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# Recommendations for the Prevention and Management of *Chlamydia trachomatis* Infections, 1993

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**
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# Contents

# Recommendations for the Prevention and Management of *Chlamydia trachomatis* Infections, 1993

***Summary***

*In 1985, CDC published Policy Guidelines for Prevention and Control of* Chlamydia trachomatis *infections (1 ). Those guidelines highlighted the prevalence and morbidity of chlamydial infections and stressed the need to include antibiotics effective against chlamydia when treating patients for urethritis, mucopurulent cervicitis, and pelvic inflammatory disease. The recommendations presented in this report update the 1985 guidelines. In addition, these recommendations propose a national strategy for reducing the morbidity of chlamydial infections by detection and treatment and through the prevention of transmission to uninfected persons. Such an effort is now possible because of a) expanding educational efforts stimulated by the epidemic of acquired immunodeficiency syndrome and other sexually transmitted diseases, and b) the availability of chlamydia tests that are easy to use, economical, and accurate, thereby allowing health-care providers to diagnose and treat infected persons and their sex partners.*

*Education, screening, and sex partner referral require coordination of the activities of several professionals, including educators, clinicians, microbiologists, outreach workers, and program managers. Because chlamydial infections are common among adolescents and young adults throughout the United States, health-care providers and other agencies serving these groups should become more involved if a sufficiently large proportion of the chlamydia-infected population is to be reached. Health departments should establish consortia of these organizations to pool resources and to coordinate activities. To facilitate such collaborations, this document outlines the elements of a chlamydia prevention program.*

*These recommendations were developed by CDC after consultation with experts attending a chlamydia prevention workshop held in Atlanta, Georgia, March 26–28, 1991. Commentary from additional public health, medical, and laboratory practitioners also was considered in developing these recommendations.*

## INTRODUCTION

*Chlamydia trachomatis* infections are common in sexually active adolescents and young adults in the United States (*CDC, unpublished review* ). More than 4 million chlamydial infections occur annually (*2,3* ). Infection by this organism is insidious—symptoms are absent or minor among most infected women and many men. This large group of asymptomatic and infectious persons sustains transmission within a community. In addition, these persons are at risk for acute illness and serious long-term sequelae. The direct and indirect costs of chlamydial illness exceed $2.4 billion annually (*2–4* )*.

* **NOTE:** Direct and indirect costs were calculated from figures previously published.

Until recently, chlamydia prevention and patient care were impeded by the lack of suitable laboratory tests for screening and diagnosis. Such tests are now available. Through education, screening, partner referral, and proper patient care, public health workers and health-care practitioners can combine efforts to decrease the morbidity and costs resulting from this infection.

## Prevalence of Chlamydial Infection

Adolescents and young adults are at substantial risk of becoming infected with chlamydia. Unrecognized infection is highly prevalent in this group (*CDC, unpublished review*).

In the United States, published studies of sexually active females screened during visits to health-care providers indicate that age is the sociodemographic factor most strongly associated with chlamydial infection. Prevalence has been highest (>10%) among sexually active, adolescent females (*CDC, unpublished review*). The prevalence of chlamydial infection also has been higher among those patients who live in inner cities, have a lower socioeconomic status, or are black (*5–11*). Although prevalences have been higher in these subgroups, with few exceptions prevalences are ≥5% regardless of region of the country, urban/rural location of provider, or race/ethnicity (*CDC, unpublished review*).

Fewer screening studies have been reported for men, but prevalences have been >5% among young men seeking health care for reasons other than genitourinary tract problems. Published reports of these studies from North America and Europe have included male high school students (*12*), military personnel (*13,14*), semen donors (*15,16*), adolescents in detention centers (*17–20*), and teens attending adolescent clinics (*17,20*), adolescents attending university health centers (*20,21*), and chemical dependency units (*22*).

## Clinical Spectrum of Chlamydial Infection Among Nonpregnant Women

Pelvic inflammatory disease (PID) accounts for most of the serious acute illness, morbidity, and economic cost resulting from chlamydial infection. Treating women with acute, symptomatic PID is not a sufficient prevention strategy because treatment does not always prevent sequelae and because many women with tubal infection have symptoms too mild or too nonspecific for them to seek treatment.

A woman's exposure to chlamydia is usually a result of sexual intercourse. The site of initial infection is most often the cervix; the urethra and the rectum may also be infected (*23–28*). Chlamydia causes symptoms in a minority of infected women (*9, 29-38*). When symptoms occur, they include vaginal discharge and dysuria (*9,23,25–27,29–33,35–38*). The ascension of lower, genitourinary tract infection to the endometrium and fallopian tubes may cause lower abdominal pain and menstrual abnormalities. Untreated infections among women often persist for months (*7,34, 39–41*). During this period, complications may develop, and many of these women transmit their infection to others.

The proportion of women with chlamydial infection who develop infection of the upper reproductive tract (endometritis, salpingitis, and pelvic peritonitis) is uncertain; however, an estimated 8% of women with chlamydia also had overt salpingitis (*42*). A second study of women with dual gonococcal and chlamydial infections, but who were treated only for gonorrhea, revealed that 30% developed salpingitis during

follow-up (*43*). Chlamydia, alone or with other microorganisms, has been isolated from 5% to 50% of women seeking care for symptoms of PID (*CDC, unpublished review*). Symptomatic PID prompts 2.5 million outpatient visits to physicians annually (*44,45*). More than 275,000 women are hospitalized and more than 100,000 surgical procedures are performed yearly because of PID (*45*). Both the diagnosis and the treatment of PID are unsatisfactory: approximately 17% of women treated for PID will be infertile; an equal proportion will experience chronic pelvic pain as a result of infection (*46,47*); and 10% who do conceive will have an ectopic pregnancy (*48*).

The importance of undetected, untreated fallopian tube infections as a cause of infertility and ectopic pregnancy is clear. In two studies of chlamydia and PID in infertile women, PID was the cause of the infertility in half of the women, and anti-chlamydial antibody was strongly associated with a tubal etiology for infertility (*49,50*). Of concern in these studies was the small proportion of women with tubal-factor infertility who reported a past history of salpingitis. Other studies indicate that many of these women may have had salpingitis, but were not treated because symptoms were absent or nonspecific (*49,51–60*). Unrecognized PID also may be a contributor to the occurrence of ectopic pregnancies (*60,61*). Because chlamydial infections are not usually associated with overt symptoms, prevention of infection is the most effective means of preventing sequelae.

Pregnant women with chlamydial infection are at risk for postpartum PID. Postpartum and perinatal disease are preventable by treating infected pregnant women and their sex partners. Endometritis, and possibly salpingitis, developed among 10%–28% of pregnant women with untreated chlamydial infection who underwent induced abortions (*27,62–64*). Similarly, endometritis may develop during the late postpartum period among 19%–34% of infected pregnant women who deliver vaginally and at-term (*65,66*).

## Clinical Spectrum of Chlamydial Infection Among Infants

Nearly two-thirds of the infants born vaginally to mothers with chlamydial infection become infected during delivery (*67,68*). Even after ophthalmia prophylaxis with silver nitrate or antibiotic ointment, 15%–25% of infants exposed to chlamydia developed chlamydia conjunctivitis, and 3%–16% developed chlamydia pneumonia (*41,68–73*). *C. trachomatis* is the most common cause of neonatal conjunctivitis (*72,74–78*) and is one of the most common causes of pneumonia during the first few months of life (*79–85*). Infants with chlamydia pneumonia are at increased risk for abnormal pulmonary function tests later in childhood (*86–88*).

## Clinical Spectrum of Chlamydial Infection Among Men

Although urethritis is the most common illness resulting from chlamydia, chlamydial infections among men rarely result in sequelae. However, asymptomatic infected men may unknowingly infect their sex partner(s) before seeking treatment.

Chlamydial infections among heterosexual men are usually urethral. Symptoms are similar to gonorrhea (e.g., urethral discharge or dysuria). In contrast to gonorrheal urethritis, chlamydia symptoms are often absent or mild (*13–22,89*). Therefore, the number of heterosexual men with asymptomatic chlamydial infections is larger than the number of such men with gonorrhea.

Chlamydial infections of the lower genitourinary tract account for 30%–40% of the 4-6 million physician visits for nongonococcal urethritis (NGU), and 50% of the 158,000 outpatient visits and 7,000 hospitalizations for epididymitis among adolescent and young adult males (*2,3,90,91* ). Chlamydial infections among men readily respond to treatment with antibiotics. Most of the morbidity and economic costs of chlamydial infections among heterosexual men result from infection of female sex partners who develop sequelae (*3* ).

The rectum is a common site of initial chlamydial infection for men who engage in receptive anal intercourse. Rectal infections are generally asymptomatic, but may cause symptoms characteristic of proctitis (e.g., rectal discharge, pain during defecation) or proctocolitis (*92–96* ).

### Other Chlamydial Illnesses

Among adolescents and young adults of both sexes, chlamydial infection is an important part of the differential diagnosis for other, less common, illnesses. Chlamydia salpingitis may progress to perihepatitis—the Fitz-Hugh-Curtis syndrome (*97* ). Although chlamydia is an uncommon cause of cystitis symptoms among female patients, chlamydia has been an important cause of such symptoms in some groups of young women who have pyuria, but sterile urine cultures (acute dysuria-pyuria syndrome or urethral syndrome) (*5,38,98* ).

