

Burden of Recurrent *Chlamydia trachomatis* Infections in Young Women

Further Uncovering the “Hidden Epidemic”

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Objective: To determine the frequency and patterns of recurrent *Chlamydia trachomatis* infections, the most common bacterial sexually transmitted infection in young women.

Design: Cohort study using different data collection methods, including face-to-face interviews, medical record reviews, urine-based screening for *C trachomatis* infections, and a review of state health department reports of *C trachomatis* diagnoses.

Setting: Ten community-based health centers that provided reproductive health care from June 1998 to September 2001.

Participants: Eligibility criteria included being nulliparous, between the ages of 14 and 19 years, and human immunodeficiency virus–negative, all at the time of recruitment. This convenience sample (N=411) was recruited by word of mouth, clinician referrals, and advertisements in the clinics. Prospective follow-up data were available for 93.9% (386/411) of the sample. The exposure of interest was prior chlamydia infection.

Main Outcome Measure: Diagnosis of recurrent *C trachomatis* infection.

Results: During the follow-up period of 23 318 person-months (mean, 4.7 years per person), 216 participants (52.6%) were diagnosed as having *C trachomatis* infection, and 123 participants (29.9% of the total sample and 56.9% of those with initial infections) were diagnosed as having recurrent *C trachomatis* infections. Of 456 *C trachomatis* diagnoses made during the study period, 241 (52.9%) were recurrent infections. The rate of recurrent infections was 42.1 per 1000 person-months. The median time to recurrent infection was 5.2 months.

Conclusion: Recurrent *C trachomatis* infections comprise a substantial health burden among young women, possibly higher than previously recognized in this vulnerable population.

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THE INSTITUTE OF MEDICINE reported that sexually transmitted infections (STIs) are a “hidden epidemic” because their scope and effect are underrecognized by the public and by health care professionals.¹ Young women are at especially high risk for STIs because of several factors.² Behaviorally, young women are at high risk for STIs because they tend to have multiple sex partners.³ Psychologically, adolescents are at increased risk for STIs because of the inability to conceptualize long-term effects of current actions and low perceptions of vulnerability.^{4,5} Finally, young women may experience additional risk for STIs because of lower use of health care due to embarrassment or transportation barriers.⁶

These elevated risk factors are manifested in young women as evidenced by the substantially higher STI rates in this population. Persons aged 14 to 24 years have the

highest rates of *Chlamydia trachomatis* infection, the most common bacterial STI in the United States.⁷ The rates per 100 000 population among females aged 15 to 19 years and 20 to 24 years are 2761.5 and 2630.7, respectively, compared with the rates of 1039.5 and 364.8, respectively, among women aged 25 to 29 years and 30 to 34 years.⁷ Approximately 5% to 15% of routinely screened young women (aged <25 years) are infected with *C trachomatis*.⁸ However, studies⁹⁻¹³ among higher-risk populations such as patients attending public health clinics found the prevalence to be substantially higher at 10% to 30%. The high prevalence of *C trachomatis* infection is of clinical and public health concern because of the association with infertility, chronic pelvic pain, pelvic inflammatory disease, and increased risk for human immunodeficiency virus acquisition.

Several studies have examined recurrent *C trachomatis* infections in young

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women. For example, Blythe et al¹⁰ found that 38% of sexually active adolescent girls and young women aged 11 to 20 years at urban public health clinics had a recurrent *C trachomatis* infection, most of which occurred within 9 months of the initial diagnosis. Fortenberry et al¹⁴ reported recurrent infections in 18% of young women at 1 to 6 months after initial diagnosis, and Oh et al¹¹ reported recurrent infections in 18% of adolescent girls followed up for 1 to 2 years. Whittington et al¹⁵ reported that 7% of young women had recurrent infections at 4 months after treatment. