

# Recent advances in understanding and managing *Chlamydia trachomatis* infections

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## Abstract

Worldwide, *Chlamydia trachomatis* infections rank among the most common sexually transmitted infections (STI), and cause notable reproductive morbidity in women. Although advances in highly accurate and non-invasive diagnostic testing have allowed for better estimation of the burden of disease—especially the asymptomatic state—we still lack a true point-of-care test, and many infections go undetected and untreated. Moreover, limited resources and effort for managing sexual partners of those in whom infection is actually identified comprise a major challenge to control. Here, we review the current state of understanding of this common infection, and efforts to control it.

## Introduction

*C. trachomatis* is the most commonly reported bacterial infection in the US and the most common cause of urethritis in men and cervicitis in women, and certain strains can cause severe proctitis in men who have sex with men (MSM) [1]. Because most infections cause neither symptoms nor signs—especially in women, 90% of whom are asymptomatic—a large reservoir of untreated persons provides an ongoing source for efficient disease transmission. Unfortunately, the asymptomatic nature of chlamydial infections in the female reproductive tract facilitates the silent immunopathogenesis that causes scarring of the Fallopian tubes, ovaries, endometrial lining, and occasionally the adjacent perineum, promoting future ectopic pregnancy and tubal infertility. For this reason, *C. trachomatis* is thought to be the most costly non-viral sexually transmitted infection STI, with total lifetime direct medical costs estimated at \$516.7 million [2].

Screening programs aimed at preventing pelvic inflammatory disease (PID) in women began in the late 1980s and were endorsed by the US Preventive Screening Task Force (USPSTF) and the Centers for Disease Control and Prevention (CDC) in the mid-1990s [3]. Although the

adverse sequelae of chlamydial infections in women have generally declined in countries with established screening programs, generalized prevalence has not—an observation that has prompted several intriguing hypothetical explanations. Has there been a shift in the natural history of the pathogen? Has screening promoted a shorter duration of infection and thus modified the host immune response? Have screening programs simply continued to target new populations at high risk over time? Is single-dose treatment of uncomplicated genital infections with azithromycin—widely used—adequate? These questions have generated considerable controversy, and the answers to them are critical to informing our future approach to control of this important STI.

## Current epidemiologic trends

In 2012, 1,422,976 chlamydial infections were reported to the CDC in 50 states and Washington, DC—a rate of 456.7 cases per 100,000 population—remarkably, the largest number of cases of any disease ever reported to the CDC during a year's time [1]. However, these surveillance data had encouraging trends. The case count represented a small increase (only 0.7%) from the prior year, the smallest such increase recorded since this surveillance began. Also, the rate in women did not increase from

the prior year. However, the overall rate of infection in the US in women (643.3 cases per 100,000 women) was more than twice that among men (262.6 cases per 100,000 men), likely reflecting the fact that women are considerably more likely to be screened than are men. More men are probably being tested as urine-based assays are increasingly used: the CDC STD Surveillance Report notes that, over the years of 2008 to 2012, the chlamydia rate in men increased by 25%. Because 90% of cervical infections in women cause neither signs nor symptoms and at least 60% of urethral infections in men are asymptomatic, these rates are undoubtedly an underestimate of the true burden of disease.

Selective screening of appropriate women is necessary to control this infection and its sequelae, and most experts agree that it has effected widespread declines in reproductive tract sequelae; whether it has effected declines in prevalent infection is a question of debate [4]. The USPSTF and the CDC recommend that all sexually active women age 25 years or younger be screened annually for *C. trachomatis* and that screening of older women be based on behavioral risk criteria [5,6]. Despite this, rates of appropriate screening in young women remain sub-optimal, and interventions to enhance screening in target populations are needed [7].

Some features of chlamydia epidemiology have remained constant since surveillance was initiated in the US. Prevalence is consistently highest among young women (15 to 24 years of age), and rates peak among men at a slightly older age (20 to 24 years) [1]. In one prospective study of a cohort of 14,322 individuals between the ages of 18 and 26 years, the prevalence of chlamydial infection was 4.2% [8]. The highest rates were in African-American women (14%) and overall were higher in women than men. Some experts believe that a decline in prevalence with age may be related to the development of partial immunity to clinical infection through periodic repeated exposures as well as to changes in behavior [9,10].

