process of closing the gap with DNA polymerase and the ligase enzyme make this technique more specific than PCR)
Leucocyte esterase (LE) method						
LE test	1. Dipstick test to detect enzymes produced by polymorphonuclear cells (inflammatory cells that accumulate in urine during an infection) 2. Dipstick holds an absorbent purple patch containing indoxylcarbonate ester, which forms a purple colour when hydrolysed by LE	5 min	85	60	1. Test can diagnose urethritis, but not the specific cause; thus, a positive test requires specific testing for *C. trachomatis* or *N. gonorrheae* infection 2. Does not have adequate sensitivity for specimens from women and older men	1. Noninvasive 2. Uses urine as specimen 3. Only adequate sensitivity for urine specimens from adolescent men

a High specificity with the use of monoclonal antibody reagents which are directed against LPS and MOMP antigens. Initial reagents were polyclonal and nonspecific (i.e. cross-reacted with other Gram-negative bacteria).

b Sensitivity lower with urethral specimens than endocervical (□70%).

c Specificity increases to 99% when blocking assays to verify positive EIA results are performed. These assays involve repeating the EIA with monoclonal antibodies specific for *C. trachomatis* LPS layer.

d Varies according to assay and type of specimen.

e Although specificity is high, a confirmatory assay is available which is based on probe competition (similar to EIA and the blocking antibody test).

Abbreviations: LPS = lipopolysaccharide; Sens. = sensitivity; Spec. = specificity.

and specificity of this test are low (31 and 83%),[41] except when the test is used for adolescent men. Because further studies are required to assess its usefulness, the LE test is not recommended for use in older men or in women as a *C. trachomatis* screening test.

Serological tests designed to detect chlamydial antibodies include microimmunofluorescence (MIF), indirect immunofluorescent antibody (IFA), complement fixation (CF) and enzyme-linked immunosorbent assay (ELISA). These tests are laborious, require a high level of technical expertise and are of little value in the routine clinical care of patients with *C. trachomatis* genital infection, since the antibodies to this organism are long lived and a positive test will not distinguish active infection from previous contact.

With the availability of a wide array of nonculture tests, many STD clinics and laboratories have been faced with making a decision with respect to the most cost-effective strategy for the diagnosis and screening of *C. trachomatis*. Clinicians recognise that while DFA, EIA and DNA hybridisation probe offer advantages for widespread specimen screening, higher costs are associated with the confirmatory testing that is required when testing asymptomatic men and women and low-prevalence populations. In contrast, PCR and LCR, which do not require confirmatory testing, are more expensive than cell culture; however, they also have higher sensitivities than the traditional 'gold standard' method and do not require invasive specimens to be used. Thus, noninvasive specimens, such as urine, could be used for high volume screening of asymptomatic individuals and low prevalence populations, and for diagnostic testing in symptomatic patients. In addition, the higher sensitivity and increased screening using noninvasive specimens may capture more asymptomatic women with *C. trachomatis* infection, thereby preventing PID and its sequelae, and decreasing costs associated with this disease.

5. Pharmacotherapy

The CDC currently recommends treating: all patients with a positive *C. trachomatis* test, as well as presumptively treating women with MPC, PID or urethral syndrome; men with urethritis or epididymitis; men and women with a gonococcal infection; and partners of patients known to be positive for *C. trachomatis*.[2] Treatment of infected patients is warranted to: relieve symptoms; prevent complications and morbidity; prevent transmission to sexual partners, which in turn prevents transmission to other partners and reinfection of index patient. For pregnant women, treatment of chlamydial infection prevents transmission to infants during birth, thus avoiding pneumonia and neonatal conjunctivitis.

In most countries, the current drugs of choice for the treatment of *C. trachomatis* infection in adolescents, adult men and nonpregnant women are doxycycline and azithromycin (table III).[2,44] Second-line antimicrobial agents include ofloxacin, erythromycin, tetracycline and sulfamethoxazole.[2,44] The drug of choice for pregnant women is erythromycin. Alternatives to erythromycin in pregnancy are amoxicillin (all trimesters) and sulfamethoxazole (first and second trimester).

5.1 Tetracyclines

Before 1993, tetracyclines were the first-line agents for the treatment of *C. trachomatis* infection. Clinical trials evaluating tetracycline,[45-48] minocycline[49,50] and doxycycline[51-56] showed efficacy rates ranging from 83 to 100%. Nausea and vomiting were the most common adverse effects associated with tetracyclines, and occurred more commonly with doxycycline than tetracycline or minocycline.

Administration of tetracyclines during the second or third trimester of pregnancy can cause tooth discoloration or inhibition of bone growth in infants.[57] Therefore, these agents should be avoided in pregnant and lactating women with chlamydial infection.

Table III. Recommendations for management of *Chlamydia trachomatis* infection[a]

	Recommended	Alternative
Adolescents and adults	Doxycycline 100mg 12-hourly (□ 7 days)	Ofloxacin 300mg 12-hourly (□ 7 days)
	Azithromycin 1g single dose	Erythromycin base 500mg 6-hourly (□ 7 days)
		Erythromycin ethylsuccinate 800mg 6-hourly (□ 7 days)
		Sulfamethoxazole 500mg 6-hourly (□ 10 days)
Pregnant women	Erythromycin base 500mg 6-hourly (□ 7 days)	Erythromycin base 250mg 6-hourly (□ 14 days)
		Erythromycin ethylsuccinate 800mg 6-hourly (□ 7 days)
		Erythromycin ethylsuccinate 400mg 6-hourly (□ 14 days)
		Amoxicillin 500mg 8-hourly (□ 7-10 days)

a Derived from Centers for Disease Control and Prevention. Recommendations for the prevention and management of *Chlamydia trachomatis* infections.[2]

5.2 Erythromycin

Erythromycin has similar *in vitro* activity against *C. trachomatis* to that of the tetracyclines.[47,48,58] Comparative clinical trials evaluating erythromycin base or various salts for 7 to 14 days show efficacy rates of 63 to 100% in men and 66 to 100% in women.[47] In addition, investigators evaluating the 1 g/day dosage versus 2 g/day of erythromycin reported better efficacy rates with the higher dose. However, 2 g/day of erythromycin was also frequently associated with more gastrointestinal adverse drug reactions, which limited compliance.[47,59,60]

Hepatotoxicity from erythromycin salts is increased in pregnant women.[57] This toxicity is more likely to occur with the estolate form than with other preparations, and should therefore be avoided in pregnant women.[57,61] The safety of erythromycin base has been established in pregnant women and therefore is the drug of choice.[62]

5.3 Azithromycin

Azithromycin is an azalide antibacterial that has recently been marketed for the treatment of uncomplicated *C. trachomatis* infections. This new antimicrobial agent has excellent *in vitro* activity against *C. trachomatis* (MIC 0.03 to 0.25 mg/L), achieves high tissue concentrations after oral administration and has a long tissue half-life (approximately 3 days), which allows for single-dose treatment.[63,64]

Clinical studies have demonstrated that the efficacy of a single 1g oral dose of azithromycin is similar to that of doxycycline 100mg orally twice daily for 7 days.[51-56] Toxicities were also similar between azithromycin and doxycycline, with diarrhoea, nausea and abdominal pain being the predominant adverse effects with both agents.

The safety of azithromycin in pregnant women with *C. trachomatis* has not been clearly established. Although animal studies have not shown any fetal damage with the use of azithromycin, its use in pregnancy is recommended only if symptoms persist or reinfection is suspected because of treatment failure.[65]

5.4 Ofloxacin

Unlike ciprofloxacin, ofloxacin has excellent *in vitro* activity against *C. trachomatis*, with MICs ranging from 0.5 to 2 mg/L.[64] Clinical studies have shown that ofloxacin at doses between 200 and 400mg twice daily for 7 to 10 days is as efficacious as doxycycline 100mg orally twice daily for 7 days.[66-71] The treatment success rates among these studies ranged from 97 to 100% for men with urethritis and women with cervicitis. Adverse reactions of ofloxacin therapy include rash (1%), pruritus (1%) and anaphylactoid reactions (<0.001%).

Like all fluoroquinolones, the use of ofloxacin in pregnant women is contraindicated, since its safety has not been established in this population.[72]

5.5 Pregnant Women

Tetracycline, doxycycline, erythromycin estolate, azithromycin and ofloxacin should be avoided in pregnancy because of potential toxicity to the fetus or a lack of information in this population. A 7-day course of erythromycin ethylsuccinate (400mg orally 4 times daily) administered to women who were in their 36th week of pregnancy with *C.trachomatis* infection achieved a cure rate of 92%.[73] A similar trial evaluating erythromycin 1g daily versus 2g daily in 91 pregnant women with culture-proven *C. trachomatis* showed cure rates of 95 and 92%, respectively.[74] The higher dosage (500mg orally 4 times daily) may be associated with gastrointestinal intolerance, in which case the lower dosage (250mg orally 4 times daily) may be used for 14 days.

