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Canada

CHLAMYDIAL INFECTIONS

This chapter from the Canadian Guidelines on Sexually Transmitted Infections 2006 Edition has undergone revisions and has been updated as of October 2007. The chart below summarizes the most significant changes made to the chapter and cross-references the corresponding page numbers in the current hard copy version of the guidelines.

Section	Page	Current Wording/Problem	Update/Clarification
Numerous		Updates to other guideline chapters have affected the recommendations contained in this chapter, as such, it has been significantly revised.	Changes are too numerous to list, please print the entire chapter and discard/disregard previous version.

CHLAMYDIAL INFECTIONS

(*For Lymphogranuloma venereum*, see Genital Ulcer Disease *and* LymphogranulomaVenereum *chapters*)

Etiology

- Caused by *Chlamydia trachomatis* serovars D to K.

Epidemiology

- Reported rate in Canada and elsewhere has been increasing since 1997.[1]
- According to preliminary data, over 65, 000 cases were reported in Canada in 2006 (202 per 100,000 population).[2]
- Sexually active youth and young adults are disproportionately represented in the case reports for Chlamydia. The reported rate in 2004 was highest in youth/young adults 15 to 24 years of age, accounting for approximately 2/3 of the national reported cases.
- Chlamydia is underdiagnosed because the majority of infected individuals are asymptomatic.[3–8]
- Underscreening is a gap in high-risk males and females. Males, the forgotten reservoir, have infrequent health-maintenance visits.[9–11]
- The usual incubation period from time of exposure to onset of symptoms is 2 to 3 weeks, but can be as long as 6 weeks.
- In the absence of treatment, infection persists for many months.
- Individuals infected with *Neisseria gonorrhoeae* are often co-infected with *C. trachomatis.*[12,13]
- Risk factors:
  - Sexual contact with a chlamydia-infected person.
  - A new sexual partner or more than two sexual partners in the past year.
  - Previous sexually transmitted infections (STIs).
  - Vulnerable populations (e.g., injection drug users, incarcerated individuals, sex trade workers, street youth etc.) (see Specific Populations section).

Prevention

- Infection and its sequelae can be prevented by:
  - Consistent practice of safer sex (see *Primary Care and Sexually Transmitted Infections* chapter).
  - Identifying barriers to prevention practices and the means to overcome them.
  - Increased acceptance of testing by using a non-invasive urine-based nucleic acid amplification test (NAAT).
  - Screening of at-risk groups (as per risk factors listed above):
    - Sexually active females under 25 years of age.
    - Infected men under the age of 25 are a hidden reservoir for infections and re-infections of their partners. There is an evidence gap to determine whether routine screening of asymptomatic young males decreases the incidence of anogenital Chlamydia infection in women.[14,15] While waiting for such data, it is prudent to

screen all sexually active males under the age of 25 for *Chlamydia trachomatis*.[7,8,10,16–24]

- Pregnant women. All pregnant women should be screened at the first prenatal visit. For those who are positive or who are at high risk for reinfection, rescreening at third trimester is indicated.[25–31]

– Repeat screening of individuals with chlamydia infection after 6 months.[26,32-35]

- To prevent reinfection, partners need to be assessed, tested, treated, and counselled.
- Patients and contacts should abstain from unprotected intercourse until treatment of both partners is complete (i.e., after completion of a multiple-dose treatment or for 7 days after single-dose therapy).

Manifestations

Table 1. Symptoms and signs[36]

Females	Males	Neonates and infants
• Most often asymptomatic • Cervicitis • Vaginal discharge • Dysuria • Lower abdominal pain • Abnormal vaginal bleeding • Dyspareunia • Conjunctivitis • Proctitis (commonly asymptomatic)	• Often asymptomatic • Urethral discharge • Urethritis • Urethral itch • Dysuria • Testicular pain • Conjunctivitis • Proctitis (commonly asymptomatic)	• Conjunctivitis in neonates • Pneumonia in infants <6 months of age

Table 2. Major sequelae

Females	Males
• Pelvic inflammatory disease • Ectopic pregnancy • Infertility • Chronic pelvic pain • Reiter syndrome	• Epididymo-orchitis • Reiter syndrome

Diagnosis

Laboratory diagnosis

(See *Laboratory Diagnosis of Sexually Transmitted Infections* chapter.)

- Results are highly dependent on the type of test available; specimen collection and transport; and laboratory expertise. Consult with your local laboratory regarding available tests and their test performance.
- NAATs (e.g., polymerase chain reaction [PCR], transcription-mediated amplification [TMA]) are more sensitive and specific than culture, enzyme immunoassay (EIA) and direct fluorescent antibody assay (DFA). For non–medico-legal purposes, NAATs should be used whenever possible for urine, urethral or cervical specimens. Blood and mucus interfere with NAAT performance and can result in false-negative results, therefore culture is recommended in such situations.
- Although some NAATs have not been approved in Canada for use with vaginal or rectal specimens, recent data show that NAATs for *C. trachomatis*, *N. gonorrhoeae* and *Trichomonas vaginalis* may identify as many or more infected women using vaginal swabs than cervical swabs, urethral swabs or urine.[37] Check with your laboratory to see if this is an option.* (see *Specimen collection* in this chapter).
- There are promising data on the use of rectal and oral swabs for *C. trachomatis* and *N. gonorrhoeae* tested by NAATs and current clinical trials are underway through the U.S. National Institutes of Health.** (see *Specimen collection* in this chapter).
- Currently, only culture is recommended for throat specimens.
- Due to its non-invasive nature a urine-based NAAT is ideal for screening asymptomatic females when a pelvic examination is not warranted for other reasons. However, a physical examination remains essential, and more invasive specimens may be needed for diagnostic purposes in symptomatic individuals.
- Post exposure NAAT testing can be taken at the time of presentation without waiting for 48 hours; this is based on expert opinion, which assumes that NAATs are able to detect inoculum (DNA or RNA).
- Both chlamydia and gonorrhea can be detected from a single specimen by some NAATs.
- Culture is the preferred method for medico-legal purposes, but NAATs may be suitable, provided that positive results are confirmed. Confirmation of positive results can be done with a NAAT using a different set of primers or by DNA sequencing techniques.
- *C. trachomatis* IgM serology is useful for diagnosing *C. trachomatis* pneumonia in infants less than 3 months of age.
- Serology is not useful for the diagnosis of acute genital chlamydial infections.

Specimen collection

Potential specimen sites:

- Cervix in pubertal or older females for NAAT.
  - If the cervix has been surgically removed:
    - urine or urethral swab for NAAT

    or

    - vaginal swab for culture or NAAT* (see *Laboratory Diagnosis* section in this chapter).

    or

    - rectal swab for culture or NAAT** (see *Laboratory Diagnosis* section in this chapter.
- Urethral swab in males for NAAT (preferably not have voided for at least 2 hours, but this does not preclude testing).
- Urine NAAT, vaginal/rectal swab for culture in prepubertal girls.
- Urine NAAT for females and males of any age.
  - Any time of day.
  - Initial 10 to 20 mL of the urine stream (not mid-stream).
  - Preferably not having voided for at least 2 hours, but this does not preclude testing.
- Endometrial or fimbrial biopsy specimens for NAAT in women undergoing laparoscopy for investigation of pelvic inflammatory disease.
- Conjunctival swab for culture, EIA, DFA.
- Nasopharyngeal aspirate for culture in infants <6 months of age.
- Oropharyngeal and rectal specimens as required.

For information on specimen transport, see *Laboratory Diagnosis of Sexually Transmitted Infections* chapter.

Management

- Evaluation should be appropriate for the presenting symptoms, signs and sexual history.
- Treatment for chlamydia is indicated for the following:
  - A positive chlamydia test.
  - Diagnosis of a syndrome compatible with a chlamydial infection, without waiting for the test results of *C. trachomatis*.
  - Diagnosis of chlamydial infection in a sexual partner.
  - Empirical co-treatment when a diagnosis of *N. gonorrhoeae* is made without waiting for test results of *C. trachomatis* due to the significant probability of co-infection (20–42%)[12,13] and the possibility of false-negative results, especially with non-NAAT methods.

Treatment

- Efficacy and use-effectiveness studies evaluating single-dose azithromycin and a 7-day course of doxycycline have demonstrated similarly high cure rates; azithromycin is much more expensive.[38–47]
- Ofloxacin has an efficacy similar to doxycycline and azithromycin, but it is more expensive and needs to be taken as a multiple-dose course.[48–56]
- Erythromycin is associated with significantly higher gastrointestinal side effects than other regimens.[56–60]
- Drug resistance is rare but may become an emerging issue.[61,62]
- In the absence of a contraindication, the following treatment options are recommended.