In both men and women, race, ethnicity, economic disadvantage, and geographic region modify the likelihood of infection being detected. For example, in 2012, the rate in blacks was over seven times the rate in whites. State-specific prevalence was highest in Alaska, where disease is heavily focused in the Native Alaskan population. Among women, prevalence was very high among those economically disadvantaged women who were 16 to 24 years old and who entered the National Job Training Program; median state-specific prevalence was 11.0% (range 5.5% to 19.4%). Among men entering this program, median state-specific prevalence was 7.0% (range 0.6% to 13.5%).

## Global epidemiology

Few nationally representative data—as opposed to convenience samples—are available for most countries in the world. The World Health Organization estimated that, in 2008, 105.7 million new cases of chlamydia occurred worldwide, a 4.1% increase since the last comprehensive assessment, in 2005 [11]. A population-based study in China estimated the prevalence of *C. trachomatis* infection at the surprisingly high rate of 2.1 per 100 population; unprotected sex with a commercial sex worker was a significant risk factor for infection among men from 20 to 44 years of age [12]. One interesting feature of recent *C. trachomatis* epidemiology is the so-called Swedish new variant, first reported in 2006 in Sweden and initially undetected by the nucleic acid amplification test (NAAT) in use at the time, thus allowing infections caused by this strain to go undetected and cause a nationwide network of related infections [13]. Subsequent modification of testing protocols has resulted in relatively lower proportion of chlamydial infections due to this organism, and it remains most common in the Nordic countries.

## Sexual minority populations

*C. trachomatis* is likely to be diagnosed as an asymptomatic infection through routine annual screening at the rectal site or as a cause of proctitis in men who engage in receptive anal intercourse with other men in the form of lymphogranuloma venereum (LGV). Whereas uncomplicated genital chlamydial infections are caused by *C. trachomatis* serovars D-K, LGV is caused by serovars L1, L2, and L3. LGV strains of *C. trachomatis* continue to cause discrete outbreaks of ulcerative proctitis in industrialized countries, and some data suggest that this pathogen is not sought as a cause of proctitis as often as is warranted [14-16]. Nearly all cases reported in such outbreaks are among HIV-infected MSM who report unprotected receptive anal sex, and the L2 serovar is the dominant pathogen. In an outbreak of LGV described in the UK among 282 MSM, the majority (96%) had proctitis with either severe or systemic symptoms, and there was a high level of coinfection documented with HIV (76%), hepatitis C (19%), and other STIs (39%) [15].

Despite the clinical picture associated with LGV, the majority of rectal chlamydial infections, especially non-LGV, are asymptomatic [17]. Moreover, in the most recent study, 85% of chlamydial infections in this population of MSM occurred at the rectum and would have been missed if only urethral screening was performed; thus, routine screening of sexually exposed anatomic sites (urethra and rectum) should be performed in MSM.

Women who were 15 to 24 years old, who were attending family planning clinics in the US Pacific Northwest during

1997 through 2005, and who reported same-sex behavior had higher positivity of *C. trachomatis* than women who reported exclusively heterosexual behavior [18]. Of note, there was also high chlamydia positivity among American Indian/Alaska Native women who reported sex with women, a finding consistent with racial/ethnic disparities previously noted. Possible explanations for this observation relate to differences in these two groups' use of reproductive health-care services (including chlamydia screening), biological susceptibility to lower genital tract infection, infrequent use of barrier methods to prevent STI transmission with female partners, trends toward higher risk behavior, and differential characteristics of their respective sexual networks.

### Natural history and the immune response

The natural history of *C. trachomatis* varies, and efforts to define its determinants are ongoing, particularly in light of declines in incidence of its complications in women. Several prospective studies have documented high rates of repeat infection in the months after an initial chlamydial infection. In the most rigorous of these, test-of-cure was performed approximately 30 days after treatment to document antibiotic cure; participants then returned at 3 months for repeat screening, thus documenting that repeat infection actually occurred. Among 272 men followed for 4 months after a diagnosis of chlamydial infection in Baltimore, Denver, and San Francisco, repeat infection occurred in 13% (incidence, 45.4 infections per 100 person-years) [19]. Among 897 female adolescents attending school-based health centers, 236 had one or more subsequent positive tests for a cumulative incidence of reinfection in one year of 26.3% (95% confidence interval [CI] 23.4 to 29.2) [20]. Rescreening several months after a diagnosis of chlamydia is recommended as a population-level prevention method. This intervention, unfortunately, is underutilized [21] and should be prioritized for widespread benefit.

Some investigators have hypothesized that high rates of reinfection are due in part to antibiotic therapy being provided, on average, earlier in the course of infection than would have been the case had screening programs not been in place. This "arrested immunity hypothesis" suggests that early antibiotic treatment effectively attenuates the optimal development of protective immunity, leaving individuals as susceptible as before to reinfection with the same or a new serovar [9,10]. Population-based surveillance data certainly support high rates of reinfection. The most relevant animal data are from the murine model, which show that when primary chlamydial infection resolves in the absence of antibiotic therapy, the animals show evidence of immunity against subsequent challenge [22,23]. Geisler and colleagues

evaluated whether spontaneous resolution of chlamydial infection in humans was associated with decreased reinfection in women returning for treatment for a positive chlamydia screening test [24]. Of the women who experienced spontaneous resolution, reinfection was less frequent relative to those women who had persistent infection detected at follow-up (19.9% versus 4.5%;  $P = 0.016$ ). Again, these data suggest that treatment may attenuate protective immunity in some persons and conversely that natural immunity may protect against reinfection.

The main question that remains is how much reinfection is attributable to these biologic mechanisms or simply to a high likelihood of re-exposure to untreated (or inadequately treated) sex partners. There is no doubt that rates of successful partner treatment—discussed below—remain suboptimal and contribute to this problem.

### Screening and testing to control disease

Because the minority of chlamydial infections present with symptoms, screening of asymptomatic persons plays a critical role in detecting the majority of infections. The premise of selective screening approaches relies on the identification of risks that are specific and sensitive for detection of asymptomatic infection. In the 1990s, a randomized controlled trial designed to determine whether selective screening for chlamydial infection reduces the risk of subsequent PID showed that women randomly assigned to undergo screening had a 56% lower rate of PID over the following year than did women receiving the usual care without screening [25]. This report helped prompt US national guidelines for risk-based chlamydial screening of young women to reduce the incidence of PID and the prevalence of post-PID sequelae while also reducing sexual transmission of *C. trachomatis*. The CDC and the USPSTF recommend that sexually active women of not more than 25 years of age be screened for genital chlamydial infection annually [5,6]. Later studies that examined this issue generally support the benefits of this intervention; one study that did not, the POPI (Prevention of Pelvic Infection) Trial, had serious limitations, the most significant being low statistical power for the end-points of interest (PID incidence overall was 1.6%) and incomplete ascertainment of the microbiologic and clinical end-points (only 17% of women defined as having PID had this documented by medical record review) [26]. Despite the recommendations for routine screening and despite widespread availability of accurate NAATs that can be performed on urine and self-collected vaginal swabs without the need for pelvic examination [27], screening coverage in many primary care settings remains low.

Retesting is performed for the express purpose of evaluating whether a patient has been reinfected. The majority of recurrent chlamydial infections result from resumption of unprotected sex with an untreated sex partner, although some do result from sex with a new sex partner. In women, repeat infections confer an increased risk of developing complicated genital infections, such as pelvic inflammatory disease. Thus, recently infected persons should have repeat testing for *C. trachomatis* infection approximately 3 to 6 months after treatment, regardless of whether patients believe their sex partners were treated.

### Treatment

Treatment of *C. trachomatis* infection requires special consideration, largely due to its somewhat unique life cycle. The infectious form of the organism, the extracellular elementary body, is metabolically inert and resistant to killing. Thus, antibiotics must target the sequestered intracellular and intravacuolar phases of the life cycle of this pathogen. For this reason, antibiotics with good intracellular penetration must be used. Antibiotic concentrations must be present throughout the entire 36- to 48-hour life cycle of the organism. Thus, either a prolonged course of therapy or selection of an antibiotic with a long half-life is required to ensure adequate levels of the antibiotic agent. Azithromycin, the prototype for chlamydia treatment, has excellent intracellular and tissue penetration. Owing to its half-life of 5 to 7 days, it can be administered as single-dose therapy (1 gram orally) under direct observation and can be used in pregnant women.

More recently, there has been debate about the relative efficacy of the azithromycin and doxycycline regimens. In a large randomized controlled trial of different antibiotic regimens in men with non-gonococcal urethritis, the microbial clearance rates among 115 men with *C. trachomatis* were 94.8% for the doxycycline arm and 77.4% for the azithromycin arm [28]. A recent meta-analysis of 23 randomized trials including over 2000 patients compared the efficacy and safety of doxycycline and azithromycin for treatment of uncomplicated genital chlamydial infections in men and women [29]. The analysis found a pooled efficacy in favor of doxycycline of 1.5%, with a larger estimate for symptomatic men (7.4%). Although an earlier study had documented very close microbial cure rates between both agents (97% and 98% for azithromycin and doxycycline, respectively), most of the microbiological cure in these earlier studies was documented with culture or enzyme immunoassay testing rather than the more sensitive NAAT assay [30]. The implications of these findings are not clear, and the quality of the

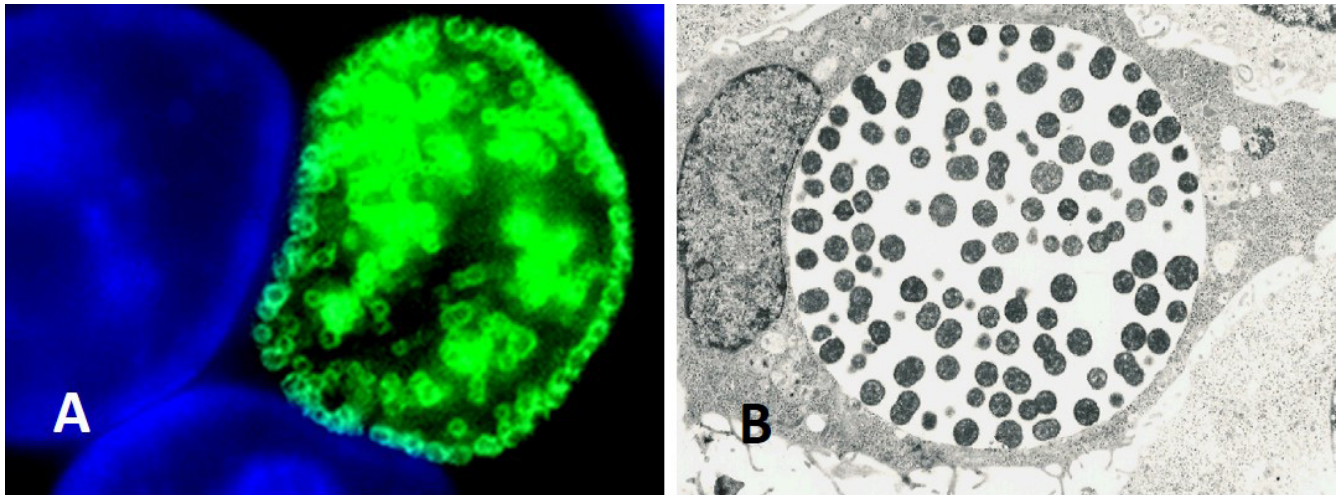
studies included varied widely. The response of expert opinion about a possible threat has ranged from acknowledgment of a need for more data to suggestions that study of longer or enhanced dosing regimens of azithromycin be considered [31,32].

These concerns notwithstanding, antibiotic resistance appears to be exceedingly rare in *C. trachomatis*. In fact, the Chlamydia species has been such a successful pathogen most likely due to its intricate but elegant life cycle (Figures 1 and 2). The intracellular nature of the pathogen eliminates the opportunity for rapid evolution of cell surface components that could contribute to drug resistance. Furthermore, the elementary body is relatively inert and this limits opportunities for replication and the generation of antibiotic-resistant mutations. However, spontaneous antibiotic-resistant mutations are relatively easily selected for in *in vitro* cell culture, and lateral gene transfer of tetracycline resistance has been demonstrated [33]. These findings point to the fact that *C. trachomatis* has the biological potential to acquire antibiotic resistance. These features may also explain the paucity of inflammatory responses and the asymptomatic nature of most chlamydial infections. That said, new antibiotic options are always welcome and eventually needed. A recent proof-of-concept clinical trial found that the microbiologic cure rate of single-dose oral rifalazil (25 mg) was not non-inferior to that seen with standard azithromycin therapy; cure rates, respectively, were 84.8% versus 92.1%, the difference in cure rate was 7.3%, and a lower limit of the 95% CI was 22.5; thus, non-inferiority was not established at the prespecified margin (lower limit of CI of 15%). However, this was a proof-of-concept study, and the number of treatment failures at a mid-study secondary end-point was not different [34]. Larger studies are required to pursue this potential therapeutic option.

### Role of management of sex partners

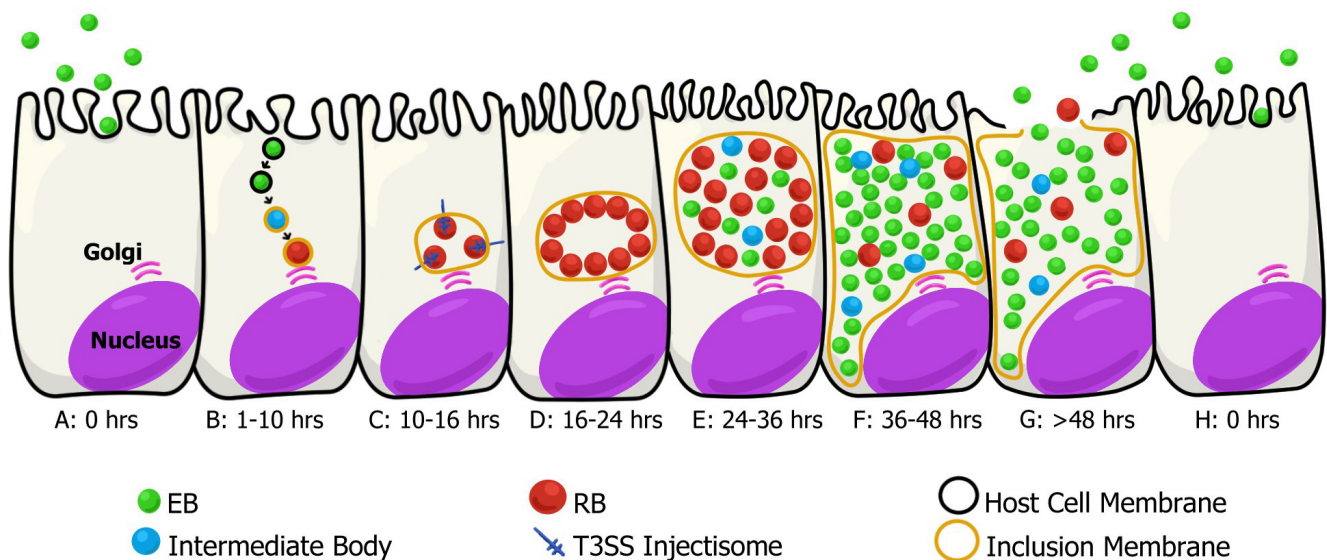
Unfortunately, rates of successful treatment of sex partners of persons with *C. trachomatis* remain low, and resources to detail public health staff to assist in partner notification efforts are not available. In the absence of such efforts, patients are often asked to notify their partners of the need for medical evaluation and treatment. This approach has been deemed a public health failure. A strategy termed "expedited partner management" (EPM) is an alternative way to increase the proportion of sex partners receiving treatment and to decrease rates of reinfection in the index patient. With EPM, treatment (without examination) is facilitated by giving an antibiotic or a prescription to the index patient or by calling in a prescription directly for the

Figure 1. Developed Chlamydial inclusion



Images of developed *Chlamydia trachomatis* inclusions in human epithelial cells. **(A)** Immunofluorescent image demonstrating Chlamydia reticulate bodies (green) located near the periphery of the inclusion at 30 hours post infection. The inclusion can be seen to be pressed up next to the cell nucleus (blue). **(B)** Electron micrograph of a similar inclusion at 40 hours post infection with reticulate bodies next to the inclusion membrane as well as elementary and intermediate bodies within the inclusion. Copyright © American Society for Microbiology, Infection and Immunity, 68, 2000, 360-367, and doi: 10.1128/IAI.68.1.360-367.2000