Amoxicillin may also be used in pregnancy if the woman cannot tolerate erythromycin. Crombleholme et al.[75] conducted a study comparing amoxicillin (500mg orally 3 times daily) with erythromycin (500mg orally 4 times daily) for 7 days in pregnant women.[75] The cure rate for amoxicillin was 99%, compared with 93% with erythromycin. Amoxicillin was better tolerated than erythromycin, with only 2 women (2%) discontinuing treatment because of adverse drug reactions compared with 14 women (16%) in the erythromycin group. However, a more recent study evaluating the efficacy of amoxicillin in pregnant women with chlamydial infection in comparison with erythromycin showed an efficacy of 86% for amoxicillin compared with 94% for erythromycin.[76] The data from this recent study as well as *in vitro* evidence suggesting incomplete inhibitory effects of the □-lactams on *C. trachomatis* has placed amoxicillin as a second-line agent for treatment of *C. trachomatis* in pregnancy.[77]

5.6 Compliance

There are few data in the literature regarding compliance with antibacterials for treatment of *C. trachomatis* infections. Authors of 2 recent reports of compliance with doxycycline – electronically measured with a Medication Event Monitoring System (MEMS) – reported noncompliance rates of 70% with doxycycline.[78,79] These rates are higher than self-reported noncompliance rates, which were 44%.[78,79]

There are no published data with respect to compliance with ofloxacin; however, compliance rates should be similar to those reported for recipients of doxycycline, since both regimens are administered twice daily for 7 days.

High dosages of erythromycin (2g daily) are poorly tolerated; up to 71% of patients develop adverse reactions while receiving such dosages, which could be a contributing factor to noncompliance.[59] Compliance with azithromycin can only be assumed to be 100% if the 1g single dose is administered under the supervision of a healthcare professional.

6. Economic Impact

As a result of the frequent and serious sequelae, the socioeconomic burden of *C. trachomatis* infection is enormous. Unfortunately, the lack of successful prevention and control strategies in many parts of the world means that these costs continue to escalate.

The enormity of the costs associated with *C. trachomatis* infection were first outlined in a well-designed, cost-of-illness study by Washington et al.,[80] who estimated the total direct and indirect costs of *C. trachomatis* infections in men, women and infants in the US, from national, state and locally derived data.[80] In this analysis, direct costs included those specifically incurred in the treatment of *C. trachomatis* infections and its sequelae, whereas indirect costs were estimates of lost productivity. Although this analysis used medical charge data to estimate costs and several assumptions for the computation of indirect costs, the authors believed that their overall annual estimate of $US1.4 billion (1987 values) was conservative. The reasons for this opinion included the use of the lower end of the range of costs for the treatment of each condition, the fact that the costs of treatment of several sequelae in men and infants were omitted

and the failure to include the costs of psychosocial effects (i.e. quality of life). Based on this study, the most current estimate of the annual direct and indirect costs of treating *C. trachomatis* infections and their sequelae in the US is over $US2.4 billion (1993 values).[2]

Several economic studies have been conducted to evaluate the cost effectiveness of various follow-up, screening and treatment strategies, including:

- routine versus selective screening
- different types of screening techniques
- prenatal testing
- field follow-up
- test of cure
- empirical versus laboratory-confirmed treatment of *C. trachomatis* infection
- various antimicrobial treatment strategies.

These studies are summarised in tables IV to VII. The authors of most of these studies have used decision analysis. This technique has been defined as a process that quantifies both the likelihood and the valuation of the expected outcomes associated with competing alternatives.[81] A detailed overview of the use of decision analysis in economic studies has been published elsewhere.[82]

6.1 Routine Versus Selective Screening

The clinical effectiveness of routine screening in reducing the incidence of chlamydial infection has been demonstrated by authors of several European and North American studies.[83-86] However, only 2 studies have been conducted to evaluate the cost effectiveness of selective versus routine/universal screening procedures (table IV).[87,88]

The earliest study was conducted by Trachtenberg et al.[87] who used a predictive model to estimate the cost effectiveness of DFA screening versus no screening of all women who attended a family planning clinic (cohort of 400 000) at the time of their annual Papanicolaou smear.[87] The assumptions used in this analysis included a 98% specificity and a 90% sensitivity of the DFA test, and a 9.8% baseline rate of *C. trachomatis* infection (i.e. a high-prevalence population). The treatment strategy employed in this model was doxycycline 100mg orally twice daily for 7 days for *C. trachomatis*–positive patients and their partners; the effectiveness of this regimen was assumed to be 95%. The perspective of this study was that of a third-party payer and only direct medical care costs were considered.

This analysis[87] showed that regular screening of women would eradicate 33 516 *C. trachomatis* infections, prevent 8379 cases of PID, 335 cases of ectopic pregnancy and 1760 cases of tubal infertility, which would result in an annual cost saving of $US13 million (1987 values). Extensive sensitivity analyses were employed to determine the effects of changing several of the key assumptions used in the model. The model was robust to these variations across a range that was clinically feasible. Shortcomings of this study included the use of charges to estimate costs and failure to account for the clinical impact that noncompliance with the doxycycline regimen would have on clinical outcome.

The most recent study was conducted by Marrazzo et al.[88] Their goals in this study were to develop and test simple selective-screening criteria for chlamydial infection in women, to assess the contribution of cervicitis to screening criteria and to evaluate the cost effectiveness of selective versus universal screening.[88] The authors used a cross-sectional study design to evaluate 31 025 women from both family practice (FP) and STD clinics in the states of Washington, Oregon, Alaska and Idaho in the US from 1989 to 1993. For women in the FP cohort (11 141), a DFA test was used whereas in STD clinic patients (19 884), either a cell-culture, DNA probe or EIA test was used for screening. From this cohort, the authors observed a prevalence of chlamydial infection of 6.6% and identified that the independent predictors for chlamydial infection were:

- age less than 20 years
- signs of cervicitis
- new sexual partner
- multiple sexual partners

Table IV. Economic studies that have assessed different screening strategies for *Chlamydia trachomatis* in the management of chlamydial infection

Country	Study design	Study population (number of patients, if known)	Perspective (costs included; currency)	Baseline conditional probabilities and costs used in the model			Results	Sensitivity analysis
				factor	probability (%)	total cost		
No screening *vs* selective screening *vs* universal screening								
USA[87]	Screening *vs* no screening	Women attending for annual pap smear (400 000)	Third-party payer (direct; $US)	Chlamydial prevalence	9.8		The total costs for the screening strategy is $US7 307 717 compared with $US20 347 401 for the nonscreening strategy	The chlamydial prevalence in the population necessary for the screening programme to break even (i.e. the threshold prevalence) is 1.84%
				DFA test: specificity	98			
				DFA test: sensitivity	90	6.75		
				Effectiveness of treatment[a]	95	16		
				Complications of treatment	10		Screening programme would eradicate 33 516 chlamydial infections each year	
				PID rate	25			
				PID outpatient	79	180		
				PID inpatient	21	4259	This would prevent 8379 cases of PID, 1005 surgical procedures for PID, 335 ectopic pregnancies, 1760 cases of tubal infertility	
				PID surgery	12	1500		
				Ectopic pregnancy	4	5759		
				Tubal infertility	21	2500		
				Epididymitis outpatient	4	50	An ongoing chlamydial screening programme would have generated net savings of $US13 million from the annual chlamydial related direct medical care costs	
				Epididymitis inpatient	10	1876		
				Birth rate	5			
				Neonatal pneumonia	10	1375		
				Neonatal conjunctivitis	20	55		
USA[88]	Universal *vs* selective *vs* no screening	Women from family planning (FP) and STD clinic (1 million)	Societal (direct, indirect; $US)	Chlamydial prevalence	6.6		Compared with no screening, selective screening for both FP and STD patients saved about $US1000 for every case prevented	Universal screening was more cost effective than selective screening at chlamydial prevalences of >3.1% in FP patients and >7% in STD patients
				DFA test: specificity				
				DFA test: sensitivity	75	5		
				Effectiveness of treatment[a]	95	1.95		
				Complications of treatment	5	9.50		
				Compliance	70-100		Selective screening in STD patients cost less ($US987) than FP patients ($US1044). Selective screening in STD patients also prevented more cases of chlamydial infection (44 674) than FP patients (47 025)	
				PID rate	25			
				PID outpatient	81	125 (800)[b]		
				PID inpatient	19	12 079 (1680)[b]		
				Surgery for PID	23	2261		
				PID silent	60			
				PID symptomatic	40			