Another important, but uncommon complication of urogenital chlamydial infection is Reiter's syndrome (reactive arthritis, conjunctivitis, and urethritis), which occurs primarily among men. Chlamydia is receiving greater emphasis in the differential diagnosis of arthritis in young women because of the availability of diagnostic tests for chlamydia. Chlamydial infection is more likely to be missed among women than among men who have arthritis because of the less obvious role of urethritis.

Chlamydia is also part of the differential diagnosis of chronic conjunctivitis among adolescents and young adults (*99–102* ). Ocular or ophthalmic infections may result from exposure to infectious genital secretions during oral-genital sexual contact, or by autoinoculation. Although chlamydia can be detected in the pharynx after inoculation from oral-genital exposure (*103–111* ), chlamydia has not been established as a cause of pharyngitis (*103,104,110–114* ).

## PREVENTION STRATEGIES

The principal goal of chlamydia prevention strategies is to prevent both overt and silent chlamydia salpingitis and its sequelae. Other goals include the prevention of perinatal and postpartum infection and other adverse consequences of chlamydial infection.

### General Approach

The prevention of chlamydia salpingitis, pregnancy-related complications, and other chlamydial illnesses requires that chlamydia prevention programs include both primary and secondary prevention strategies.

### *Primary Prevention Strategies*

Primary prevention strategies are efforts to prevent chlamydial infection. Primary prevention of chlamydia can be accomplished in two general ways.

- Behavioral changes that reduce the risk of acquiring or transmitting infection should be promoted (e.g., delaying age at first intercourse, decreasing the number of sex partners, partner selection, and the use of barrier contraception [condoms]). Efforts to effect behavioral changes *are not specific* to chlamydia prevention but are also critical components in preventing sexual transmission of the human immunodeficiency virus (HIV) and other sexually transmitted diseases (STDs) (*45,115–117*).
- Identify and treat persons with genital chlamydial infection before they infect their sex partners, and for pregnant women before they infect their babies. Efforts to detect chlamydial infection are essential to chlamydia prevention. Identifying and treating chlamydial infections require active screening and referral of sex partners of infected persons, since infections among women and men are usually asymptomatic.

### *Secondary Prevention Strategies*

Secondary prevention strategies are efforts to prevent complications among persons infected with chlamydia. The most important complication to be prevented is salpingitis and its potential sequelae (i.e., ectopic pregnancy, tubal infertility, and chronic pelvic pain). Secondary prevention of chlamydia salpingitis can be accomplished by a) screening women to identify and treat asymptomatic chlamydial infection; b) treating the female partners of men with infection; c) recognizing clinical conditions such as mucopurulent cervicitis (MPC) and the urethral syndrome, and then applying or using appropriate chlamydia diagnostic tests and treatment, as appropriate.

## Target Population

Chlamydial infection is especially prevalent among adolescents. Furthermore, PID occurs more commonly after chlamydial infection among adolescent females than among older women (*42*). Therefore, chlamydia prevention efforts should be directed toward young women.

All sexually active adolescents and young adults are at high risk for chlamydia; the infection is broadly distributed geographically and socioeconomically. Therefore, chlamydia prevention programs should target all sexually active adolescents and young adults. All private and public health-care providers should be involved in these prevention efforts.

## Specific Strategies

Specific strategies for the prevention of chlamydia are grouped into two categories. Those categories are: a) community-based strategies, and b) health-care provider strategies.

### *Community-Based Strategies*

Since the prevalence of chlamydia is consistently high among adolescents and young adults regardless of socioeconomic status, race, or geographic location, prevention efforts should be implemented communitywide.

**Public Awareness.** Community-based strategies should increase public awareness of chlamydia, its consequences, and the availability and importance of diagnosis and treatment. Groups at high risk for chlamydial infection and the persons who educate and care for them (e.g., parents, teachers, and health-care providers) must be informed about the high rate of genital chlamydial infection and its sequelae among sexually active adolescents and young adults.

**HIV/STD Risk Reduction Programs.** Programs designed to reduce the risk of sexual transmission of HIV and other STDs by means of behavioral changes should emphasize the especially high risk of chlamydial infection. In addition, chlamydial infection may be a sentinel for unsafe sexual practices. Concern about chlamydia may provide additional motivation for persons to delay initiation of sexual activity, limit the number of sex partners, avoid sex partners at increased risk for STDs, and use condoms.

**Schools.** Because of their access to adolescents, educators have an important role to play in chlamydia prevention programs. Chlamydia-specific material should be integrated into educational curricula that address HIV and other STDs. In addition, school programs should assist students in developing the social and behavioral skills needed to avoid chlamydial infection, HIV, and other STDs.

Although most school health education curricula address HIV, fewer discuss other STDs (including chlamydia). Information that should be provided through school health education programs are listed below:

- Rates of chlamydial infection among adolescents
- Adverse consequences of chlamydia (e.g., PID and infertility)
- Symptoms and signs of chlamydial infection (and other STDs)
- Asymptomatic infection
- Treatment for sex partners
- Where and how to obtain health care (including locations, telephone numbers [e.g., STD hot-line number], costs, and issues of confidentiality)

Some schools may offer more than classroom instruction (e.g., access to health care for infected persons and screening programs to identify asymptomatic chlamydial infection). Personnel in school-based clinics that perform pelvic examinations should use the opportunity to test for chlamydial infection. However, tests also are needed to identify asymptomatic males (e.g., by screening urine collected during sports physical examinations or other health-screening programs). The leukocyte esterase test (LET) of urine is one possible method for testing males, but the accuracy of the test requires additional evaluation (*118*). Such approaches to identifying and

treating young men with asymptomatic chlamydial infection may prove important since these persons may account for most of the transmission of chlamydia to young women (see Laboratory Testing and Patient Care: An Expanded Role for the Use of Chlamydia Tests).

**Out-of-school Adolescents.** The prevalence of chlamydia may be even greater among adolescents who have dropped out of school. Therefore, organizations serving these adolescents (e.g., Job Corps, vocational training centers, detention centers, community-based recreational programs) should offer health care that addresses chlamydial infection as part of STD/HIV risk reduction programs.

### *Health-Care Provider Strategies*

Reducing the high prevalence of chlamydial infection requires that health-care providers be aware of the high prevalence of chlamydia and recognize chlamydial illness, screen asymptomatic patients, arrange for the treatment of sex partners, and counsel all sexually active patients about the risks of STD infections. Medical providers should be trained to recognize and manage the following conditions that may be caused by chlamydia: MPC, PID, urethral syndrome (women), and urethritis and epididymitis (men).

**Screening.** The screening of women for chlamydial infection is a critical component in a chlamydia prevention program since many women are asymptomatic, and the infection may persist for extended periods of time. Many women of reproductive age undergo pelvic examination during visits for routine health care or because of illness. During these examinations, specimens can be obtained for chlamydia screening tests.

Female patients of adolescent-care providers, women undergoing induced abortion, women attending STD clinics, and women in detention facilities should be screened for chlamydial infection. Screening of these women is important because a) many are adolescents or young adults, b) they are at high risk for salpingitis, and c) they or their partners are likely to transmit infection.

Chlamydia screening at family planning and prenatal care clinics is particularly cost-effective because of the large number of sexually active young women who undergo pelvic examinations.

Providers such as family physicians, internists, obstetricians-gynecologists, and pediatricians who provide care for sexually active young women also should implement chlamydia screening programs—although a lower volume of such patients may increase the cost of testing. The following criteria can help identify women who should be tested for chlamydia:

- Women with MPC
- Sexually active women <20 years of age
- Women 20–24 years of age who meet either of the following criteria, or women >24 years of age who meet both criteria—inconsistent use of barrier contraception, or new or more than one sex partner during the last 3 months.

Patient selection criteria should be evaluated periodically. Although the incidence of chlamydial infection among all women previously tested for chlamydia is unknown, the incidence of chlamydial infection among previously infected adolescent females has been as high as 39% (*118*). Because of the high incidence of chlamydial infection among sexually active adolescent females, recommendations for the frequency of testing are listed below:

- Women <20 years of age should be tested when undergoing a pelvic examination, unless sexual activity since the last test for chlamydia has been limited to a single, mutually monogamous partner.
- All other women who meet the suggested screening criteria (listed above) should be tested for chlamydia annually.

Although young men infrequently seek routine health care, medical providers should use such opportunities to evaluate them for asymptomatic chlamydial infection, possibly by means of the LET (*119*) (see Laboratory Testing and Patient Care: An Expanded Role for the Use of Chlamydia Tests).

**Treatment of Sex Partners.** Treatment of sex partners of infected persons is an important strategy for reaching large numbers of men and women with asymptomatic chlamydial infection. Also, if partners are not treated, reinfection may occur. In addition, treating the male partners of infected women is critical since this is the principal way to eliminate asymptomatic infection among males. If chlamydia screening is widely implemented, the number of infected women identified may exceed the capacity of some public health systems to notify, evaluate, and treat partners. Therefore, health department personnel should assist health-care providers in developing cooperative approaches to refer partners for treatment. Where possible, health-care providers who treat female patients for chlamydia should offer examination and treatment services for the patients' male sex partner(s), or should arrange the appropriate referral of such partners.

**Risk Reduction Counseling**. In addition to screening, treatment, and referral of sex partners(s) of persons with chlamydial infection, health-care providers should:

- Educate sexually active patients regarding HIV and other STDs,
- Assess the patients' risk factors for infection,
- Offer at-risk patients advice about behavior changes to reduce the risk of infection,
- Encourage the use of condoms.

**Preventing Chlamydial Infection During Pregnancy.** To prevent maternal postnatal complications and chlamydial infection among infants, pregnant women should be screened for chlamydia during the third trimester, so that treatment, if needed, will be completed *before* delivery (see Primary Prevention Strategies). The screening criteria already discussed can identify those at higher risk for infection. Screening during the first trimester prevents transmission of the infection and adverse effects of chlamydia

during the pregnancy. However, the evidence for adverse effects during pregnancy is minimal. If screening is performed only during the first trimester, a longer period exists for infection before delivery.

Infants with chlamydial infections respond readily to treatment; morbidity can be limited by the early diagnosis and systemtic treatment of infants who have conjunctivitis and pneumonia caused by chlamydial infection (secondary prevention strategies). Further, the mothers of infants diagnosed with chlamydial infection and the sex partner(s) of those mothers should be evaluated and treated.

## LABORATORY TESTING

Diagnostic test manufacturers have introduced a variety of nonculture tests for chlamydia, including enzyme immunoassays (EIAs) to detect chlamydia antigens, fluorescein-conjugated monoclonal antibodies for the direct visualization of chlamydia elementary bodies on smears, nucleic acid hybridization tests, and rapid (stat) tests. Because nonculture tests do not require strict handling of specimens, they are easier to perform and less expensive than culture tests; consequently the numbers of laboratories and health-care providers offering chlamydia testing have increased. The expanded use of nonculture tests is a cornerstone of chlamydia prevention strategies.

Although nonculture tests have advantages that make them more suitable than cell culture tests for widespread screening programs, nonculture tests also have limitations. In particular, nonculture tests are less specific than culture tests and may produce false-positive results. All positive nonculture results should be interpreted as *presumptive* infection until verified by culture or other nonculture test. The decision to treat and perform additional tests should be based on the specific clinical situation.

The test methodologies discussed in these recommendations are for the detection of *Chlamydia trachomatis*—not other chlamydia species (e.g., *C. psittaci* and *C. pneumoniae*). A number of commercial products for the detection of *C. trachomatis* are available; however, most information relating to the performance of most of these products is the manufacturers' data. When possible, health-care providers and laboratory staff should compare a potential nonculture test's performance with that of an appropriate standard in their own laboratory.

### Specimens for Screening

The proper collection and handling of specimens are important in all the methods used to identify chlamydia. Even diagnostic tests with the highest performance ratings cannot produce accurate results when specimens submitted to the laboratory are improperly collected. Clinicians require training and periodic assessment to maintain proper technique.

Because chlamydia are obligate intracellular organisms that infect the columnar epithelium, the objective of specimen collection procedures is to obtain columnar epithelial cells from the endocervix or the urethra. The following recommendations for specimen collection apply to all screening tests.

### *Preferred Anatomic Sites*

The endocervix is the preferred anatomic site to collect screening specimens from women. When culture isolation is to be used, processing an additional specimen from the urethra may increase sensitivity by 23% (*120*). Placing the two specimens in the same transport container is acceptable. For nonculture tests, the usefulness of a second specimen from the urethra has not been determined.

The urethra is the preferred site for collecting screening specimens from men.

### *Collecting Specimens*

The following guidelines are recommended for obtaining endocervical specimens:

- Obtain specimens for chlamydia tests after obtaining specimens for gram-stained smear, *Neisseria gonorrhoeae* culture, or Papanicolaou smear.
- Before obtaining a specimen for a chlamydia test, use a sponge or large swab to remove all secretions and discharge from the cervical os.
- For nonculture chlamydia tests, use the swab supplied or specified by the manufacturer of the test.
- Insert the appropriate swab or endocervical brush 1–2 cm into the endocervical canal (i.e., past the squamocolumnar junction). Rotate the swab against the wall of the endocervical canal several times for 10–30 seconds. Withdraw the swab without touching any vaginal surfaces and place it in the appropriate transport medium (culture, EIA, or deoxyribonucleic acid [DNA] probe testing) or prepare a slide (direct fluorescent antibody [DFA] testing).

The following guidelines are recommended for obtaining urethral specimens:

- Delay obtaining specimens until 2 hours after the patient has voided.
- Obtain specimens for chlamydia tests after obtaining specimens for gram-stain smear or *N. gonorrhoeae* culture.
- For nonculture chlamydia tests, use the swab supplied or specified by the manufacturer.
- Gently insert the urogenital swab into the urethra (females: 1–2 cm, males: 2–4 cm). Rotate the swab in one direction for at least one revolution for 5 seconds. Withdraw the swab and place it in the appropriate transport medium (culture, EIA, or DNA probe testing) or use the swab to prepare a slide for DFA testing.

### *Quality Assurance of Specimen Collection*

Without specimen quality assurance, ≥10% of specimens are likely to be unsatisfactory because they contain secretions or exudate, but lack urethral or endocervical columnar cells (*6,121–122*). Periodic cytologic evaluation of specimen quality is recommended when using non-DFA tests to ensure continued proper specimen collection.

## Cell Culture

Compared with other diagnostic tests for *C. trachomatis*, a major advantage of cell culture isolation is a specificity that approaches 100%. In cell culture, organisms from each of the three chlamydia species (*C. trachomatis*, *C. pneumoniae*, *C. psittaci* ) grow and produce intracytoplasmic inclusions. The direct visualization of these inclusions contributes to the specificity of cell culture in identifying chlamydia. The preferred method for identifying inclusions is to stain the infected cells with a species-specific, monoclonal fluorescein-labeled antibody (FA) for *C. trachomatis*. Alternative antibodies used to stain chlamydia inclusions that bind to chlamydia lipopolysaccharide (LPS) are NOT specific for *C. trachomatis* and also will stain *C. psittaci* and *C. pneumoniae* inclusions. In these recommendations, the use of *C. trachomatis*-specific, anti-major outer membrane protein (MOMP) antibody is the presumed method used for the detection of *C. trachomatis* isolated in cell culture.

Culture sensitivity is approximately 70%–90% in experienced laboratories (*123* ). Since culture amplifies small numbers of organisms, it is preferred for specimens in which low numbers of organisms are anticipated (e.g., asymptomatic infection). Culture also allows the organism to be preserved for additional studies, including the determination of immunotype (serovar) and antimicrobial susceptibilities.

Cell culture isolation has several disadvantages. First, the method is technically difficult and requires 3–7 days to obtain a result. Second, since only viable organisms are detected, special transport media must be used, and transportation and storage temperature requirements are stringent. Finally, some specimens contain contaminating microorganisms or substances that are toxic to the cell monolayers used for isolating chlamydia.

### *Indications for the Use of Cell Culture*

A high-quality culture system for chlamydia is the diagnostic method of choice and is essential for the diagnosis of chlamydia in all medical/legal situations.

Culture serves as the standard for the quality assurance of nonculture tests and for the evaluation of new diagnostic methods. Culture is recommended for detection of chlamydia in specimens for which nonculture methods have not been developed, have not been adequately evaluated, or perform poorly. Culture is recommended for specimens from the following sites:

- Urethral specimens (women and asymptomatic men).
- Nasopharyngeal specimens (infants).
- Rectal specimens (all patients, regardless of age).
- Vaginal specimens (prepubertal girls).

### *Collecting Specimens for Cell Culture*

Swabs with plastic or wire shafts can be used to obtain cell cultures. Swab tips can be made of cotton, rayon, dacron, or calcium alginate. Swabs with wooden shafts should not be used because the wood may contain substances that are toxic to chlamydia. As part of routine quality control, samples of each lot of swabs that are

used to collect specimens for chlamydia isolation should be screened for possible toxicity to chlamydia.

The substitution of an endocervical brush for a swab may increase the sensitivity of culture for endocervical specimens from nonpregnant women (*124*). However, the use of the endocervical brush may induce bleeding. Although such bleeding does not interfere with the isolation of *C. trachomatis*, patients should be advised about possible spotting.

### *Transporting Cell Culture Specimens*

The viability of chlamydia organisms must be maintained during transport to the laboratory. Consult with the laboratory regarding the selection of appropriate transport medium and procedures (*125,126*). Specific recommendations for transporting specimens are listed below:

- Specimens for culture should be stored at 4 C and inoculated in cell culture as quickly as possible after collection. The elapsed time until inoculation should not exceed 24 hours. If specimens cannot be inoculated within 24 hours, the specimens should be maintained at -70 C or colder.
- Specimens for culture should never be stored at -20 C or in "frost-free" freezers. These conditions cause a decrease in chlamydia viability.

### *Analyzing Cell Culture Specimens*

Cycloheximide-treated McCoy cells are commonly used to culture chlamydia. Different McCoy cell lines exist and some have reduced susceptibility to chlamydial infection. McCoy cells are available commercially and from the American Type Culture Collection. Specific recommendations for analyzing specimens include the following are listed below (*125,126*):

- Only cell lines that have been checked for their ability to support chlamydial growth should be used.
- The identification of *C. trachomatis* should be based on visualizing characteristic chlamydia inclusions using species-specific FA staining.
- Laboratories should determine periodically whether multiple passages will increase sensitivity.

**NOTE:** The specificity of culture is based on the identification of inclusions. The identification of chlamydia after culture by EIA, or any other method that does not identify characteristic intracytoplasmic inclusions, is NOT recommended.

### *Interpreting Cell Culture Results*

A positive cell culture and visualization of characteristic inclusions by species-specific monoclonal FA staining is required to diagnose a chlamydial infection. With proper technique, the specificity of cell culture isolation of *C. trachomatis* is nearly 100%.

A negative chlamydia culture does not rule out the presence of a chlamydial infection. The sensitivity of culture is approximately 70%–90% when recommended laboratory and specimen collection techniques are performed.

### *Quality Assurance of Cell Culture Specimen Collection*

The isolation and detection of chlamydia in cell culture are technically demanding. The training of clinicians and laboratorians, along with quality assurance of laboratory performance and specimen collection, is critical to performing cell culture adequately. Specific recommendations to follow for cell culture specimens are listed below:

- To monitor the sensitivity and specificity of the cell culture system, laboratories should include known samples to analyze appropriate positive and negative controls when clinical specimens are cultured.
- Periodically (i.e., monthly or bimonthly), positive controls should be submitted from patient settings to verify the effectiveness of transport systems.
- Reference laboratories should provide a quality assurance system for monitoring culture performance and specimen adequacy. These laboratories also should provide assistance in the evaluation of unexpected or discrepant results.

Educational materials developed by CDC are available through the National Laboratory Training Network for the training of laboratory personnel who perform cell culture isolation of *C. trachomatis* (CDC, Public Health Practice Program Office, Division of Laboratory Systems, Laboratory Practice Training Branch, 1600 Clifton Road, MS A-16, Atlanta, GA 30333). Clinical training in genital examinations, including correct specimen collection techniques, is available through CDC's Sexually Transmitted Diseases Prevention/Training Centers (CDC, National Center for Prevention Services, Division of STD/HIV Prevention, Training and Education Branch, 1600 Clifton Road, MS E-27, Atlanta, GA 30333).

## Nonculture Chlamydia Tests

More aggressive prevention strategies are now possible with the availability of nonculture test methods for the detection of chlamydia. Published evaluations of the performance of nonculture chlamydia tests are based primarily on the MicroTrak® DFA (Syva) test and the Chlamydiazyme® EIA (Abbott) test. Additional tests have been approved by the FDA for the detection of chlamydial infection. Published information on these other tests is increasing rapidly, but is still limited. The recommended uses of nonculture chlamydia tests for presumptive diagnosis, with and without additional testing, to verify a positive result are summarized in these recommendations (Table 1).

### *Description of Nonculture Tests*

Nonculture chlamydia tests include several categories that differ in format and execution.

**Direct Fluorescent Antibody (DFA) tests.** Depending on the commercial product used, the antigen that is detected by the antibody in the DFA procedure is either the MOMP or LPS. Specimen material is obtained with a swab or endocervical brush which is then rolled over the specimen "well" of a slide. After the slide has dried and the fixative has been applied, the slide can be stored or shipped at ambient temperature. The slide should be processed by the laboratory within 7 days after the specimen has been obtained. Staining consists of covering the smear with fluorescent monoclonal antibody that binds to chlamydia elementary bodies. Stained elementary bodies are then identified by fluorescence microscopy. Total processing time is 30–40 minutes. Only *C. trachomatis* organisms will stain with the anti-MOMP antibodies used in commercial kits. Cross-reactions can occur between the anti-LPS antibodies used in commercial kits and other bacterial species, as well as with *C. pneumoniae* and *C. psittaci*.

**Enzyme Immunoassay (EIA) Tests.** EIA tests detect chlamydia LPS with a monoclonal or polyclonal antibody that has been labeled with an enzyme. The enzyme converts a colorless substrate into a colored product. The intensity of the color is measured with a spectrophotometer, which provides a numerical readout. The specimens for EIA are collected by using specimen collection kits supplied by the manufacturer. These kits include swabs, transport tubes, and instructions (to obtain optimum performance of the test kit, manufacturer's instructions should be followed). Specimens can be stored

**TABLE 1. Recommended use of nonculture chlamydia tests**

| Population | Specimen | Prevalence* | Adverse effects of false-positive† | Nonculture chlamydia test |
|---|---|---|---|---|
| Women | Cervical | High | No† | Yes§ |
| | | High | Yes | With verification§ |
| | | Low | Yes or No | With verification§¶ |
| Men | Urethral | High (symptomatic) | No | Yes** |
| | | | Yes | With verification** |
| | | Low (asymptomatic) | Yes or No | Insufficient data |
| Women and men | Rectal | Any | Yes or No | No |
| Infants | Genital/rectal | Any | Yes or No | No |
| | Nasopharyngeal | Any | Yes or No | No |
| | Conjunctival | Any | Yes or No | Yes†† |

*High=≥5%.
†Includes adverse effects for a patient being misdiagnosed as having a sexually transmitted chlamydial infection.
§Includes the following tests: Chlamydiazyme®EIA, IDEIA®, Pace 2®, MicroTrak® DFA, and MicroTrak® EIA. Other tests cannot be recommended because of insufficient data.
¶Chlamydia tests in low-prevalence patient populations have not been extensively evaluated.
**Includes the following tests: Chlamydiazyme® and MicroTrak® DFA. Other tests cannot be recommended because of insufficient data.
††In a limited number of evaluations, nonculture test performance with conjunctival specimens has been at least as good as with genital specimens.

and transported at ambient temperature and should be processed within the time indicated by the manufacturer. Total processing time is 3–4 hours.

One disadvantage of the EIA methods that detect LPS is that cross-reaction of the antibody with other microorganisms leads to false-positive results (*125,127–129*). In addition, the LPS-based EIA tests detect all three chlamydia species and, therefore, are not specific for *C. trachomatis*. Some manufacturers have developed blocking assays that are used to verify positive EIA test results. The test is repeated on initially positive specimens with the addition of a monoclonal antibody specific for chlamydia LPS. The monoclonal antibody competitively inhibits chlamydia-specific binding by the enzyme-labeled antibody; a negative result with the blocking antibody is interpreted as verification of the initial positive test result.

**Nucleic Acid Hybridization Tests (DNA Probe).** Nucleic acid hybridization methods can be used for the diagnosis of chlamydial infections. In the hybridization assay, a chemiluminescent DNA probe that is complimentary to a specific sequence of *C. trachomatis* ribosomal RNA (rRNA) is allowed to hybridize to any chlamydia rRNA that is present in the specimen. The resulting DNA:rRNA hybrids are adsorbed to magnetic particles and are then detected by using a luminometer that provides a numerical readout. The test kit includes a specimen collection swab and transport medium. Specimens should be maintained at temperatures of 2–25 C during transport and storage. The manufacturer suggests that assays be performed within 7 days after collection; otherwise the specimens should be stored at -20 C or colder. Total processing time is 2–3 hours.

The technical requirements and the necessary expertise to perform nucleic acid hybridization tests are similar to those of the EIA methods. The probe assay is specific for *C. trachomatis*; cross-reactions with organisms other than *C. trachomatis*, including *C. pneumoniae* and *C. psittaci*, have not been reported. A competitive probe assay has been developed to provide a means of assuring high specificity. The usefulness of the competitive assay is being evaluated in clinical trials and has not been approved for in vitro use by the Food and Drug Administration (FDA).

**Rapid Chlamydia Tests.** Chlamydia tests have been developed that can be performed within 30 minutes, do not require expensive or sophisticated equipment, and are packaged as single units. The results are read qualitatively. These rapid or stat tests can offer advantages in physicians' offices, small clinics and hospitals, and settings in which results are needed immediately (e.g., when making decisions about additional testing or treatment while the patient is still present). Like EIAs, these tests use antibodies against LPS that detect all three chlamydia species, but are subject to the same potential for false-positive results due to cross-reactions with other microorganisms. The performance characteristics of these tests have not been extensively evaluated. In addition, since rapid chlamydia tests are designed to be performed by nonlaboratory personnel, quality assurance is essential. Personnel requirements, quality assurance, and quality control requirements relating to the use of these and other tests are published in the Clinical Laboratory Improvement Amendments (CLIA) (*130*) and are governed by the test categorization compilation.

**Leukocyte Esterase Test (LET).** The LET is a dipstick test that is applied to urine specimens to screen for urinary tract infection. The LET detects enzymes that are produced by polymorphonuclear leukocytes. These enzymes hydrolyze an indoxylcarbonic acid ester on the dipstick to indoxyl, which reacts with an indicator in the strip to produce a purple color. The procedure requires <2 minutes to perform after the specimen is collected.

### *Accuracy of Nonculture Tests and Recommendations for Use*

For small-volume testing, DFA may be preferred because the quality of the specimen can be assessed. Automated tests are probably preferable for high-volume testing, but a quality control system is essential for monitoring the adequacy of specimens.

Published evaluations of the performance of nonculture chlamydia tests are based primarily on the MicroTrak® DFA (Syva) test and the Chlamydiazyme® EIA (Abbott) test. Additional tests have been approved by the FDA for the detection of chlamydial infection. Published information on these other tests is increasing, but is still limited.

**Cervical Specimens from Women (Sensitivity).** The performance characteristics of MicroTrak® DFA and Chlamydiazyme® nonculture chlamydia tests have been reported in published evaluations of women in high-prevalence (≥5%) patient populations. Sensitivities, using culture as a standard, have varied greatly but generally exceed 70% (*CDC, unpublished review* ). This variability in reported sensitivity is a result of differences in specimen collection technique, performance of the culture system used as a standard, and patient characteristics (e.g., age, MPC, and other factors such as prevalence of chlamydial infection, duration of infection, and previous exposure to chlamydia) (*121,122,128,131–136* ). A sensitivity of at least 70% is adequate for screening, but not sufficient to exclude chlamydial infection (see Patient Care: An Expanded Role for the Use of Chlamydia Tests).

Evaluations have been presented or published for the use of a number of tests for cervical specimens from women. Such tests include IDEIA® (Dako Diagnostics), Pace 2® (Gen-Probe), MicroTrak® EIA (Syva), and Clearview® (Unipath) tests. Sensitivities reported for these tests are comparable to sensitivities reported for Chlamydiazyme® and MicroTrak® DFA. However, chlamydia diagnostics experts recommend additional evaluation of these tests. First, the true sensitivity of these tests may be less than that indicated in published reports. The number of evaluations published for any given test is small and the number of patients with chlamydial infections studied in most evaluations is also small. Therefore, sensitivities may prove to be lower (or higher) as more evaluations are reported. More evaluations need to be conducted by laboratories that have quality assurance programs for culture including, for example, exchange of specimens with other laboratories (proficiency testing). Evaluations that compare new tests directly with established tests would aid in determining the performance of new tests. Second, none of these tests have been adequately evaluated in low-prevalence patient populations. Diagnostics experts are concerned that differences in factors such as previous exposure to chlamydia and duration of infection may result in lower test sensitivities in low-prevalence populations (*128* ). Third, although the reported performance of the Clearview® rapid (stat) test approaches that of Chlamydiazyme®

and MicroTrak® DFA, additional evaluations are needed to determine its performance when the test is used in an outpatient setting during the patient's visit. Too few evaluations have been reported for other chlamydia tests to assess their sensitivities (≤3 patient care-laboratory settings or 240 patients with chlamydia isolated by cell culture).

***Specificity and Predictive Value Positive***. The specificity of nonculture tests for cervical specimens has been high (97%–99%). However, clinicians should be aware that even with these high specificities, false positive results account for an important proportion of all positive test results among groups of patients with a low prevalence of chlamydial infection. The effect of false-positive tests in a population can be quantified by the predictive value positive (PVP). The PVP is the proportion of all persons who have a positive test result for a condition who actually have that condition. In chlamydia screening applications, the PVP is influenced primarily by the specificity of the test and the prevalence of chlamydia. For example, when a nonculture test with a specificity of 98% and a sensitivity of 80% is used to screen 1,000 patients from a high-risk patient population with a chlamydia prevalence of 15% (150 patients have an infection), the test produces 137 positive results: 120 patients are actually infected and 17 are not infected (false-positives). The PVP is 120/137=0.88. When this same test is used to screen 1,000 patients from a low-risk patient population with a chlamydia prevalence of only 2% (20 patients have an infection), 36 positive results are obtained: 16 patients are infected and 20 are not. The PVP is 16/36=0.44. In the low-risk patient population, fewer than half the patients with positive tests actually have chlamydial infection; the remainder are at risk of being incorrectly identified as having an STD unless the clinician takes other measures, such as arranging for verification when screening results are positive.

Specificities of the nonculture tests have been <99% in most published evaluations even when a third test was used to detect false-negative cultures. Contamination of cervical specimens with vaginal secretions is responsible for some false-positive tests when using Chlamydiazyme. The polyclonal anti-LPS antibody used in Chlamydiazyme crossreacts with LPS on other bacteria found in the vagina and urinary tract of these patients (*121,122,125,127,128,137* ). The source of nonspecific fluorescence with MicroTrak® DFA and of nonspecific signals with tests using monoclonal antibodies or genetic probes has not been determined. **NOTE:** Hereafter, a prevalence of <5% is considered to be "low prevalence." At a 5% prevalence (specificity 99% and sensitivity 80%), the PVP would be 80%. Although defining low prevalence as <5% is arbitrary, the potential for 20% of positive test results to be falsely positive (in the absence of a second test for verification) supports the utility of this cutoff.

***Verifying Positive Screening Test Results***. Clinicians should verify positive screening test results with a supplemental test if a false-positive test result is likely to have adverse medical, social, or psychological consequences (Table 1). Verification should probably be routine in low-prevalence patient populations, but might be selective in high-prevalence populations. Methods that are suitable for verifying positive nonculture tests for cervical specimens are recommended below:

- Verify positive tests by culture, using fluorescein-conjugated *C. trachomatis*-specific antibody. Culture is the most sensitive and specific method for verification. However, verification with culture requires a second specimen that is collected either at the time the first specimen is collected or during a return visit. Because of the limited availability of culture testing and the requirement for a second specimen, culture should be used for verification only if very high specificity is required (e.g., medical/legal situations).
- Perform a second nonculture test that identifies a *C. trachomatis* antigen or a nucleic acid sequence that is different from that identified by the screening test. Theoretically, detecting a second, highly specific antigen or nucleic acid sequence should provide adequate specificity for verification. However, this approach has had limited evaluation in field trials. A positive screening test may be verified by a second test using a second specimen that is collected either at the time the first specimen is collected or during a return visit. To avoid taking a second specimen, some EIA test manufacturers suggest using the excess specimen in the EIA transport medium for verification of positive EIA tests with a DFA test.
- Use an unlabeled "blocking" antibody or "competitive" probe that verifies a positive test result by preventing attachment of the labeled antibody or probe that is used in the standard assay. These methods are theoretically less desirable because they identify the same molecules as those identified by the initial nonculture tests. However, the Chlamydiazyme® blocking antibody test appears to produce adequate results (*127,138–142*). These methods do not require collecting a second specimen.

With the exception of the Chlamydiazyme® blocking antibody test, nonculture methods of verifying initial positive chlamydia test results have received insufficient evaluation. Since the sensitivity of tests used for verification of positive chlamydia tests is uncertain but <90%, failure to verify the initial positive test does not rule out chlamydial infection. Evaluation studies are needed to determine which of the above approaches is preferable in relation to sensitivity, specificity, and cost (see Clinician-Laboratory Protocols for Verifying Positive Tests).

**Urethral Specimens from Men.** The use of the Chlamydiazyme® EIA test and the MicroTrak® DFA test for urethral specimens from males with symptomatic urethritis has been evaluated in published studies. Reported sensitivities of the Chlamydiazyme® EIA and MicroTrak® DFA tests among men with chlamydial urethritis have been highly variable but usually exceed 70%. These sensitivities are sufficiently high to recommend using these tests to detect chlamydial infections among men with symptomatic urethritis. In such men, detection of chlamydial infection may be useful in promoting examination and treatment of sex partners and managing the patient's infection. Neither nonculture tests nor tissue culture isolation are sufficiently sensitive to rule out chlamydial infection based solely on a negative test result.

Positive Chlamydiazyme® and MicroTrak® DFA tests have been highly predictive of chlamydial infection among adolescent and young adult men with symptomatic urethritis. The reported specificities of the Chlamydiazyme® EIA and MicroTrak® DFA tests for urethral specimens from men with symptomatic urethritis have been sufficiently high (97%–≥99%). Because Chlamydiazyme® may yield false-positive results from the urine of men with bladder infections, a positive nonculture test result may be less predictive of chlamydial infection among older men who have a higher incidence of nonchlamydial urinary tract infection (*143*).

Because information on the performance of the nonculture tests among asymptomatic men is limited and tests for identifying asymptomatic urethral infection among men may be insensitive, none of the nonculture tests are recommended for this group of patients.

### *Other Nonculture Test Specimens*

**Urine.** The LET can be used to screen sexually active teenage males for urethritis, which is often caused by chlamydia or gonorrhea. Patients with positive results indicating the presence of urethritis require specific tests for *C. trachomatis* and *N. gonorrhoeae*. Reported sensitivities of the LET in screening for chlamydia and gonorrhea range from 46% to 100% and specificities range from 83% to 100% (*19,20,144,145*). Data are insufficient to recommend its use for older males or for women.

**Rectum**. Culture is the preferred method for detecting chlamydia in rectal specimens. Some DFA reagents have been approved by the FDA to evaluate rectal specimens; however, the specificity of the test for rectal specimens may be less than that for specimens from the cervix or the urethra. If DFA is used, slides should be read only by highly experienced microscopists.

**Conjunctiva**. Although data are limited, the performance of nonculture tests with conjunctival specimens has been at least as effective as with genital specimens.

**Nasopharynx (Infants)**. Nonculture tests have not been adequately evaluated for the detection of *C. trachomatis* in nasopharyngeal specimens. Many of these tests cannot distinguish between *C. trachomatis*, *C. pneumoniae*, or *C. psittaci*.

**Serum**. Chlamydia serology has little value in the routine clinical care of genital tract infections. Commercial serologic tests are not useful in routine diagnosis because previous chlamydial infections elicit long-lasting antibodies that cannot be easily distinguished from the antibodies produced in a current infection.

Immunoglobulin M microimmunofluorescence (MIF) is the test used frequently for the diagnosis of chlamydial pneumonia among infants. Chlamydia serology is also useful for persons with symptoms consistent with lymphogranuloma venereum

(LGV). For such persons, a fourfold rise in MIF titer to LGV antigens or a complement fixation titer of ≥1:32 supports a presumptive diagnosis of LGV. The difficulties in preparing antigens and in performing these tests restrict their use to a limited number of reference and research laboratories.

**Post-Treatment Tests**. If a post-treatment test is performed using a nonculture test, the test should be scheduled a minimum of 3 weeks after completion of antimicrobial therapy. Tests performed earlier may be false-negative because of small numbers of chlamydia organisms; the presence of dead organisms also causes false-positive nonculture test results (see Follow-up of Patients Treated for Chlamydial Infection).

### *Quality Assurance of Nonculture Tests*

As more laboratories begin to provide diagnostic services for chlamydial infections, the development of an infrastructure for laboratory quality assurance is increasingly important. Sites in which laboratory testing is performed must adhere to the CLIA regulations for staffing, professional training, patient test management, quality assurance, and quality control (*130*). Federal and state regulatory agencies that monitor quality assurance and quality control may have additional requirements and should be consulted for specific information.

Each laboratory should verify the accuracy of nonculture test methods by periodically comparing its results with those obtained by using a high-quality culture system. In addition, CLIA recommends that laboratories enroll in proficiency testing programs, such as those provided by the College of American Pathologists and the American Proficiency Institute. These quality assurance measures are especially important when a laboratory implements a new test method.

Training is recommended for the performance of all laboratory tests for chlamydia. Sources of training include product manufacturers, the National Laboratory Training Network (a source of instructional material that also may assist in locating or cosponsoring training workshops), and individual state public health laboratories.

All clinicians, particularly new providers of chlamydia testing services, should be trained in order to obtain adequate specimens. This training should include a) instruction in obtaining sufficient numbers of cells from any particular site, and b) instruction in obtaining endocervical cells rather than ectocervical cells or vaginal material from the cervix.

## Laboratory Testing for Sexual Assault and Abuse Victims

Detailed information concerning the evaluation and treatment of suspected victims of sexual assault or abuse may be obtained from the *1993 Sexually Transmitted Diseases Treatment Guidelines* (*146*) and the *Sexually Transmitted Diseases Clinical Practice Guidelines 1991* (*147*).

Specimens that are taken for chlamydia testing immediately after sexual assault may yield false-negative results because of small numbers of organisms present early in infection. Also, tests may be positive because of prior — not assault-acquired — infection. Specimens for chlamydia cultures should be obtained from adults and adolescents during the initial evaluation and at a follow-up visit 2 weeks later. Specimens should be obtained from all sites of exposure.

Among children, specimens should be routinely collected from the pharynx and the rectum in addition to the vagina (girls). In the absence of signs of urethral infection, obtaining a urethral specimen from boys may not be justified because of a relatively low yield of positive test results and the discomfort associated with obtaining the specimen. The decision to obtain specimens at a follow-up examination must be determined according to each case. Obtaining such follow-up specimens may not be justified if the exposure occurred several days or more before the initial examination, or if the examination would be psychologically traumatic.

Only cell culture isolation using standard methods employing *C. trachomatis*-specific antibodies should be used to detect *C. trachomatis* infection in the investigation of possible sexual abuse (*129*). Nonculture tests are not sufficiently sensitive or specific to be used in the investigation of sexual abuse (*129,138,148–151*). All specimens and isolates from both suspected victims and alleged assailants should be stored at -70 C or colder in case additional testing by a qualified reference laboratory is needed.

## Future Directions for Laboratory Testing

The availability of sensitive and noninvasive *C. trachomatis*-specific screening tests for men and women (e.g., urine tests) will greatly expand the population that can be screened. For women, such tests are not now available. For men, sensitivities for EIA methods for detecting chlamydia in first-voided urine range from 30% in a group of asymptomatic men (*152*) to approximately 88% in men with symptoms (*153*). Although specificity is ≥97%, increased rates of false-positive results have been reported with specimens from men with urinary tract infections caused by *Escherichia coli* and *Klebsiella pneumoniae* (*143*). Further studies are needed before noninvasive *C. trachomatis* screening tests for asymptomatic men can be recommended.

Recent evidence suggests that the numerical results of nonculture tests, together with the cutoff point for a positive result, might aid laboratories and clinicians in determining when to perform a second test to verify the initial results (*139,154*). Positive results that substantially exceed the cutoff point may be more likely to be true positives than those near the cutoff point. Similarly, negative results that are close to the cutoff point may be less likely to be true negatives than those with lower values. By establishing a zone just above and just below the cutoff, specimens giving low-positive or high-negative results would be evaluated by a second test. The desired effect would be to increase both the sensitivity and specificity of tests. Although studies are in progress, data are insufficient for a formal recommendation on the use of numerical results.

Technologies will continue to be refined, thereby improving both the sensitivity and the specificity of available tests for sexually transmitted chlamydial infections. Because of their ability to amplify chlamydia DNA in the specimen, new technologies such as polymerase chain reaction (CPCR) and ligase chain reaction (LCR) promise specificities equal to, and sensitivities higher than, those of culture.

## PATIENT CARE: AN EXPANDED ROLE FOR THE USE OF CHLAMYDIA TESTS

The *Chlamydia trachomatis* infections policy guidelines published in 1985 (*1*) emphasized the need to include treatment for chlamydia in regimens for patients whose diagnoses were strongly associated with chlamydial infection. The increasing availability of accurate and economical chlamydia tests permits widespread screening of asymptomatic persons, but also suggests that chlamydia treatment for symptomatic patients and the referral of sex partners *in the absence of testing*, a key strategy in past guidelines, should be discouraged. These tests should be used to diagnose chlamydia for patients with symptoms or signs suggestive of chlamydial infection even if therapy is administered and partners are referred before test results are available. A specific chlamydia diagnosis should facilitate sex partner referral since a positive chlamydia test result indicates that the patient's infection is sexually transmitted. A specific diagnosis may also facilitate medical care for patients who do not respond as expected to initial chlamydia therapy.

Some providers do not have resources to screen asymptomatic patients for chlamydia and to also test patients whose conditions warrant presumptive treatment and partner referral. If presumptive treatment of patients with symptoms or signs of chlamydia without testing is elected, efforts must be made to ensure the treatment of partners.

Although the benefits of chlamydia tests for screening and diagnosis justify their use, the potential for adverse consequences must also be recognized and steps taken to minimize them. The adverse consequences for infected patients and their sex partners, including disease complications and transmission of chlamydial infection, may occur if chlamydia treatment is delayed while waiting for test results or if treatment is withheld because of a false-negative test result. Adverse consequences also may occur if uninfected patients and their sex partners are treated unnecessarily because the chlamydia test result is unavailable or false-positive. The adverse consequences of treating uninfected persons are more likely to be psychosocial, resulting from the misdiagnosis of a sexually transmitted infection; adverse effects of the antibiotic used to treat chlamydia are relatively uncommon and mild.

These adverse consequences can be avoided by a) treating patients who are symptomatic or have a substantially increased risk of chlamydial infection and treating their sex partners for chlamydia without waiting for chlamydia test results, and b) arranging for a second test to verify an initial positive screening test result for patients and their sex partners who are susceptible to the adverse psychosocial consequences of having a false diagnosis of an STD.

### Presumptive Diagnosis of Chlamydial Infection

Several conditions—NGU, PID, epididymitis, and gonococcal infection—are consistently associated with an increased prevalence of chlamydial infection among patients and their sex partners (Table 2). Patients with these illnesses require immediate treatment to relieve symptoms and/or to prevent complications. Treatment for these conditions should include an antibiotic regimen for chlamydia. Sex partners of infected patients should be evaluated and treated for chlamydia without waiting for the patient's test results.

Immediate chlamydia treatment of MPC is warranted by an increased prevalence of chlamydia among women with this condition in most patient care settings. However, immediate chlamydia treatment of MPC or urethral syndrome among females or proctitis among homosexual males—and the referral of sex partners of patients with any of these conditions before obtaining a microbiologic diagnosis—may not always be warranted (Table 3). Chlamydia risk factors (e.g., age <25 years, having new or multiple sex partners) and the likelihood of compliance with follow-up visits should be considered when deciding whether to defer chlamydia treatment and referral of sex partners until chlamydia test results are available. Whenever possible, these decisions should be based on local estimates of chlamydia prevalence.

### Chlamydia Tests for Patients Who Are Treated Presumptively

Even if a patient with a presumptive diagnosis of chlamydial infection will be treated and counseled to refer partners before test results are known, chlamydia tests should be performed:

- Ensuring appropriate medical care, particularly if symptoms persist,
- Facilitating counseling of the patient,
- Providing firm grounds for partner notification,
- Improving compliance.

Limited resources may require health-care providers to decide between performing chlamydia tests for patients who would be treated for chlamydia because of symptoms or signs and patients who are asymptomatic and would not otherwise receive chlamydia treatment. If the health-care provider elects to provide presumptive treatment for patients with symptoms or signs—but without chlamydia testing—efforts must be made to ensure treating the sex partners of patients.

**TABLE 2. Conditions warranting a presumptive diagnosis of chlamydial infection**

| Condition | Chlamydia prevalence (%)* | |
|---|---|---|
| | Patients | Partners |
| NGU (heterosexual men) | 30–40 | 10–43 |
| PID | 8–54 | 36 |
| Epididymitis (men <35 years of age) | 50 | 10–43† |
| Gonococcal infection | | |
| Men | 5–30 | 40 |
| Women | 25–50 | Unknown |

*Unpublished review of literature.
†Expected to approximate or exceed prevalence for partners of men with NGU.

**NOTE:** Chlamydia may be a relatively uncommon cause of NGU or PID in some patient care settings. In such settings, immediate treatment, including an antibiotic regimen for chlamydia is warranted, but clinicians may refer sex partners contingent upon a positive test result for *C. trachomatis* or *N. gonorrhoeae*.

## Screening Women for Chlamydial Infection

Screening of women for chlamydial infection is a principal element of a chlamydia prevention program (see Health-Care Provider Strategies). The decision to provide treatment for patients whose screening results are positive and to evaluate and treat their sex partners depends upon the patient's risk for a sexually transmitted infection and the potential for adverse psychosocial consequences. A positive second chlamydia test strongly supports the validity of a positive screening test; a negative second test following a positive second test does not rule out chlamydial infection.

Verification of the initial positive chlamydia test result should be obtained for persons who have a positive nonculture chlamydia test and who are at low risk for infection (e.g., involved in a monogamous relationship, have no history of sexually transmitted infection, member of low-prevalence [<5%] patient populations) or for whom a misdiagnosis of chlamydial infection could lead to social/psychological distress. If verification of the initial positive chlamydia test result is indicated, these patients and their sex partners should be treated while waiting for the results of the supplementary test. The health-care provider should postpone treatment and partner referral only if the likelihood and adverse consequences of a false-positive test outweigh the risks of transmission and disease progression. Risk factors for chlamydial infection and the probability that the patient will return for follow-up visits should also be considered. (see Nonculture Chlamydia Tests and Clinician-Laboratory Protocols for Verifying Positive Tests).

## Screening Men for Chlamydial Infection

Screening tests for chlamydia would be more acceptable if urine rather than intraurethral swab specimens could be used. Chlamydia-specific nonculture tests (i.e., EIA, DFA, and nucleic acid probe tests) have not been adequately evaluated for use with urine. However, the LET detects inflammatory cells in urine. Persons whose LET test results are positive require further evaluation of the cause of inflammation, which generally will be urethritis due to chlamydia, *N. gonorrhoeae* or other sexually transmitted agents, or occasionally a urinary tract infection unrelated to a sexually transmitted agent. The utility of the LET in detecting urethritis has been evaluated primarily among adolescent males for whom urinary tract infections other than urethritis are rare. In this group, the sensitivity of the LET in detecting asymptomatic chlamydial infection has varied from 46% to 100% (*19,20,144,145*). Compared with the use of chlamydia-specific tests, the LET is inexpensive, easy-to-use, and provides

**TABLE 3. Conditions that may not warrant a presumptive diagnosis of chlamydial infection**

| Condition | Chlamydia prevalence (%)* | |
|---|---|---|
| | Patients | Partners |
| MPC | 9–51 | 2–27[†] |
| Proctitis (homosexual males) | 8–16 | Unknown |
| Acute urethral syndrome | 13–63 | Unknown |

*Unpublished review of literature.
[†]Lower value is the product of lowest reported prevalence among women with MPC multiplied by lowest reported prevalence among partners of women with chlamydia; highest value is the product of the highest reported prevalence among women with MPC and the highest reported prevalence among partners of women with chlamydia.

immediate results. Although the test cannot exclude infection among asymptomatic males, continued evaluation of the LET is recommended to better define its usefulness in detecting asymptomatic chlamydial (and gonococcal) infections.

### Physical Examination of Sex Partners

Female partners of males with chlamydial infection should be referred for examination, chlamydia testing, and treatment. The examination and testing of female partners is recommended because a) sensitive tests are available, and a positive test result may lead to additional partners who are likely to be infected; b) women can be asymptomatic but, when examined, have signs of PID, which requires more intensive therapy; and c) women may be asymptomatically infected with other STDs. However, information is needed on the rates of PID and other STDs among female partners of infected men.

Male sex partners of females with chlamydial infections should be evaluated for symptoms of chlamydia and other sexually transmitted infections and for allergy to the treatment drug. A physical examination of male sex partners should be encouraged, but an examination is less important than treatment.

The examination and testing of asymptomatic male partners are recommended because a) a positive test result may lead to the treatment of additional partners who are likely to be infected, b) men can be asymptomatically infected with other STDs, and c) male partners may be allergic to the treatment drug. However, chlamydia tests for asymptomatic males are insensitive. Further, low rates of other STDs among asymptomatic male partners of women with chlamydial infection have been demonstrated in limited studies. Also, many males do not have readily identifiable sources of medical care for STDs and so may be unlikely to be evaluated by a clinician even if asked to do so by a sex partner. For some male partners of women with chlamydial infection, therefore, it may be reasonable for the woman's clinician to evaluate the male partner even if, in the case of providers who do not offer health-care services for men, this means evaluation without a physical examination. Although approaches to evaluating male partners without a physical examination have not been adequately studied, evaluation of the male partner could be performed at the clinician's office or possibly by telephone. Before prescribing treatment without an examination, the clinician should determine that the male partner does not have symptoms suggestive of another STD and is not allergic to the treatment drug.

### Exposure Periods

For women with chlamydial infections and for asymptomatically infected men, health-care providers should treat all sex partners with whom patients have ongoing sexual relations and all other partners with whom patients have had sexual exposures within 60 days before the date of the patient's examination/test.

For males with symptomatic chlamydial infection, the 30-day period is sufficient to detect person(s) who probably transmitted the infection to the index patient, as well as recent sex partners who may have been exposed to the infection by the patient.

For males and females with asymptomatic infections, a longer exposure period helps to identify additional infected partners. These extended periods, however, have received insufficient evaluation to support specific recommendations. If no sexual exposure has occurred within the specified exposure periods, the most recent sex

partner is presumed to be at increased risk for chlamydial infection and should be evaluated.

## Responsibility for Referral of Sex Partners

Health-care providers should inform infected patients that they must have their sex partners evaluated and treated. Health-care providers or health departments should ensure the notification, evaluation, and treatment of the sex partners of patients with chlamydial infection. Partner referral can be performed by patients (patient referral) or by providers (provider referral). Patients who do comply with partner referral notify their sex partners of their exposure and encourage them to be examined and treated. Provider referrals require that third parties (e.g., health department personnel) assume responsibility for notifying sex partners of their exposure and providing evaluation and treatment.

Provider referral of partners—including field follow-up by health department staff—is cost effective (*155*). However, because of the high prevalence of chlamydial infection among some populations and the limited number of health department outreach workers, patient referrals remain the only method of referral available to most clinicians.

The responsibility for evaluating the sex partners of persons with chlamydial infection is often unclear and is a major reason partners remain untreated. This is a particular problem for male partners of females with chlamydial infection; male partners (who are often asymptomatic) may be reluctant to visit an STD clinic. Health-care providers who treat women with chlamydial infection should assist in making arrangements for the evaluation and treatment of male partner(s). Health departments can assist health-care providers in developing effective referral systems.

## Clinician-Laboratory Protocols for Verifying Positive Tests

Clinician-laboratory protocols for chlamydia testing are necessary to maximize the benefits of testing for chlamydia while minimizing adverse consequences and cost. These protocols should address which initial and supplementary tests the laboratory will perform, how clinicians should request these tests, and what specimens the clinicians should collect and submit to the laboratory during the patient's initial and follow-up visits. State and local health departments should facilitate the collaboration between health-care providers and laboratories that is necessary to develop suitable testing protocols (See Nonculture Chlamydia Tests).

When developing clinician-laboratory protocols for chlamydia testing, the prevalence of chlamydial infection in the patient population should be considered. In settings with a high prevalence of infection (e.g., false-positive test results account for a small proportion of total positive test results), initial positive test results might only be verified if requested by the clinician on the basis of an assessment of a patient's risk for infection and the potential adverse effects of a false-positive result. In settings with a low prevalence of infection (e.g., false-positive test results account for a substantial proportion of total positive test results), an additional test for verification should be performed on all patients whose screening test results are positive.

Three alternative testing protocols are suitable for supplementary testing. With the first protocol, a test system is chosen that permits performing the supplementary test on the residual material from the initial specimen. With the second protocol, a test

system is chosen in which the supplementary test is performed on a second specimen. The clinician routinely obtains the second specimen at the same time as the initial specimen and submits both specimens to the laboratory; the supplementary test is performed on the second specimen if the initial test is positive and verification is required. With the third protocol, the laboratory reports a positive result from the initial test to the clinician who arranges the patient's return visit for treatment and then obtains a second specimen for a supplemental test. In most settings, one of the first two protocols is preferable since they do not require a return visit to collect an additional specimen. The choice of supplementary test systems and related protocols is difficult because insufficient information is available regarding their comparative performance and cost.

## ANTIMICROBIAL REGIMENS

Recommendations for the treatment of genital chlamydial infections have been published (*146,156*). Two new antimicrobials approved by the FDA for the treatment of chlamydia—ofloxacin and azithromycin—offer the clinician additional therapeutic choices. A substantial advantage of azithromycin, in comparison with all other therapies, is that a single dose is effective; this antimicrobial may prove most useful in situations in which compliance with a 7-day regimen of another antimicrobial cannot be ensured. In view of the high efficacy of tetracycline and doxycycline, cost also should be considered when selecting a treatment regimen.