Adults (non-pregnant and non-lactating): urethral, endocervical, rectal, conjunctival infection

(For pelvic inflammatory disease, see *Pelvic Inflammatory Disease* chapter; for epididymitis, see *Epididymitis* chapter.)

Table 3. Adults (non-pregnant and non-lactating): urethral, endocervical, rectal, conjunctival infection

Preferred	Alternative
• Doxycycline 100 mg PO bid for 7 days *[A-I]* OR • Azithromycin 1 g PO in a single dose if poor compliance is expected* *[A-I]*	• Ofloxacin 300 mg PO bid for 7 days *[B-II]* OR • Erythromycin 2 g/day PO in divided doses for 7 days† *[B-II]* OR • Erythromycin 1g/day PO in divided doses for 14 days† *[B-I]*

*If vomiting occurs more than 1 hour post-administration, a repeat dose is not required.
†Erythromycin dosages refer to erythromycin base. Equivalent dosages of other formulations may be substituted (with the exception of the estolate formulation, which is contraindicated in pregnancy). If erythromycin has been used for treatment, test of cure should be performed 3-4 weeks after completion of therapy.

Children

- Topical therapy alone for conjunctivitis is NOT adequate and is unnecessary when systemic treatment is used.
- The use of erythromycin in infants under 6 weeks of age has been associated with infantile hypertrophic pyloric stenosis (IHPS).[63-66] The risk of IHPS with other macrolides (e.g., azithromycin, clarithromycin) is unknown. The risks and benefits of using erythromycin in such infants should be explained to parents. When erythromycin is used in such infants, it is important to monitor for signs and symptoms of IHPS. IHPS following erythromycin use should be reported to the Canadian Adverse Drug Reaction Monitoring Program at 1-866-234-2345.

- The need to treat infants less than 6 weeks of age for *C. trachomatis* can be avoided by screening pregnant women and treating before delivery.
- Doxycycline is contraindicated in children under 9 years of age.
- Quinolones have been associated with articular damage in young animals. Such joint changes have not been clearly attributable to quinolone use in children. Its safety in children has not been established. Quinolones should not be used in prepubertal patients. Experience in pubertal patients under 18 years of age is limited.

Table 4. Children

First week of life	>1 week to 1 month	>1 month to <9 years	9–18 years
Infants ≤ 2000 g • Erythromycin 20 mg/kg/day PO in divided doses for at least 14 days*† *[B-II]* **Infants >2000 g** • Erythromycin 30 mg/kg/day PO in divided doses for at least 14 days*† *[B-II]*	• Erythromycin 40 mg/kg/day PO in divided doses for at least 14 days*† *[B-II]*	• Azithromycin 12–15 mg/kg (max. 1 g) PO in a single dose *[B-II]* **Alternatives** • Erythromycin 40 mg/kg/day PO in divided doses (max. 500 mg qid for 7 days or 250 mg qid for 14 days)*† *[B-II]* OR • Sulfamethoxazole 75 mg/kg/day PO in divided doses (max. 1 g bid) for 10 days† *[B-II]*	**Preferred** • Doxycycline 5 mg/kg/day PO in divided doses (max. 100 mg bid) for 7 days *[A-I]* OR • Azithromycin 12–15 mg/kg (max. 1 g) PO in a single dose if poor compliance is expected *[A-I]* **Alternatives** • Erythromycin 40 mg/kg/day PO in divided doses (max. 500 mg qid for 7 days or 250 mg qid for 14 days)*† *[B-I]* OR • Sulfamethoxazole 75 mg/kg/day PO in divided doses (max. 1 g bid) for 10 days† *[B-II]*

*Erythromycin dosages refer to the use of erythromycin base. Equivalent dosages of other formulations may be substituted (with the exception of the estolate formulation, which is contraindicated in pregnancy).
†If erythromycin or sulfamethoxazole has been used for treatment, repeat testing after completion of therapy is advisable.

Notes:

- Neonates born to infected mothers need to be tested for *C. trachomatis.* Neonates should be treated if their test results are positive. They should be closely monitored for signs of chlamydial infection (e.g., conjunctivitis, pneumonitis). Prophylaxis is not recommended unless follow-up cannot be guaranteed.
- Test of cure should be performed 3-4 weeks after the completion of treatment in all prepubertal children.

Pregnant women and nursing mothers: urethral, endocervical, rectal infection

- Clinical trials comparing amoxicillin, erythromycin and azithromycin have demonstrated similar microbiological and clinical cure, but maternal gastrointestinal side effects are more common with erythromycin.[67–75]
- To date, there are limited data collected on azithromycin in pregnancy, but it is considered to be safe in this context by many experts.[68–70,72–74]
- Doxycycline and quinolones are contraindicated in pregnancy and in lactating women.
- Clindamycin requires dosing three to four times a day for 10-14 days and does not offer any advantage. In addition, it is even more expensive than azithromycin and is thus not being listed as an option.
- Data on neonatal outcomes are limited.

Table 5. Pregnant women and nursing mothers: urethral, endocervical, rectal infection

- Amoxicillin 500 mg PO tid for 7 days* *[A-I]*

OR

- Erythromycin 2 g/day PO in divided doses for 7 days*† *[B-I]*

OR

- Erythromycin 1g/day PO in divided doses for 14 days*† *[B-I]*

OR

- Azithromycin 1 g PO in a single dose, if poor compliance is expected‡ *[B-I]*

*****If erythromycin or amoxicillin has been used for treatment in nursing mothers, test of cure should be performed 3-4 weeks after the completion of treatment.

†Erythromycin dosage refers to the use of erythromycin base. Equivalent dosages of other formulations may be substituted (with the exception of the estolate formulation being contraindicated in pregnancy). Gastrointestinal side effects are more severe with erythromycin than amoxicillin.

‡If vomiting occurs more than 1 hour post-administration, a repeat dose is not required.

Note: Test of cure should be performed 3-4 weeks after the completion of treatment in all pregnant women.

Considerations for Other STIs

- See *Primary Care and Sexually Transmitted Infections* chapter.
- Obtain specimen(s) for the diagnosis of *N. gonorrhoeae*.
- Obtain a blood sample for serologic testing for syphilis (see *Syphilis* chapter).
- HIV testing and counselling are recommended (see *Human Immunodeficiency Virus Infections* chapter).
- Immunization against hepatitis B is recommended in non-immune non-immunized individuals (see *Hepatitis B Virus Infections* chapter).
- Discuss HPV vaccine with women as per the recommendations outlined in the Canada Communicable Disease Report, Volume 33 ACS-2, (2007) *National Advisory Committee on Immunization (NACI) statement on Human papillomavirus vaccine.*

Reporting and Partner Notification

- *C. trachomatis* infections are reportable by laboratories and physicians to local public health authorities in all provinces and territories.
- All partners who have had sexual contact with the index case within 60 days prior symptom onset or date of diagnosis (if asymptomatic) should be tested and empirically treated regardless of clinical findings and without waiting for test results. If there was no partner during this period, then the last partner should be tested and treated.
- Parents of infected neonates (i.e., mother and her sexual partner[s]) should be located, clinically evaluated and treated.
- Local public health authorities are available to assist with partner notification and help with appropriate referral for clinical evaluation, testing, treatment and health education. If resources for local public health authority support are limited, priority for partner notification should be directed toward youth/young adults <25 years of age.

Follow-up

- Test of cure for *C. trachomatis* is not routinely indicated if a recommended treatment is taken AND symptoms and signs disappear AND there is no re-exposure to an untreated partner except:
  - Where compliance is suboptimal.
  - If an alternative treatment regimen has been used.
  - In all prepubertal children.
  - In all pregnant women.
- Test of cure using a NAAT, if needed, should be performed at 3-4 weeks after the completion of effective treatment to avoid false-positive results due to the presence of non-viable organisms.
- Repeat testing in all individuals with *C. trachomatis* infection is recommended 6 months post-treatment, as reinfection risk is high.
- In patients with apparent treatment failure, possibilities include the following:
  - Failure to take medication correctly or to finish course of therapy.
  - Re-exposure to an untreated partner.
  - Infection acquired from a new partner.
  - A false-positive result.
  - Rarely, resistance is an issue.
- In patients with persistent symptoms, infection with other pathogens and a non-infective etiology should also be considered.

Special Considerations

Children

- **It is essential** that neonates born to infected mothers be tested for *C. trachomatis.* Neonates should be treated if test results are positive. They should be closely monitored for signs of chlamydial infection (e.g., conjunctivitis, pneumonitis). Prophylaxis is not recommended unless follow-up cannot be guaranteed.
- Sexual abuse needs to be considered when genital, rectal or pharyngeal chlamydial infection is diagnosed in any prepubertal child, although perinatally acquired *C. trachomatis* can persist in an infant for up to 3 years. Consultation with a colleague experienced in such cases should be sought. Siblings and other children possibly at risk should also be evaluated.
- Sexual abuse of children must be reported to the local child protection agency (see *Sexual Abuse in Peripubertal and Prepubertal Children* chapter).
- All persons named as suspects in child sexual abuse cases should be located and clinically evaluated; prophylactic treatment may or may not be offered and the decision to treat or not should be based on history, clinical findings and test results (See *Sexual abuse in Peripubertal and Prepubertal Children* chapter).
- Follow-up cultures for “test of cure” are indicated approximately 3-4 weeks after completion of therapy in prepubertal children.

References

1. Patrick DM, Wong T, Jordan R. Sexually transmitted infections in Canada: recent resurgence threatens national goals. *Can J Hum Sexuality* 2000;9:149–165.
2. Public Health Agency of Canada. Reported cases of notifiable STI from January 1 to June 30, 2006 and January 1 to June 30, 2005. Available at: http://www.phac-aspc.gc.ca/std-mts/stdcases-casmts/cases-cas-07_e.html. Accessed on September 17, 2007
3. Farley TA, Cohen DA, Elkins W. Asymptomatic sexually transmitted diseases: the case for screening. *Prev Med* 2003;36:502–509.
4. Stamm WE, Koutsky LA, Benedetti JK, Jourden JL, Brunham RC, Holmes KK. *Chlamydia trachomatis* urethral infections in men. Prevalence, risk factors, and clinical manifestations. *Ann Intern Med* 1984;100:47–51.
5. Stamm WE. Expanding efforts to prevent chlamydial infection. *N Engl J Med* 1998;339:768–770.
6. Gaydos CA, Howell MR, Pare B, et al. *Chlamydia trachomatis* infections in female military recruits. *N Engl J Med* 1998;339:739–744.
7. Marrazzo JM, White CL, Krekeler B, et al. Community-based urine screening for *Chlamydia trachomatis* with a ligase chain reaction assay. *Ann Intern Med* 1997;127:796–803.
8. Marrazzo JM, Whittington WL, Celum CL, et al. Urine-based screening for *Chlamydia trachomatis* in men attending sexually transmitted disease clinics. *Sex Transm Dis* 2001;28:219–225.
9. Chen MY, Donovan B. Screening for genital *Chlamydia trachomatis* infection: are men the forgotten reservoir? *Med J Aust* 2003;179:124–125.
10. Andersen B, Olesen F, Moller JK, Ostergaard L. Population-based strategies for outreach screening of urogenital *Chlamydia trachomatis* infections: a randomized, controlled trial. *J Infect Dis* 2002;185:252–258.
11. Ginocchio RH, Veenstra DL, Connell FA, Marrazzo JM. The clinical and economic consequences of screening young men for genital chlamydial infection. *Sex Transm Dis* 2003;30:99–106.
12. Creighton S, Tenant-Flowers M, Taylor CB, Miller R, Low N. Co-infection with gonorrhoea and chlamydia: how much is there and what does it mean? *Int J STD AIDS* 2003;14:109–113.
13. Lyss SB, Kamb ML, Peterman TA, et al; Project RESPECT Study Group. *Chlamydia trachomatis* among patients infected with and treated for *Neisseria gonorrhoeae* in sexually transmitted disease clinics in the United States. *Ann Intern Med* 2003;139:178–185.
14. U.S. Preventive Services Task Force. Screening for Chlamydial Infection: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2007;147:128-134.
15. Meyers DS, Halvorson H, Luckhaupt S. Screening for Chlamydial Infection: An evidence update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007;147:135-142.
16. Braverman PK, Biro FM, Brunner RL, Gilchrist MJ, Rauh JL. Screening asymptomatic adolescent males for chlamydia. *J Adolesc Health Care* 1990;11:141–144.
17. Chernesky MA, Jang D, Lee H, et al. Diagnosis of *Chlamydia trachomatis* infections in men and women by testing first-void urine by ligase chain reaction. *J Clin Microbiol* 1994;32:2682–2685.
18. LaMontagne DS, Fine DN, Marrazzo JM. *Chlamydia trachomatis* infection in asymptomatic men. *Am J Prev Med* 2003;24:36–42.
19. Marrazzo JM, Celum CL, Hillis SD, Fine D, DeLisle S, Handsfield HH. Performance and cost-effectiveness of selective screening criteria for *Chlamydia trachomatis* infection in