				Ectopic pregnancy	5-10	9071 (1842)[b]	Universal screening in STD patients incurred a net expenditure ($US53 per case prevented). In contrast, universal screening was more cost effective than selective screening in FP patients ($US667 per case prevented)	
				Tubal infertility	10-20	2950 (1083)[b]		
				Chronic pelvic pain	15-20	9937 (1382)[b]		
				Transmission to partner	33			
				Epididymitis	1	112 (480)[b]		
				Urethritis	40	12		
				Neonatal pneumonia	15	2270		
				Neonatal conjuctivitis	35	91		
Prenatal testing for screening *C. trachomatis*								
USA[89]	Culture DFA, EIA	Pregnant women	Not stated (direct; $US)	Chlamydial prevalence	5		Screening all patients was not cost effective	Extensive sensitivity analyses were performed
				Culture: specificity	100			
	DFA/EIA, if positive, reconfirm by culture			Culture: sensitivity	82		DFA/EIA was cost effective when prevalence of infection is >6% while culture is cost effective when prevalence is >14.8%	
				DFA/EIA: specificity	96			
				DFA/EIA: sensitivity	95	8		
	No testing			Effectiveness of treatment[c]	92	10		
				Adverse effects of treatment	3.3	35	If prevalence is >8.7%, then DFA/EIA with culture confirmation becomes cost effective	
				PID rate	10			
				PID outpatient	84	196		
				PID inpatient	16	3071		
				Ectopic pregnancy	7	4115		
				Men, epididymitis	4			
				Men, epididymitis, outpatient	90	50		
				Men, epididymitis, inpatient	10	1876		
				Infant, conjunctivitis	25	100		
				Infant, pneumonia	15			
				Infant, pneumonia, outpatient	75	272		
				Infant, pneumonia, inpatient	25	2500		

a Doxycycline 100mg orally twice daily for 7 days.

b Indirect costs.

c Erythromycin 500mg orally 4 times daily for 7 days.

Abbreviations: DFA = direct fluorescent antibody; EIA = enzyme immunosorbent assay; PID = pelvic inflammatory disease; STD = sexually transmitted disease.

- symptomatic partner.

From these identified risk factors, Marrazzo et al.[88] developed selective-screening criteria and applied them to hypothetical cohorts of 1 million FP and STD patients using a predictive model. In addition, they performed an incremental cost-effectiveness analysis to compare universal, selective screening with DFA and no screening in the hypothetical cohorts.

In the economic evaluation, the study authors[88] incorporated both direct medical costs and indirect costs (lost productivity related to chlamydial infection) from the societal perspective in 1993 US dollars. Intangible costs such as pain, suffering and effects on quality of life were not included. The authors assumed that PID developed in 25% of untreated patients, a DFA cost of $US5 and a DFA sensitivity of 75%. The treatment strategy that was employed in the analysis was doxycycline 100mg orally twice daily for 7 days. The efficacy of doxycycline therapy was assumed to be 95%, which was further adjusted to account for compliance rates from 70 to 100%. Other conditional probabilities for the analysis were obtained from the literature and are summarised in table IV. The authors calculated both incremental cost-effectiveness ratios for both cohorts and determined the threshold values above which universal screening would generate cost savings relative to selective screening.

The incremental cost-effectiveness ratios for each screening strategy in both cohorts has been summarised in table IV. For both cohorts, selective screening was the dominant strategy (i.e. more effective and less costly). However, in the FP cohort, universal screening prevented more cases of *C. trachomatis* (47 025) compared with selective screening (36 680) and was still cost effective when compared with no screening. For the STD cohort, universal screening prevented slightly more chlamydial cases than selective screening (47 025 *vs* 44 674). However, this small incremental change in effect resulted in an increased cost and was no longer cost saving when compared with no screening. Therefore, the authors[88] concluded that for the FP cohort, universal screening was the preferred strategy; whereas, in the STD cohort, selective screening should be employed. Extensive sensitivity analyses revealed the results of this analysis to be robust with threshold values for prevalence of 3.1% in FP patients and 6.9% in STD clinics. The substitution of a more costly test (LCR) for screening had a minimal effect on the model. The study authors did not attempt to determine what effect a more costly, but more effective, treatment strategy (azithromycin) would have on the economic model.

6.2 Population Screening Techniques

The introduction of nonculture diagnostic methods for detecting *C. trachomatis* has precipitated numerous studies to compare the incremental cost effectiveness of these different screening techniques (table V).[90-94]

Phillips et al.[90] estimated the clinical and economic impact of testing for cervical *C. trachomatis* in sexually active nonpregnant women. The diagnostic strategies that were compared in this analysis were cell culture and nonculture testing (DFA or EIA), while the treatment strategy employed was tetracycline 500mg orally 4 times daily for 7 days for patients with positive cultures. The analysis was conducted from the societal perspective, and both indirect and direct costs were considered. The authors[90] based their pecuniary estimations on the cost-of-illness study by Washington et al.[80] and they used published studies as well as expert opinions to determine the relative incidences of complications with this disease and effectiveness of the treatment regimens. The authors assumed that the sensitivity of cervical swabs was 70 to 80% (single cervical culture 75%) and the specificity of culture was 100%. In contrast, the DFA and EIA tests were assumed to have a sensitivity of 60% and a specificity of 98%.

The results of this analysis[90] showed that DFA or EIA testing would reduce costs in a population in which the prevalence of *C. trachomatis* infection was 7% or greater. However, if only direct costs were considered, the threshold prevalence for the DFA/EIA tests was 12%. The only limitation of this

Table V. Economic studies involving different population screening methods to detect *Chlamydia trachomatis* infection

Country	Study design	Study population (number of patients, if known)	Perspective (costs included; currency)	Baseline conditional probabilities and costs used in the model			Results	Sensitivity analysis
				factor	probability (%)	total cost		
USA[90]	Culture DFA EIA No test	Women seeking routine gynaecological care	Societal (direct, indirect; $US)	Chlamydial prevalence			Using DFA or EIA and treating women with a positive result would be more cost effective than the no test strategy if the prevalence of infection was 7% or greater (threshold is 12% when using direct costs only) Routine cultures have a similar impact if the prevalence of infection is 14% or greater (threshold is 25% when using direct costs only)	Extensive sensitivity analysis conducted
				Culture: specificity	100			
				Culture: sensitivity	75	40		
				DFA, EIA: specificity[a]	98	15		
				DFA, EIA: sensitivity[a]	80			
				Effectiveness of treatment[b]	90			
				Acute salpingitis, outpatient	79	770		
				Acute salpingitis, inpatient	21	4767		
				Ectopic pregnancy	5	5175		
				Tubal infertility	18	4488		
				Chronic pelvic pain	15	4974		
				PID, inpatient, death	2.5	301 570		
				Ectopic pregnancy, death	0.9	301 570		
				Women seeking medical attention:				
				asymptomatic	32			
				with acute salpingitis	15			
				with cervicitis	17	172		
USA[91]	LE Culture DFA No test	Male adolescents (1000)	Third-party payer (direct; $US)	Chlamydial prevalence	15		The LE urine dipstick test has the lowest cost per cure ($US51) compared with culture ($US414) and DFA ($US192) Compared with DFA and culture, the LE test saves $US9727 and $US28 429 per cohort of 1000 sexually active adolescent boys screened	Extensive sensitivity analysis conducted
				LE: specificity	85			
				LE sensitivity	75	0.50		
				Culture: specificity	99			
				Culture: sensitivity	90	30		
				DFA: specificity	97			
				DFA: sensitivity	80	10		
				Test collection, processing		10		
				Lost to follow-up	3	10.67		
				Follow-up		10.67		
				Effectiveness of treatment[c]	90	10		
				Compliance	65			
				PID rate (infected partners)	20			
				Probability of infecting a female	30	366.72		
				Complications of untreated men		34.34		
Canada[92]	Culture DFA EIA No test	Women	Third-party payer (direct, indirect; ($Can)	Chlamydial prevalence	0-20		DFA and EIA were cost effective in populations where prevalence of chlamydial infection is greater than 6% and 7%, respectively	Probability of developing PID and cost of the test were the 2 most important factors
				Culture: specificity	99			
				Culture: sensitivity	73	0.50		
				DFA: specificity[d]	99			
				DFA: sensitivity[d]	96	11		
				EIA: specificity[e]	98			
				EIA: sensitivity[e]	83	11		
				Effectiveness of treatment[b,c]	95-100	7.50		
				Compliance	70			