The recommended treatment regimens for uncomplicated urethral, endocervical, or rectal chlamydial infections among adults are listed below:

- Doxycycline 100 mg orally 2 times a day for 7 days

  or

- Azithromycin 1 gm orally in a single dose

**NOTE:** Doxycycline and azithromycin are not recommended for use during pregnancy.

### Alternative Treatment Regimens

Alternative treatment regimens for uncomplicated urethral, endocervical, or rectal chlamydial infections among adults are listed below:

- Ofloxacin 300 mg orally 2 times a day for 7 days

  or

- Erythromycin base 500 mg orally 4 times a day for 7 days

  or

- Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days

  or

- Sulfisoxazole 500 mg orally 4 times a day for 10 days

**NOTE:** Ofloxacin is not recommended for treating adolescents ≤17 years of age nor for pregnant women. The efficacy of sulfisoxazole is inferior to other regimens.

The recommended treatment regimen for chlamydial infection during pregnancy is stated below:

- Erythromycin base 500 mg orally 4 times a day for 7 days

*If this regimen cannot be tolerated, the following regimens are recommended:*

- Erythromycin base 250 mg orally 4 times a day for 14 days

or

- Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days

or

- Erythromycin ethylsuccinate 400 mg orally 4 times a day for 14 days

*If the patient cannot tolerate erythromycin, the following regimen is recommended:*

- Amoxicillin 500 mg orally 3 times a day for 7–10 days

**NOTE:** Erythromycin estolate is contraindicated during pregnancy, since drug-related hepatotoxicity can result.

For the treatment of complicated chlamydial infection, chlamydia-associated conditions, and chlamydial infection among infants or children, see the *1993 Sexually Transmitted Diseases Treatment Guidelines* (*146*) for the treatment of adults, and the *American Academy of Pediatrics Report of the Committee on Infectious Diseases* (*157*) for the treatment of infants and children.

## Follow-up of Patients Treated for Chlamydial Infection

Treatment failure, indicated by positive cultures 7–14 days after therapy, is uncommon after successful completion of a ≥7 day regimen of tetracycline or doxycycline; failure rates of 0%–3% have been reported for males and 0%–8% for females (156,158 ). However, in one study of adolescents followed up to 24 months after therapy for chlamydial infection, rates of infection were 39% (*118*). Whether these infections are reinfections or cases of latent, unsuccessfully treated chlamydial infection is unknown. Further, some studies suggest that women with chlamydial infections are at increased risk for subsequent infection.

Although routine test-of-cure visits during the immediate post-treatment period are not recommended, health-care providers should consider retesting females infected with chlamydia weeks to months after initial therapy (see Nonculture Chlamydia Tests).

## SURVEILLANCE AND PROGRAM EVALUATION

Information should be collected at the national, state, and local levels to provide quantitative estimates of disease occurrence, monitor trends, and monitor interventions and evaluate their impact. The epidemiologic analysis of surveillance and intervention data should be the basis for decision-making in chlamydia prevention programs, including allocation of intervention resources and evaluation of prevention efforts. In addition, these data can be used to develop hypotheses for etiologic and intervention research.

Surveillance of chlamydial infections is difficult for four reasons. First, the prevalence rate is high and the potential burden of reporting cases correspondingly large. Second, many infected patients are asymptomatic and, therefore, are difficult to identify except through screening programs. Third, because the duration of infection cannot be determined for many patients, prevalence and incidence are difficult to distinguish. Finally, maintaining a surveillance system requires substantial resources for laboratory testing and information systems.

### Reporting Laws

All states should have laws or regulations requiring that information on cases of chlamydial infection be reported to the appropriate public health departments.

- Reporting laws or regulations should acknowledge chlamydia as a public health problem and should provide the legal basis for establishing chlamydia surveillance systems.
- Reporting laws or regulations should allow states to collect information regarding cases of chlamydial infection from health-care providers and laboratories. Specific categories of data should include demographics (age, race/ethnicity, sex, geographic location, source of report), clinical characteristics (anatomic site, symptoms/signs, treatment), and behaviors (risk factors).

**NOTE:** In many areas, reporting laws or regulations are also important because they are linked to the laws and regulations that authorize health departments to initiate and support prevention activities such as screening and partner notification.

### Reportable Conditions

The recommended surveillance definition is a case of chlamydial infection diagnosed by a positive laboratory test result. If tests are performed to verify a positive chlamydia test result, reporting should be contingent on verification of the initial positive test result. Reports of chlamydial complications or of conditions serving as surrogates for chlamydial infection—when chlamydia tests are not available—should be analyzed separately.

NGU, PID, ophthalmia neonatorum, and epididymitis are the principal conditions that might be reported as complications of, or surrogates for, chlamydial infection. The performance of chlamydia tests and their results should be included with reports of these conditions.

## Establishing a Surveillance System

To measure chlamydia trends accurately, identify populations with an increased frequency of chlamydial infection and to estimate the burden of chlamydia disease, health departments should develop active chlamydia surveillance systems. These systems should incorporate the following recommendations:

- Encourage participation by private and public health-care providers and laboratories to ensure that results are representative of the whole population.
- Include measures of incidence as well as prevalence of chlamydial infections.
- Use screening results as an index of the prevalence of asymptomatic chlamydial infection.

### *Monitoring Incidence*

Health departments should monitor chlamydia incidence by collecting information regarding men who seek care because of symptoms of urethritis. If tests are performed, the results of chlamydia and gonorrhea laboratory tests should be included with reported cases of urethritis. If chlamydia testing is not performed, the reported incidence of NGU should be used as an index of chlamydia incidence.

### *Monitoring Prevalence (Screening)*

The number of chlamydia cases identified by community screening programs should be monitored as an index of chlamydia prevalence. Information on the following factors that affect the number of chlamydia cases detected should also be collected:

- Number of chlamydia tests being performed
- Reason for chlamydia testing (e.g., asymptomatic screening or diagnostic testing performed because of symptoms)
- Characteristics of the population undergoing chlamydia testing

In some states, the volume of chlamydia cases precludes collecting sufficient information on each case of chlamydia. These states should develop community-based sentinel surveillance to monitor trends in the distribution of chlamydial infections and disease burden by demographic, behavioral, and clinical factors.

With a sentinel system, a group of health-care providers serving patients who are representative of select populations in the community are recruited to monitor chlamydial infection rates. Examples of potential sentinel sites include STD clinics, family planning clinics, prenatal-care providers, community health centers, school health providers, jails and detention centers, and group practices or health maintenance organizations.

A sentinel site monitoring the prevalence of chlamydia should test all patients (or a given number of consecutive patients or a random or systematic sample of patients) for chlamydial infection regardless of the patient's chief complaint or symptom status. Demographic, behavioral, and clinical information should be recorded for all patients tested. A sentinel site that monitors the incidence of NGU should collect information

on all male patients with symptoms of urethritis and negative test results for gonorrhea. When possible, sentinel sites should monitor the prevalence of gonococcal infections and the incidence of gonococcal urethritis for all patients and the key sequelae of chlamydial and gonococcal infections (e.g., PID, infertility, ectopic pregnancy).

### *Laboratory Surveillance*

Because the surveillance definition of chlamydial infection requires laboratory testing, local laboratories are an important component of a chlamydia surveillance system. Health departments should establish an inventory of laboratories conducting chlamydia testing and poll them regularly for the number of chlamydia tests performed and the number of positive test results.

### Monitoring Interventions

Chlamydia prevention programs should monitor intervention activities. Health departments should monitor the extent and quality of the interventions (process evaluation). Data should be analyzed to determine whether chlamydia trends (measured by surveillance systems) can be linked to interventions (outcome evaluation). Screening and partner notification are interventions of particular interest. The following guidelines are recommended:

- To permit health departments to monitor screening programs, participating health-care providers should provide screening test results (see Monitoring Prevalence).
- Where substantial resources are allocated to partner notification or other interventions, health departments should monitor these activities to ensure optimal distribution of those resources.

## ORGANIZING STRATEGIC PARTNERSHIPS

The primary goal of a chlamydia prevention strategy should be to secure the resources to provide adolescents and young adults with access to information regarding chlamydial infection, screening and treatment services, and partner notification. Meeting this goal will require the cooperation of all agencies and programs that serve the health-care needs of adolescents and young adults. Every community has an opportunity to provide appropriate educational material regarding STDs and sexual behaviors, and to make screening and treatment for STDs more readily available to those at high risk for chlamydial infection. For example, some family planning programs provide chlamydia testing and treatment for their clients and their male sex partners, and a similar service is provided in some STD clinics. However, these efforts reach only a portion of the population that is infected with chlamydia. Such programs should be expanded to include other primary care providers who deliver medical services to sexually active adolescents and young adults—community health centers, migrant health centers, Native-American health centers, school-based clinics, Job Corps, detention centers, active-duty military facilities, hospital emergency rooms, and providers in the private sector. Schools, community-based recreational and after-

school programs such as YMCAs, and other agencies can offer information about STDs (including HIV infection).

A successful chlamydia prevention program should effectively coordinate all resources in a community. State STD/HIV prevention programs can provide solutions since their staff have experience in organizing clinical, educational, and laboratory resources within states, and they have developed partnerships with providers (e.g., family planning, prenatal, and migrant health clinics) who are part of any prevention program. The challenge is to focus on the common problem—high rates of chlamydial infection throughout the country—and to develop the interagency relationships and coalitions that are needed to deliver appropriate chlamydia services in both public and private settings.

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