women. Implications for a national Chlamydia control strategy. *Sex Transm Dis* 1997;24:131–141.
20. Moncada J, Schachter J, Shafer MA, et al. Detection of *Chlamydia trachomatis* in first catch urine samples from symptomatic and asymptomatic males. *Sex Transm Dis* 1994;21:8–12.
21. Domeika M, Bassiri M, Mardh PA. Diagnosis of genital *Chlamydia trachomatis* infections in asymptomatic males by testing urine by PCR. *J Clin Microbiol* 1994;32:2350–2352.
22. Anestad G, Berdal BP, Scheel O, et al. Screening urine samples by leukocyte esterase test and ligase chain reaction for chlamydial infections among asymptomatic men. *J Clin Microbiol* 1995;33:2483–2484.
23. Ciemins EL, Kent CK, Flood J, Klausner JD. Evaluation of chlamydia and gonorrhea screening criteria: San Francisco sexually transmitted disease clinic: 1997 to 1998. *Sex Transm Dis* 2000;27:165–167.
24. Health Protection Agency. New Frontiers – National Chlamydia Screening Programme Annual Report 2005/6. Available at: http://www.hpa.org.uk/publications/2006/ncsp/. Accessed on September 17, 2007.
25. Davies HD, Wang EE. Periodic health examination, 1996 update: 2. Screening for chlamydial infections. Canadian Task Force on the Periodic Health Examination. *CMAJ* 1996;154:1631–1644.
26. Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment Guidelines 2006. *MMWR Recomm Rep* 2006;55(RR-11):1–94.
27. Cohen I, Veille JC, Calkins B. Improved pregnancy outcome following sucessful treatment of chlamydial infection. *JAMA* 1990;263:3160–3163.
28. Ryan GM Jr, Abdella TN, McNeeley SG, Baselski VS, Drummond DE. *Chlamydia trachomatis* infection in pregnancy and effect of treatment on outcome. *Am J Obstet Gynecol* 1990;162:34–39.
29. Black-Payne C, Ahrabi MM, Bocchini JA Jr, Ridenour CR, Brouillette RM. Treatment of *Chlamydia trachomatis* identified with Chlamydiazyme during pregnancy. Impact on perinatal complications and infants. *J Reprod Med* 1990;35:362–367.
30. Schachter J, Sweet RL, Grossman M, Landers D, Robbie M, Bishop E. Experience with the routine use of erythromycin for chlamydial infections in pregnancy. *N Engl J Med* 1986;314:276–279.
31. McMillan JA, Weiner LB, Lamberson HV, et al. Efficacy of maternal screening and therapy in the prevention of chlamydia infection of the newborn. *Infection* 1985;13:263–266.
32. Whittington WL, Kent C, Kissinger P, et al. Determinants of persistent and recurrent *Chlamydia trachomatis* infection in young women: results of a multicenter cohort study. *Sex Transm Dis* 2001;28:117–123.
33. Schillinger JA, Kissinger P, Calvet H, et al. Patient-delivered partner treatment with azithromycin to prevent repeated *Chlamydia trachomatis* infection among women: a randomized, controlled trial. *Sex Transm Dis* 2003;30:49–56.
34. Gunn RA, Fitzgerald S, Aral SO. Sexually transmitted disease clinic clients at risk for subsequent gonorrhea and chlamydia infections: possible “core” transmitters. *Sex Transm Dis* 2000;27:343–349.
35. Rietmeijer CA, Van Bemmelen R, Judson FN, Douglas JM Jr. Incidence and repeat infection rates of *Chlamydia trachomatis* among male and female patients in an STD clinic: implications for screening and rescreening. *Sex Transm Dis* 2002;29:65–72.