Continued over page

Table V. Contd

Country	Study design	Study population (number of patients, if known)	Perspective (costs included; currency)	Baseline conditional probabilities and costs used in the model			Results	Sensitivity analysis
				factor	probability (%)	total cost		
				PID rate	14			
				PID outpatient	75	347.90		
				PID inpatient	25	4196.10		
				Symptomatic cervicitis	20	132.20		
				Asymptomatic cervicitis	66			
				Ectopic pregnancy	5.5	3879.60		
				Tubal infertility	15.2	3916.30		
USA[93]	Culture	Women at moderate risk	Third-party payer (direct; $US)	Chlamydial prevalence	7.9		Screening of all patients with DFA/EIA which cost less than $US12 was more cost effective than not testing patients	Extensive sensitivity analysis performed
	DFA			Culture: specificity	99.9			
	EIA			Culture: sensitivity	78	25		
	DFA/EIA, if positive, reconfirm by culture			DFA/EIA: specificity	96			
				DFA/EIA: sensitivity	53	12	Use of culture alone or as a confirmatory test was less cost effective	
				IFA: specificity	87			
	IFA serological test			IFA: sensitivity	64	8		
	IFA, if positive, reconfirm by culture			Effectiveness of treatment[f]	90	1.09	Seropositivity was not highly predictive of active infection	
				Adverse effects of treatment	15	27		
				PID rate	25			
	IFA, if positive, reconfirm by DFA/EIA			PID outpatient	75	150		
				PID inpatient	25	2865		
				Ectopic pregnancy	4	4115		
	No testing			Tubal infertility	20	2500		
				Infect male partner	25	33.05		
				Lost to follow-up	5			
Sweden[94]	Screening with culture, confirmed EIA, PCR or LCR *vs* no screening	Asymptomatic women (1000)	Not stated (direct, indirect; $US)	Chlamydial prevalence			When prevalence of chlamydial infection is greater than 6%, screening of women with PCR/LCR and treating with azithromycin was the most cost-effective strategy	Extensive sensitivity analysis conducted
				Efficacy of doxycycline[c]	95-100			
				Compliance with doxycycline	50-100			
				Efficacy of azithromycin[g]	95-100			
				Compliance with azithromycin	100			
				Culture: specificity	100	22-34		
				Culture: sensitivity	50-90		EIA is also cost effective at prevalence greater than 6% and improves cure rates compared with no screening but is less cost effective than DNA amplification assay	
				Confirmed EIA: specificity	99-100	10-17		
				Confirmed EIA: sensitivity	70-80			
				PCR or LCR: specificity	99-100	22-34		
				PCR or LCR: sensitivity	87-98			
				Follow-up of women with positive results	75-90	12-18	Compared with no intervention, cell culture is cost effective when prevalence of infection is greater than 14%	
				Follow-up of disclosed men	60-90	12-18		
				Infection rate of male partners of infected women	50-70	135-329		

Sweden[95]	Screening with LE-EIA, EIA, confirmed EIA *vs* no screening	Asymptomatic men	Direct, indirect ($US)	Prevalence of chlamydia	0-100		Both LE-EIA and EIA reduced the overall costs compared with no screening when the prevalence of chlamydial infection is greater than 2 and 10%, respectively	Not conducted
	Doxycycline *vs* azithromycin			Efficacy of doxycycline[c]	97-100			
				Compliance with doxycycline	50-100			
				Efficacy of azithromycin[g]	95-100			
				Compliance with azithromycin	100			
				Spontaneous cure	5-10			
				EIA: specificity	95-99	10-17	Confirmation of EIA reduced the overall cost of LE-EIA screening strategy when the prevalence of chlamydial infection is less than 8%	
				EIA: sensitivity	70-80			
				LE: specificity	75-85	7-13		
				LE: sensitivity	70-80		Compared with doxycycline, azithromycin improved the cure rates of both EIA (15.1-16.3%) and LE-EIA (11.2-12.0%) while reducing the overall costs by 5 and 9%, respectively	
				Confirmed EIA: specificity	100	11-18		
				Confirmed EIA: sensitivity	70-80			
				Infection rate of partners	40-60			
				Follow-up rate of partners	60-80			
				Untreated infection in women		251-1489		
				Untreated infection in men		135-329		
				Medical care for women		151-248		
				Medical care for men		114-160		

a Calculated sensitivity of rapid tests was 0.60 (0.75 □ 0.80) and specificity was 0.98 (1 □ 0.98).

b Tetracycline 500mg orally 4 times daily for 7 days.

c Doxycycline 100mg orally twice daily for 7 days.

d Calculated sensitivity of DFA was 0.70 (0.73 □ 0.96) and specificity was 0.98 (0.99 □ 0.99).

e Calculated sensitivity of EIA was 0.60 (0.73 □ 0.83) and specificity was 0.97 (0.99 □ 0.98).

f Treatment regimen was not specified.

g Azithromycin 1g single dose.

Abbreviations: $Can = Canadian dollars; DFA = direct fluorescent antibody; EIA = enzyme immunosorbent assay; IFA = immunofluorescent antibody; LCR = ligase chain reaction; LE = leucocyte esterase; PCR = polymerase chain reaction; PID = pelvic inflammatory disease.

model was the high effectiveness for the tetracycline regimen. The authors assumed that 90% of patients who received this regimen would be cured, which does not account for noncompliance. In addition, the authors did not account for complications of chlamydial infection in patients who were successfully treated. This omission is important, as asymptomatic cervical chlamydial infections can ascend and persist unrecognised as chronic PID in the fallopian tubes.[96,97]

Randolph and Washington[91] determined the cost effectiveness of 3 screening tests for *C. trachomatis* in a hypothetical cohort of 1000 sexually active adolescent males. This study group was chosen, as adolescents have the highest rates of *C. trachomatis* infection and young men represent the major source of *C. trachomatis* transmission to teenage girls.[98,99] The screening strategies evaluated in the analysis were:

- LE test (sensitivity 75% and specificity 85%)
- urethral culture (sensitivity 90% and specificity 99%)
- antigen detection by DFA (sensitivity 80% and specificity 97%)
- no test procedure.

The baseline prevalence of *C. trachomatis* in this group was estimated to be 15%.[91] The authors assumed that 3% of patients in the culture and DFA groups would be lost to follow-up, whereas the instantaneous results of the LE test would prevent the loss of patients tested with this strategy. Compliance with the oral doxycycline regimen (100mg twice daily for 7 days) was estimated to be 65% and the efficacy rate was assumed to be 95%; therefore, the effectiveness was assumed to be approximately 62%. Only direct medical costs, such as those associated with screening tests, patient tracking, follow-up visits, antibacterial treatment, complications in sexual partners and complications in the infected men, were considered for this model.

This study[91] showed that the LE-testing strategy resulted in the greatest cost avoidance, followed by DFA, culture and the no-testing strategy. Screening with culture, although more costly, resulted in the highest cure rate (56%) followed by DFA (51%), LE test (49%) and no testing (5%). Extensive sensitivity analyses were conducted for disease prevalence, sensitivity and specificity of the testing strategies, PID rate, lost to follow-up rate and compliance rate. The model proved to be robust over clinically plausible values. The investigators found that the major costs associated with male adolescents with *C. trachomatis* infection were those associated with treatment of infected female partners.

A Canadian group[92] compared the cost effectiveness of early detection of asymptomatic *C. trachomatis* infection in women by: (i) culture (sensitivity 73% and specificity 99%); (ii) antigen detection by DFA (sensitivity 70% and specificity 98%); or (iii) antigen detection by EIA (sensitivity 60% and specificity 97%). In the analytical model, all women with a positive test were treated with either a 7-day course of tetracycline or doxycycline (efficacy estimated to be 95% and 100%, respectively). Compliance with either regimen was assumed to be 70%. Complication rates of *C. trachomatis* infection were obtained from published studies and were similar to those encountered in similar types of analyses. Both direct medical costs and indirect social costs were considered as outcomes for the analysis. Direct costs considered were those associated with testing, treatment of *C. trachomatis* infection and the management of complications. The indirect costs that were included were lost productivity of affected individuals.

The results of this study[92] showed early detection strategies such as DFA and EIA were cost effective in female populations in which the prevalence of *C. trachomatis* infection exceeded 6% and 7%, respectively. Sensitivity analyses conducted by the authors revealed that the probability of PID and the cost of the test were the 2 variables that were most sensitive to the outcome of the model.

Nettleman and Jones[93] evaluated the cost effectiveness of screening women at moderate risk (prevalence 7.9%) of urogenital infections with *C. trachomatis* from the perspective of a third-party payer. The screening strategies that were evaluated in this model were:

- cell culture, followed by treatment if positive
- direct antigen testing, followed by treatment if positive
- direct antigen testing, followed by culture confirmation and treatment if positive
- serological testing, followed by treatment if positive
- serological testing, followed by culture confirmation and treatment if positive
- serological testing, followed by direct antigen confirmation and treatment
- neither testing nor treatment.

The serological testing employed in the analysis was indirect immunofluorescence assay (IFA). Only direct medical costs were considered in the model.[93]

This study[93] was unique in that it was performed in 2 parts, and in terms of the authors' determination of cost effectiveness. The first part was the prospective determination of the specificity and sensitivity of the serological tests in a population at moderate risk of *C. trachomatis* infection. The second part of the analysis used predictive decision analysis to determine the most cost-effective alternative. The authors devised a utility scale from 0 to 1, with 0 representing uncured *C. trachomatis* and 1 representing the absence of *C. trachomatis* infection. Therefore, in this analysis, the cost effectiveness of a particular strategy was determined by dividing the total cost by this utility score. The authors used this methodology in other studies described in this review.[89,100]

The study authors[93] determined that the sensitivity and specificity of IFA were 87 and 64%, respectively. The specificity/sensitivity of culture and direct antigen testing were derived from the literature and assumed to be 99.9%/78% and 96%/53%, respectively. In addition, the authors assumed a 90% effectiveness of antibacterial therapy, but failed to define which agent they had used in the analysis. Other conditional probabilities have been summarised in table V.

Extensive sensitivity analyses were performed on the costs of tests, prevalence of infection, sensitivity and specificity of the tests, complication rates of uncured infections and costs and probabilities of adverse reactions to the treatment regimen. The authors[93] determined that IFA was a cost-effective strategy; however, the adoption of this strategy would result in a large number of uninfected people receiving treatment as a result of the high rate of false positives. Therefore, the authors did not recommend this strategy as a practical option. The most cost-effective and practical option for this population was the strategy that involved performing a direct antigen test on all patients and treating those with positive results, providing that the cost of the test was less than $US11.60 (1987 values).

In a recently published Swedish study conducted by Genç and Mardh,[94] the diagnostic strategies used were cell culture (sensitivity 50 to 90%, specificity 100%), confirmed EIA (sensitivity 70 to 80%, specificity 99 to 100%) and DNA amplification assays based on PCR or LCR (sensitivity 87 to 98%, specificity 99 to 100%). The 2 treatment strategies employed in this analysis were a 7-day, twice-daily course of doxycycline taken at home, or a single oral 1g dose of azithromycin administered under supervision. The compliance rate of the doxycycline strategy was assumed to be 50 to 90%, whereas that of the azithromycin strategy was determined to be 100%. The efficacy of either antibacterial to treat *C. trachomatis* infection was 95 to 100%. The spontaneous cure rate in this population was estimated at 5 to 10%.

The study authors[94] used a predictive analytical design to estimate the cost per outcome. Two decision trees were constructed to model the outcomes of screening strategies among women and the outcomes of tracing and treating sexual contacts of women with a positive diagnosis of *C. trachomatis*. Values for the probability nodes were estimated from the literature and appropriate sensitivity analyses were done. Both direct medical costs and indirect social costs were included in the analysis. The direct costs that were considered were those involved with the delivery of healthcare to infected individuals, while the indirect costs taken into account included lost wages and productivity.

Costs were estimated from reported calculations of medical care and wages in Sweden.

The authors[94] concluded that for asymptomatic female carriers of *C. trachomatis*, screening with a DNA amplification assay combined with the azithromycin treatment strategy (for patients with positive results) was the most cost-effective strategy when the prevalence of *C. trachomatis* was at least 6%. When the prevalence was lower than 6%, the DNA amplification strategy was more costly, but more effective than both competing strategies.

In summary, the results of most studies support the use of direct antigen testing (DFA) for screening in populations with a prevalence of *C. trachomatis* infection that is above 5%. Although cell culture has a higher predictive value, its use may be limited by its high cost. More recent data indicate that the DNA amplification assay is more cost effective than other strategies in populations with a prevalence above 6%.

Genç et al.[95] conducted a study to assess the cost effectiveness of identifying asymptomatic carriers of *C. trachomatis* among a hypothetical cohort of 1000 adolescent males and their sexual contacts. Specifically, this analysis assessed the cost effectiveness of using EIA on either LE-positive urine samples (LE-EIA strategy) or on all urine samples (EIA strategy) or confirming positive EIA results with a blocking assay (EIA-block strategy) compared with using no screening tests. In addition, the authors compared the cost effectiveness of treatment with a 7-day course of doxycycline 100mg orally twice daily versus a single dose of azithromycin 1g under the laboratory diagnostic strategies. The authors used 2 decision trees to graphically display all possible outcomes for both adolescent males and their female sexual contacts.

The authors assumed ranges (rather than discrete base case vales) for the outcomes for the analysis as outlines in table V. Specifically, the sensitivity of both the EIA and LE tests was assumed to be 70 to 80%, whereas the specificities of the 2 tests were assumed to be 75 to 85% and 95 to 99%, respectively. The follow-up rate for patients with a diagnosis of chlamydial genital infection was assumed to be 90 to 97%. The authors assigned cure rates for both the doxycycline and azithromycin strategies of 97 to 100% in compliant males. The compliance rate for doxycycline was assumed to be between 50 and 100% whereas that for azithromycin was assumed to be 100%. The spontaneous cure rate in untreated patients was assigned a value between 5 and 10%. Each male was assumed to disclose 1 or 2 sexual partners and the follow-up rate of these partners was assumed to be between 60 and 80%.

Both direct and indirect medical costs were assessed under the economic model. Direct medical costs included the costs of all samples, tests, appointments, counselling sessions, and medications for the index cases and their partners for the management of the initial chlamydial infection and sequelae. Indirect costs included lost wages and lost value of household management due to participation in a healthcare programme due to sickness.

Although the authors did not use sensitivity analyses to account for uncertainty in their estimations of costs and probabilities, they used spreadsheet-derived simulations to randomly choose input values within defined ranges. Different combinations of input variables were assessed in 1000 iterations to compute the outcomes of the decision-analytical model. Therefore, the overall outcomes were expressed as 95% confidence intervals on the means of the results from all the computations.

Regardless of the prevalence of chlamydial infection, the screening strategies increased the cure rate from 7.4 to 7.6% (achieved with the no screening strategy) to 37.8 to 55.4% depending on the method used and the population assessed. The LE-EIA strategy achieved a cure rate of 42.4 to 43.4 % for males, 37.8 to 38.6% for their partners, and 40.7 to 41.5% overall; whereas, the corresponding figures for the EIA strategy were 54.2 to 55.4%, 50.8 to 51.8%, and 52.9 to 54.1%, respectively. No values were given for the EIA-block strategy.

Compared with the doxycycline treatment strategy, the azithromycin strategy ensured full compliance and improved the overall cure rates of both

the LE-EIA and the EIA strategies by 11.2 to 12.0%, and 15.1 to 16.3%, respectively. The incremental cost-effectiveness ratio for these agents was not supplied by the authors thus making an economic comparison of the 2 drugs difficult from the results of this study.

The authors determined that both the LE-EIA and the EIA strategies reduced the overall costs when compared with the no screening strategy when the prevalence of chlamydial genital infection in males exceeded 2 and 10%, respectively. Compared with the LE-EIA screening and the no screening strategies, confirmation using the EIA-block strategy reduced the overall costs when the prevalence of infection was below 8% and greater than 7%, respectively. The incremental cost of switching from the LE-EIA to EIA screening strategy was $US2144 per cured male when the prevalence of chlamydial infection in males was 100% and increased as the prevalence declined to 0%. The incremental cost of switching from the LE-EIA to the EIA-block strategy was $US2202 per cured male at a prevalence of chlamydial infection in males of 100% and thereafter increased as the prevalence decreased to 0%.

6.3 Prenatal Testing

Nettleman and Bell[89] investigated the cost effectiveness of strategies for screening pregnant women for *C. trachomatis*, from the perspective of a third-party payer (table IV). This study was unique in that the screening and treatment of pregnant women was more complex than in other groups because treatment options are limited, sequelae are more varied and both mother and infant require therapy.

In their model, the authors[89] compared the direct medical costs associated with: (i) culture in all patients, followed by treatment for positive results; (ii) DFA in all patients, followed by treatment for positive results; (iii) DFA in all patients, followed by culture confirmation for positive DFA results and then treatment if both results are positive; and (iv) no screening tests or treatment. The prevalence of *C. trachomatis* in pregnant women was assumed to be 5%. The single-cell culture method used in the model was assumed to have a sensitivity of 82% and a specificity of 100%, whereas the DFA test was assumed to be 95% as sensitive and 96% as specific as the culture. Patients with positive results were treated with erythromycin for 7 days and adverse reactions were appropriately accounted for in the costing process. In addition, the treatment of a single sexual partner was factored into the analysis.

The authors[89] found that the most sensitive variables in their analysis were the prevalence of infection, the cost of the direct antigen test, the cost of the culture and the mean cost of an uncured infection. Specifically, if the cost of DFA was less than $US6.30 (1990 values) or the prevalence of infection in pregnant women was higher than 6.1%, routine screening with DFA followed by treatment for positive results was the most cost-effective option. Similarly, if the cost of DFA was less than $3.90 (1990 values) or the prevalence of infection was higher than 8.7%, the confirmation of a positive DFA result with culture followed by treatment was the more cost-effective strategy. Finally, if the prevalence of infection was higher than 14.8% or the cost of culture was less than $US7.50 (1990 values), culture followed by treatment for positive results was the preferred method. In addition, if the mean cost of uncured infection was more than $US284 (1990 values), DFA followed by treatment was the more cost-effective strategy. Therefore, the authors concluded that screening for *C. trachomatis* in pregnancy was not cost effective in low-prevalence populations (5%).

The limitation of this analysis[89] was the use of charge rather than cost data. The authors felt that it was appropriate to include charges as they represented the true burden on third-party payers in the US. In addition, the authors did not allow for noncompliance in their estimation of the 92% efficacy rate for erythromycin.

6.4 Field Follow-Up

'Field follow-up' can be defined as a situation in which a third party (i.e. healthcare personnel)

assumes responsibility for notifying sexual partners of their exposure and providing evaluation and treatment.[2] Katz et al.[101] published the results of 2 studies that assessed the efficiency and cost effectiveness of using field follow-up to contact: (i) patients with chlamydial infection detected in a screening programme; and (ii) women who were sexual partners of men with NGU (table VI).

In the first study in an STD clinic,[101] patients were either assigned to receive empirical antichlamydial therapy or had urethral/endocervical specimens cultured and were instructed to call back within 1 week. Patients who called back were scheduled a follow-up appointment if positive for *C. trachomatis*, but no further attempt was made to contact them. Patients who did not call for their results after 2 weeks were sent a letter advising them of the status of their culture and advising them to make an appointment when appropriate. Results from these 3 groups of patients were compared with those obtained from using field follow-up in another group. Field follow-up was defined as extensive interview of the index patient by a disease-intervention specialist, followed by contact using an exhaustive stepwise approach.

In the second study, Katz et al.[101] compared the effectiveness of 3 methods of contacting women who were sexual partners of men presenting to an STD clinic with NGU. During a 6-month period, patients were randomised to receive either: (i) nursing referral (nursing counselling to inform men to refer their sexual contacts) [n = 217]; interview strategy (counselling by a trained disease-intervention specialist who obtained the names of contacts, but did not attempt to contact them) [n = 240]; and field follow-up (as defined in the first study, except sexual partners were contacted instead of the index patient) [n = 221].

Katz et al.[101] used predictive decision analysis to conduct the economic evaluation. Although they did not state the perspective of their analysis, from the costs that were used it can be assumed that the analysis was conducted from the perspective of the STD clinic. The estimated costs for each of the strategies used in the analysis were determined from the clinic personnel time, phone calls made, postage used and expenses involved with healthcare personnel travel. Calculations were derived from an actual review of resources used from locating 40 consecutive culture-positive patients. Medical costs used to treat chlamydial infections were based on those reported in the literature. A detailed breakdown of the costs used in the analysis are summarised in table VI.

In the first study, of the 142 patients who had a positive *C. trachomatis* culture, only 49 (34%) called back for results and arranged an appointment. Overall, 112 (79%) returned for treatment, compared with 97% (259/266) in the field follow-up group. In the cost analysis, the cost per patient of the field follow-up strategy was less than the reminder systems for both men and women. No incremental cost-effectiveness ratios were calculated, but the average cost per patient for each strategy has been summarised in table VI.

In the second study, the field follow-up group yielded a significantly larger number of treated partners per index patient (0.72) than the nursing referral (0.22) and the interview strategy (0.18; $p < 0.001$ for both the nursing referral and interview only groups when compared with the field follow-up group). In addition, the field follow-up strategy had the lowest cost per patient, followed by nursing referral and the interview strategy (table VI). Extensive univariate sensitivity analyses were conducted, and revealed that both models were robust for the cost of each of the strategies and the cost of untreated chlamydial infection.

6.5 Test of Cure

A Norwegian group[102] used a predictive analysis to assess the cost effectiveness of a test-of-cure strategy in a hypothetical cohort of 10 000 asymptomatic women with a positive initial diagnosis of *C. trachomatis* infection (table VI). In this model, the authors compared the test-of-cure strategy (either cell culture or a rapid test) with a no-test-of-cure strategy for those who failed initial therapy. Patients were continually cycled in the model if they failed therapy until all patients were cured under

Table VI. Economic studies assessing various strategies in the management of *Chlamydia trachomatis* infection

Country	Study design	Study population (number of patients, if known)	Perspective (costs included; currency)	Baseline conditional probabilities and costs used in the model			Results	Sensitivity analysis
				factor	probability (%)	total cost		
Field follow-up of patients and partners with *C. trachomatis*								
USA[101]	Field follow-up *vs* no field follow-up	Study 1: men and women with chlamydial infection	STD clinic (direct; $US)	Study 1			Field follow-up in men ($US13.52) and women ($US20.06) was more cost effective than the reminder system in men ($US21.27) and women (67.05)	Extensive sensitivity analyses conducted
				men; field follow-up	3	2.85		
				men; reminder system	21	19.95		
				women; field follow-up	3	9.39		
				women; reminder system	21	65.73		
		Study 2: women who are sexual partners of men at STD clinic with NGU		Study 2			Field follow-up was more cost effective ($US37.50) than nursing referral ($US42.46) and interview ($US60.48)	
				nursing referral	12.8	40.06		
				interview only	13.8	43.19		
				field follow-up	0	0		
Test of cure *vs* no test of cure for *C. trachomatis*								
Norway[102]	Test of cure (culture and rapid tests) *vs* no test of cure	Asymptomatic women with diagnosis of *C. trachomatis* (10 000)	Third-party payer (direct; $US)	Chlamydial prevalence			The costs of test-of-cure strategy ($US499 947) are twice those of the no-test regimen ($US243 600)	Varying the cure rate, test sensitivity or specificity did not change the model
				Diagnostic tests (culture, rapid):				
				specificity	98			
				sensitivity	80	11.50		
				Effectiveness of treatment[a]	95	20		
				PID rate	20	140		
				Tubal infertility	20	4800		
				Ectopic pregnancy	2.5	2860		
Empirical *vs* laboratory-confirmed treatment for *C. trachomatis*								
USA[100]	Empirical *vs* lab-confirmed (culture) treatment	Women, men	Not stated (direct; $US)	Chlamydial prevalence			Empirical treatment of all patients was the most cost-effective strategy	Extensive sensitivity analysis conducted
				Culture: specificity	99			
				Culture: sensitivity[b]	68-88	15		
				Recall of patients with positive results		11.04	If only endocervical cultures are done, the next most cost-effective strategy would be empirical treatment in high risk women and culture-based treatment for women at low risk	
				Spontaneous cure rate	10			
				Effectiveness of treatment[c]	90	1.09		
				Adverse reactions from treatment:				
				women	15	27		
				men	5	11		
				PID rate in women	10-30		Obtaining cultures for men at low and high risk was not cost effective	
				PID outpatient	20	150		
				PID inpatient	5	2865		
				Ectopic pregnancy	1	4115		
				Tubal infertility	5	2500		
				Infection of male partner	25	33.05		
				Men: return visit for symptoms	75	35		
				Epididymitis	4	170		
				Infection of female partner	39	187.20		

a Lymecycline 100mg orally twice daily for 7 days.
b Sensitivity was 68% for a single endocervical culture and 88% from endocervical and endourethral culture.
c Tetracycline 500mg orally 4 times daily for 7 days.

Abbreviations: NGU = nongonococcal urethritis; PID = pelvic inflammatory disease; STD = sexually transmitted disease.

the test-of-cure strategy. Only direct costs were used in this model (diagnostic tests, repeat physician visits, antibacterial therapy and therapy for sequelae) and the analysis was conducted from a third-party payer perspective. Lymecycline 100mg orally twice daily (reported to be a cheaper alternative to doxycycline) was used as the treatment strategy at a presumed effectiveness of 95%.

The study authors[102] concluded that the cost of a test-of-cure strategy would be approximately double that of a no-test-of-cure strategy. They performed a sensitivity analysis to determine the effect of varying the values that they assigned to the diagnostic tests – they had assumed a specificity of 98% and a sensitivity of 80% – and found that the results of their model was relatively insensitive to these changes, but were more dependent on their estimate of cure rate with lymecycline. Again, the authors failed to account for noncompliance with the lymecycline regimen and to appropriately adjust for it in the determination of the effectiveness rate. In addition, the authors did not provide a definition of the rapid tests that they used in the analysis.

The recommendations of these authors[102] were in agreement with those of the CDC in that a test of cure is generally not required.[2] In addition, if a test of cure is to be used for research or other special circumstances, some authors have advocated that only cell culture should be used.[41] The reason for this is that nonculture tests are able to detect nonviable organisms and that since the prevalence of infection is so low in this treated population, most nonculture tests lack the positive predictive value to be useful.

6.6 Empirical Versus Laboratory-Confirmed Treatment

Nettleman et al.[100] used a predictive decision-analytical model to evaluate the cost effectiveness of treating various subgroups of men and women who had a positive culture for *C. trachomatis* with those who were empirically treated (based on signs and symptoms). Cell culture was used as the diagnostic test for detecting *C. trachomatis* (table VI).

The prevalence of *C. trachomatis* infection in this population was obtained from data from the 22 063 patients who had attended a STD clinic in Indianapolis, USA, between 1983 and 1984, as well as from the published literature. In this analysis, patients were stratified into high- or low-risk groups, depending on their histories and presenting signs and symptoms. Cell culture was used as the diagnostic strategy for which the specificity was assumed to be 99% in all patients, while the sensitivity was estimated to be 90% for men and 68 to 88% in women. Appropriate treatment was determined to be tetracycline 2 g/day for 7 days, as newer strategies had not been developed at the time of this evaluation. This study was conducted from the perspective of a third-party payer and only direct medical costs were considered in the analysis.

Based on their assumptions, the authors determined that the empirical treatment of all patients attending the clinic was the most cost-effective strategy. However, if empirical therapy of all patients was not feasible, the next most cost-effective strategy was the empirical treatment of high-risk women and culture-based therapy for low-risk women. For men, empirical therapy was cost effective in high-risk groups, whereas in low-risk groups, performing no cultures and providing no therapy was the most cost-effective strategy.

6.7 Treatment Strategies

As outlined in the section 5 there are a variety of treatment strategies that can be used to eradicate *C. trachomatis* infection. However, until recently, there was no information as to which of these strategies was the most cost effective. This recent interest in the determination of the incremental cost effectiveness of antichlamydial agents has been primarily fuelled by the availability of newer drugs such as the fluoroquinolones and azithromycin. These new agents have a substantially higher acquisition cost, but may have many advantages such as fewer adverse reactions and increased compliance when compared with traditional agents.[47,65,78,79]

One of the first published studies to address this question was conducted by Nuovo et al (table VII).[103] These investigators compared the cost effectiveness of 5 treatment strategies (erythromycin, tetracycline, doxycycline, ofloxacin or azithromycin) from the perspective of the healthcare system in California, USA, for the treatment of uncomplicated *C. trachomatis* infection in nonpregnant women. The study authors used decision analysis, and based the probabilities and costs in their model on published clinical and economic evaluations, state health plan reports and health insurance companies. They also conducted sensitivity analyses on the probabilities of PID and hospitalisation after treatment failure, estimations of the cost of treatment of inpatient and outpatient PID, and the cost and efficacy of azithromycin and doxycycline.

Based on their assumptions, the authors[103] concluded that the doxycycline and tetracycline strategies were the most cost-effective options, followed by azithromycin, ofloxacin and erythromycin. However, they commented that in noncompliant patients, azithromycin may be the best strategy because of the increased compliance with the single-dose regimen, although this was not accounted for in the analysis.

The main limitations of this study[103] include the use of a simplistic model for *C. trachomatis* infections, since further sequelae beyond PID (such as chronic pelvic pain, infertility and ectopic pregnancy) were not considered. In the model and their calculations, the study authors did not include the effect of noncompliance with older treatment regimens on overall cure rate or the costs incurred in managing adverse drug reactions. The latter point is especially relevant, as this analysis included drugs such as erythromycin and tetracycline, which have higher adverse event rates than the newer agents.[47,65] In addition, the costs to treat secondary transmission to sexual partners were not considered.

In another decision-analytical model, Haddix et al.[104] evaluated the cost effectiveness of azihromycin 1g orally compared with doxycycline (100mg twice daily) for 7 days for a cohort of 10 000 nonpregnant women with uncomplicated *C. trachomatis* infections (table VII).[104] The authors considered the cost effectiveness of both treatment alternatives under 2 diagnostic strategies: (i) laboratory-confirmed C. trachomatis infection; and (ii) presumptive diagnosis, based on clinical signs and symptoms. The perspectives of the analysis were those of the US healthcare system and the publicly funded clinic. The differences between these perspectives are that the publicly funded clinic would only incur expenses at the time of diagnosis and the costs of sequelae that could be managed on an outpatient basis.

The authors of that study[104] based their probabilities on the results of published clinical trials. In addition, for the effectiveness of doxycycline, the authors considered a compliance rate of 80%. Noncompliant patients were assumed to be treatment failures. Since azithromycin is administered as a 1g single dose at the time of the clinic visit, compliance was assumed to be 100%. Costs incorporated into the model were those for the treatment of an episode of PID and its sequelae (chronic pelvic pain, infertility and ectopic pregnancy). Costs of sequelae that would occur in future years were discounted at an annual rate of 5%. Costs associated with PID and its sequelae were adapted from a report by Washington and Katz.[107] The authors[104] assumed that 25% of women with tubal-factor infertility would seek treatment. Sensitivity analyses were conducted on the prevalence of *C. trachomatis* infection among those presumptively treated, doxycycline compliance rates, the cost of PID and its sequelae, the probabilities of developing PID in compliant and noncompliant patients, and the risk of developing further sequelae.

From the healthcare system perspective, the results of the study[104] with the laboratory-confirmed model showed that the use of azithromycin would cost an additional $US290 000 (1993 values) to treat chlamydial infections in a cohort of 10 000 women, but would save $US1.2 million in the treatment of PID and its sequelae. This translated into savings of $US3502 per additional case of PID prevented. For the presumptively treated

Table VII. Economic studies involving strategies used to treat *Chlamydia trachomatis*

Country	Study design	Study population (number of patients, if known)	Perspective (costs included; currency)	Baseline conditional probabilities and costs used in the model			Results	Sensitivity analysis
				factor	probability (%)	total cost		
USA[103]	Doxycycline, tetracycline, ofloxacin, azithromycin, erythromycin	Women	Third-party payer (direct; $US)	Chlamydial prevalence			Doxycycline and tetracycline are the most cost-effective agents, followed by azithromycin, ofloxacin and erythromycin	To achieve an equivalent final cost, the probability of cure with azithromycin must exceed doxycycline by 3%
				Efficacy of doxycycline	82-99	13.17		
				Efficacy of tetracycline	79-98	8.10		
				Efficacy of ofloxacin	93-99	50.45		
				Efficacy of azithromycin	88-99	36.05		
				Efficacy of erythromycin	77-91	11.39		
				PID rate	25	195		
				PID treatment, outpatient	75	3528		
				PID treatment, inpatient	25	9252		
				Ectopic pregnancy				
				Tubal infertility				
				Chronic pelvic pain				
USA[104]	Laboratory confirmed (LC) *vs* presumptive (Pr.) treatment and doxycycline *vs* azithromycin	Women (10 000)	Healthcare (HC) system *and* publicly funded clinics (PFC) [direct; $US]	Chlamydial prevalence	20		From the HC perspective, cost-per-case of PID prevented with azithromycin ranges from a savings of $US3502 for the LC model to a cost of$US792 for presumptive treatment	Extensive sensitivity analysis conducted
				Efficacy of doxycycline[a]	96.5	(2)[b] 10		
				Compliance with doxycycline	80			
				Efficacy of azithromycin[c]	96.5	(24)[b] 39		
				Compliance with azithromycin	100			
				PID rate	20			
				PID treatment, outpatient	86	(105)[b] 4575[d]	From the PFC perspective, the cost-per-case of PID prevented with azithromycin ranges from $US709 for the LC model to $US3969 for presumptive treatment	
				PID treatment, inpatient	14			
				Ectopic pregnancy	6	(0)[b] 11 167		
				Tubal infertility	20	(0)[b] 4636		
				Chronic pelvic pain	18			
				Treatment rate for infertility	25			
Canada[105]	LC *vs* Pr. and doxycycline *vs* azithromycin	Women (5000)	Third-party payer (direct; $Can)	Chlamydial prevalence	20		For both diagnostic strategies, azithromycin was more cost effective than doxycycline	The model was not robust for Pr.
				Efficacy of doxycycline[a]	96.5	4.63		
				Compliance with doxycycline	80			
				Efficacy of azithromycin[c]	96.5	18.16	For LC, the cost per cure for azithromycin was $Can184.76 compared with $Can240.59 for doxycycline	
				Compliance with azithromycin	100			
				PID rate	20			
				PID treatment, outpatient	86	1231		
				PID treatment, inpatient	14			

				Ectopic pregnancy	6	4094[d]	For Pr., the cost per cure for azithromycin was $Can 51.48 compared with $Can 51.82 for doxycycline	
				Tubal infertility	20	882		
				Chronic pelvic pain	18	5079		
				Treatment rate for infertility	25			
USA[106]	Doxycycline *vs* azithromycin	Asymptomatic women with a laboratory confirmed diagnosis of *C. trachomatis* and men (100 000)	Not stated (direct; $US)	Chlamydial prevalence			Azithromycin cost $US39.51 per patient and doxycycline cost $US69.07 per patient Azithromycin strategy incurred 938 major complications and 15 715 minor complications per 100 000 patients compared with 3330 major complications and 25 706 minor complications with the doxycycline strategy The incremental cost effectiveness was $US521 per additional major complication prevented	Extensive sensitivity analysis conducted
				Efficacy of doxycycline[a]	86	5.51		
				Efficacy of azithromycin[c]	96	18.75		
				Adverse reactions:				
				doxycycline, minor	16	35.00		
				doxycycline, major	0.1	3747.50		
				azithromycin, minor	13	35		
				azithromycin, major	0.1	3747.50		
				PID rate	15			
				PID treatment, outpatient	86	191.55		
				PID treatment, inpatient	14	5259.03		
				Ectopic pregnancy	8	4717.69		
				Tubal infertility	17	5172.68		
				Chronic pelvic pain	12	3809.11		
				Men, symptomatic urethritis	50	82.39		
				Men, epididymitis:				
				rate	2			
				treatment, outpatient	90	206.70		
				treatment, inpatient	10	3421.59		
				Neonatal conjunctivitis	20	81.80		
				Neonatal pneumonia rate	10			
				Neonatal pneumonia treatment				
				outpatient	80	225.80		
				inpatient	20	3023.80		
				Treatment of partner		50.39		

a Doxycycline 100mg orally twice daily for 7 days.

b Costs associated from the public health perspective.

c Azithromycin 1g single dose.

d Average cost of PID treatment on an outpatient basis and PID treated in hospitalised patients.

Abbreviations: LC = laboratory-confirmed; PID = pelvic inflammatory disease; $Can = Canadian dollars.

cases, the use of azithromycin would cost an additional $US290 000 and would only save $US240 000 to treat a cohort of 10 000 women. This would result in an incremental cost savings of $US800 per additional case of PID prevented for azithromycin versus doxycycline treated patients. Sensitivity analyses illustrated the robustness of the laboratory-confirmed model, such that azithromycin maintained its cost savings for all plausible values. However, the results of the presumptive model were more sensitive to changes in the estimated values.

From the public health clinic perspective, and for the laboratory confirmed model, azithromycin would cost an additional $US220 000 (1993 values) for the cohort of 10 000 women, but would save $US29 000 from reduced treatment costs of PID, resulting in a net cost of $US709 per additional case of PID prevented.[104] For the presumptively treated women, azithromycin would cost an additional $US220 000 but would only save $US5670 from reduced treatment costs of PID, resulting in a net cost of $US3969 per additional cost of PID prevented. Under sensitivity analyses for both diagnostic strategies, although azithromycin is not cost effective under base-case assumptions, it becomes more cost effective in public clinics with noncompliant populations and higher prevalence of *C. trachomatis* infection.

The authors of this study[104] concluded that from the healthcare-system perspective, the use of azithromycin is the more effective and less costly treatment alternative under the laboratory-confirmed model. For those who are presumptively treated, the use of azithromycin is still more effective, but results in an incremental cost of almost $US800 (1993 values) per case of PID prevented. From the perspective of a publicly funded clinic, the use of azithromycin is more effective, but since the clinic is responsible for a small percentage of PID-related treatment costs, this treatment strategy is also much more expensive. However, it is important to realise that although the publicly funded clinic may not manage the complications, ultimately these costs will be absorbed by other organisations and thus are artificial cost savings.

Marra et al.[105] used the models developed by Haddix et al.[104] to evaluate the cost effectiveness of azithromycin and doxycycline from the perspective of the Canadian healthcare system for a cohort of 5000 nonpregnant women (table VII). This analysis was necessary as the cost of managing the complications of PID remains considerably lower than in the US. The authors obtained their probabilities and costs for their decision model from the literature, hospital-costing departments and expert opinion.

From their results,[105] in the Canadian healthcare system, the use of azithromycin in the laboratory confirmed model translates into a cost savings of $Can279 150 (1995 values) for a cohort of 5000 women. For presumptively treated patients, the savings associated with azithromycin were only $Can1700 for the same cohort. The authors concluded that the widespread use of azithromycin in Canada for laboratory-confirmed cases of *C. trachomatis* could result in $Can3 million of medical expenses avoided per year.

The limitations of the evaluations conducted by Haddix et al.[104] and Marra et al.[105] include the use of direct medical costs only, the fact that management of adverse drug reactions was not taken into account and the failure to assess different screening strategies within the model. Furthermore, the secondary transmission of chlamydial infection to partners was not evaluated in these 2 models.

Magid et al.[106] also evaluated the economic consequences of doxycycline therapy compared with those resulting from azithromycin therapy in women with *C. trachomatis* infection (table VII). The design of this analysis was similar to those of the studies by Haddix et al.[104] and Marra et al.[105]. However, the advantages of this study over the other 2 analyses were the consideration of adverse events related to antibacterial therapy and the costing of sequelae that occurred as a result of secondary transmission of the infection. In addition, although arbitrarily determined, Magid et al.[106]

attempted to devise a cure rate for different levels of noncompliance with doxycycline.

The results of this study were similar to those of the 2 studies. Under base-case conditions, azithromycin was the dominant treatment strategy for women with uncomplicated *C. trachomatis* infections. The azithromycin strategy incurred 2392 fewer major complications and 9991 fewer minor complications than doxycycline at approximately 57% of the cost per patient. However, the authors realised that the higher acquisition cost of azithromycin may inhibit the widespread use of this agent for the treatment of this disease because of the fiscal restraints of the fragmented healthcare systems that exist in North America.

In summary, the authors of most studies evaluating the comparative cost effectiveness of pharmacotherapy for *C. trachomatis* infection in nonpregnant adults have concluded that azithromycin is the most cost-effective strategy. The increase in compliance (and thus effectiveness) that a single dose provides over a 7-day treatment course proved to be the most substantial factor in conferring this economic benefit.

7. Conclusion

Despite new control efforts, diagnostic and screening strategies and treatment modalities, *C. trachomatis* infection continues to be a major problem in adults and adolescents. The socioeconomic consequences of this disease and its sequelae are staggering and have risen to $US2.4 billion annually in the US (1993 values).[2] The bulk of these costs are borne by various healthcare systems because of the seriousness of the disease in this population. The US CDC currently recommends screening all women from groups in which the prevalence rate is 5% or greater.[2] This recommendation is supported by economic studies that have shown screening programmes to be more cost effective then not screening women when the prevalence of chlamydial infection is high (i.e. >5%).

Cell culture has been considered the 'gold standard' for the diagnosis of *C. trachomatis*. However, various nonculture diagnostic and screening tests have recently been developed to aid in the detection of *C. trachomatis*. The economic impact of these testing strategies has been evaluated in various populations. In populations with a high risk of developing infection (prevalence >5%), DNA amplification assays for diagnosis may be the most cost-effective approach. However, neither the screening of pregnant women nor a test-of-cure strategy for all patients is necessary, and neither option is cost effective. Empirical treatment of all patients based on clinical signs and symptoms has been compared with therapy guided by laboratory confirmation. The more cost-effective strategy is empirical therapy for all patients, but this strategy may not be feasible for all health systems.

New treatment modalities have been developed, which have facilitated an increase in compliance and a reduction in adverse effects when compared with traditional agents. Unfortunately, these newer agents cannot be used in pregnancy, so erythromycin remains the agent of choice in this situation. For other populations, a single dose of azithromycin has proved to be the most cost-effective strategy, compared with other treatment regimens.

There has been some research in the area of cost effectiveness for screening, diagnosing and treating *C. trachomatis*; however, as new technologies and treatment strategies are developed, economic evaluation must keep pace to keep this technology in perspective. To this end, examples of areas that require additional research include further cost-effectiveness analyses of different screening strategies, partner notification and appropriate diagnostic tests for low prevalence groups. For treatment strategies, cost-utility analyses should be performed to identify the impact patient preferences and quality of life have on this disease.

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