Figure 2. *Chlamydia trachomatis* life cycle



The bi-phasic chlamydial growth cycle involves transformation between two distinct forms: the elementary body (EB) and the reticulate body (RB). The metabolically inactive but highly infectious EB attaches to columnar epithelial cells and is internalized within a host cell membrane-bound phagosome **(A)**. During early stages of the life cycle, 1 to 10 hours post infection (hpi), the vesicle migrates to a perinuclear location near the Golgi apparatus **(B)**. It is during this migration that the nascent phagocytic vesicle begins to be modified by Chlamydia-produced inclusion membrane proteins to form a parasitophorous vacuole termed an inclusion. It is also during this time period that the EB differentiates into the RB, which is the metabolically active and the replicative form. At 10 to 16 hpi, the RB begins to divide by binary fission **(C)**. Accumulating RBs are located on the periphery of the inclusion membrane (IM), allowing type III secretory system (T3SS) needle-like structures (injectisomes) to penetrate the IM to secrete effector proteins into the cytosol which manipulate host-cellular functions, including signal transduction pathways (16 to 24 hpi). **(D)** Division continues as the inclusion expands, and between 24 and 36 hpi, the RBs begin to asynchronously differentiate back into EBs **(E)**. At 36 to 48 hpi, most of the RBs have converted back to the infectious EB form preparing for release and reinfection **(F)**. During very late stages, the infectious EBs escape the cell by lysis through proteolytic processes or by a process of extrusion **(G)**. Reinfection then occurs, initiating new cycles of infection **(H)**.

partner. Expedited partner therapy (EPT) for chlamydia can be accomplished with single-dose oral therapy (azithromycin). Patients and sexual partners should be counseled to abstain from sexual activity until the therapeutic course of antibiotics is completed or, in the case of azithromycin, for 7 days after the single-dose treatment was administered.

In one randomized controlled trial, 2751 patients (23% male) with diagnosed gonococcal infection, chlamydial infection, or both were assigned to either an "expedited treatment group" or a standard referral group [35]. Patients in the expedited treatment group were given "partner packets" of cefixime or azithromycin (or both) to distribute to their partners, without requiring a formal medical evaluation of the partners. In the standard referral arm, patients simply notified their sex partners of the need for evaluation and treatment. Patients assigned to expedited treatment of sexual partners were significantly more likely to report that all of their partners had been treated compared with those assigned to the standard referral arm (61% versus 49%). The trial also demonstrated a significant benefit in lowering the number of recurrent infections among those assigned to expedited treatment (relative risk of reinfection 0.75, 95% CI 0.56 to 0.97).

Clinicians should routinely employ EPT for the partners of persons with chlamydial infection, to the extent permitted by regional laws and regulations where they are practicing, when follow-up is in question. The legal status of EPT is state-specific, although surveys indicate that many clinicians frequently pursue the practice in managing their patients with STIs. The legal status of EPT options can be found at [www.cdc.gov/std/ept](http://www.cdc.gov/std/ept).

## Conclusions

Despite major advances in the diagnosis and management of chlamydial infections, we are still faced with several conundrums. Among the most important is how to plan for the future of effective screening programs that will guarantee that low rates of upper reproductive tract sequelae of untreated infection remain minimized. In the face of sustained positivity among the groups now being screened, can we successfully argue to funders and policymakers that screening is working? How can we communicate, and rigorously document, the impact of these programs? Second, a deeper understanding of the host immune response, and the role of sequential infection with different serovars, is urgently needed in order to inform vaccine development. Third, a rapid diagnostic test that can direct specific antibiotic therapy at the first encounter with the infected person would be a

huge advance; no available test is currently sensitive and specific enough to recommend it in this context.

## Abbreviations

CDC, Centers for Disease Control and Prevention; CI, confidence interval; EPM, expedited partner management; EPT, expedited partner therapy; hpi, hours post infection; LGV, lymphogranuloma venereum; MSM, men who have sex with men; NAAT, nucleic acid amplification test; PID, pelvic inflammatory disease; STI, sexually transmitted infection; USPSTF, US Preventive Screening Task Force.

## Disclosure

The authors declare that they have no disclosures.

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