36. Korenromp EL, Sudaryo MK, de Vlas SJ, et al. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD AIDS* 2002;13:91–101.
37. Schater J, McCormack WM, Chernesky MA, et al. Vaginal Swabs are appropriate specimens for diagnosis of genital tract infection with Chlamydia trachomatis. *Clin Microbiol* 2003;41:3784-3789.
38. Hillis SD, Coles FB, Litchfield B, et al. Doxycycline and azithromycin for prevention of chlamydial persistence or recurrence one month after treatment in women. A use-effectiveness study in public health settings. *Sex Transm Dis* 1998;25:5–11.
39. Hammerschlag MR, Golden NH, Oh MK, et al. Single dose of azithromycin for the treatment of genital chlamydial infections in adolescents. *J Pediatr* 1993;122:961–965.
40. Johnson RB. The role of azalide antibiotics in the treatment of Chlamydia. *Am J Obstet Gynecol* 1991;164(6 Pt 2):1794–1796.
41. Marra F, Marra C, Patrick DM. Cost-effectiveness analysis of azithromycin for *Chlamydia trachomatis* infection in women: a Canadian perspective. *Can J Infect Dis* 1997;8:202–208.
42. Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. The Azithromycin for Chlamydial Infections Study Group. *N Engl J Med* 1992;327:921–925.
43. Nilsen A, Halsos A, Johansen A, et al. A double blind study of single dose azithromycin and doxycycline in the treatment of chlamydial urethritis in males. *Genitourin Med* 1992;68:325–327.
44. Nuovo J, Melnikow J, Paliescheskey M, King J, Mowers R. Cost-effectiveness analysis of five different antibiotic regimens for the treatment of uncomplicated *Chlamydia trachomatis* cervicitis. *J Am Board Fam Pract* 1995;8:7–16.
45. Ossewaarde JM, Plantema FHF, Rieffe M, Nawrocki RP, De Vries A, van Loon AM. Efficacy of single-dose azithromycin versus doxycycline in the treatment of cervical infections caused by *Chlamydia trachomatis*. *Eur J Clin Microbiol Infect Dis* 1992;11:693–697.
46. Thorpe EM Jr, Stamm WE, Hook EW 3rd, et al. Chlamydial cervicitis and urethritis: single dose treatment compared with doxycycline for seven days in community based practises. *Genitourin Med* 1996;72:93–97.
47. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis* 2002;29:497–502.
48. Judson FN, Beals BS, Tack KJ. Clinical experience with ofloxacin in sexually transmitted disease. *Infection* 1986;14(suppl 4):S309–S310.
49. Fransen L, Avonts D, Piot P. Treatment of genital chlamydial infection with ofloxacin. *Infection* 1986;14(suppl 4):S318–S320.
50. Batteiger BE, Jones RB, White A. Efficacy and safety of ofloxacin in the treatment of nongonococcal sexually transmitted disease. *Am J Med* 1989;87(6C):75S–77S.
51. Nayagam AT, Ridgway GL, Oriel JD. Efficacy of ofloxacin in the treatment of non-gonococcal urethritis in men and genital infections caused by *Chlamydia trachomatis* in men and women. *J Antimicrob Chemother* 1988;22(suppl C):155–158.
52. Maiti H, Chowdhury FH, Richmond SJ, et al. Ofloxacin in the treatment of uncomplicated gonorrhea and chlamydial genital infection. *Clin Ther* 1991;13:441–447.
53. Faro S, Martens MG, Maccato M, Hammill HA, Roberts S, Riddle G. Effectiveness of ofloxacin in the treatment of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* cervical infection. *Am J Obstet Gynecol* 1991;164(5 Pt 2):1380–1383.

54. Hooton TM, Batteiger BE, Judson FN, Spruance SL, Stamm WE. Ofloxacin versus doxycycline for treatment of cervical infection with *Chlamydia trachomatis*. *Antimicrob Agents Chemother* 1992;36:1144–1146.
55. Kitchen VS, Donegan C, Ward H, Thomas B, Harris JR, Taylor-Robinson D. Comparison of ofloxacin with doxycycline in the treatment of non-gonococcal urethritis and cervical chlamydial infection. *J Antimicrob Chemother* 1990;26(suppl D):99–105.
56. Mogabgab WJ, Holmes B, Murray M, Beville R, Lutz FB, Tack KJ. Randomized comparison of ofloxacin and doxycycline for chlamydia and ureaplasma urethritis and cervicitis. *Chemotherapy* 1990;36:70–76.
57. Linnemann CC Jr, Heaton CL, Ritchey M. Treatment of *Chlamydia trachomatis* infections: comparison of 1- and 2-g doses of erythromycin daily for seven days. *Sex Transm Dis* 1987;14:102–106.
58. Cramers M, Kaspersen P, From E, Moller BR. Pivampicillin compared with erythromycin for treating women with genital *Chlamydia trachomatis* infection. *Genitourin Med* 1988;64:247–248.
59. Scheibel JH, Kristensen JK, Hentzer B, et al. Treatment of chlamydial urethritis in men and *Chlamydia trachomatis*-positive female partners: comparison of erythromycin and tetracycline in treatment courses of one week. *Sex Transm Dis* 1982;9:128–131.
60. Bowie WR, Manzon LM, Borrie-Hume CJ, Fawcett A, Jones HD. Efficacy of treatment regimens for lower urogenital *Chlamydia trachomatis* infection in women. *Am J Obstet Gynecol* 1982;142:125–129.
61. Somani J, Bhullar VB, Workowski KA, Farshy CE, Black CM. Multiple drug-resistant *Chlamydia trachomatis* associated with clinical treatment failure. *J Infect Dis* 2000;181:1421–1427.
62. Misyurina OY, Chipitsyna EV, Finashutina YP, et al. Mutations in a 23S rRNA gene of *Chlamydia trachomatis* associated with resistance to macrolides. *Antimicrob Agents Chemother* 2004;48:1347–1349.
63. Sorensen HT, Skriver MV, Pedersen L, Larsen H, Ebbesen F, Schonheyder HC. Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. *Scand J Infect Dis* 2003;35:104–106.
64. Cooper WO, Griffin MR, Arbogast P, Hickson GB, Gautam S, Ray WA. Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med* 2002;156:647–650.
65. Mahon BE, Rosenman MB, Kleiman MB. Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. *J Pediatr* 2001;139:380–384.
66. Honein MA, Paulozzi LJ, Himelright IM, et al. Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromcyin: a case review and cohort study. *Lancet* 1999;354:2101–2105.
67. Magat AH, Alger LS, Nagey DA, Hatch V, Lovchik JC. Double-blind randomized study comparing amoxicillin and erythromycin for the treatment of *Chlamydia trachomatis* in pregnancy. *Obstet Gynecol* 1993;81(5 Pt 1):745–749.
68. Kacmar J, Cheh E, Montagno A, Peipert JF. A randomized trial of azithromycin versus amoxicillin for the treatment of *Chlamydia trachomatis* in pregnancy. *Infect Dis Obstet Gynecol* 2001;9:197–202.

69. Wehbeh HA, Ruggeirio RM, Shahem S, Lopez G, Ali Y. Single-dose azithromycin for Chlamydia in pregnant women. *J Reprod Med* 1998;43:509–514.
70. Adair CD, Gunter M, Stovall TG, McElroy G, Veille JC, Ernest JM. Chlamydia in pregnancy: a randomized trial of azithromycin and erythromycin. *Obstet Gynecol* 1998;91:165–168.
71. Alary M, Joly JR, Moutquin JM, et al. Randomised comparison of amoxycillin and erythromycin in treatment of genital chlamydial infection in pregnancy. *Lancet* 1994;344:1461–1465.
72. Bush MR, Rosa C. Azithromycin and erythromycin in the treatment of cervical chlamydial infection during pregnancy. *Obstet Gynecol* 1994;84:61–63.
73. Genc MR. Treatment of genital *Chlamydia trachomatis* infection in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2002;16:913–922.
74. Jacobson GF, Autry AM, Kirby RS, Liverman EM, Motley RU. A randomized controlled trial comparing amoxicillin and azithromycin for the treatment of *Chlamydia trachomatis* in pregnancy. *Am J Obstet Gynecol* 2001;184:1352–1354.
75. Silverman NS, Sullivan M, Hochman M, Womack M, Jungkind DL. A randomized, prospective trial comparing amoxicillin and erythromycin for the treatment of *Chlamydia trachomatis* in pregnancy. *Am J Obstet Gynecol* 1994;170:829–831.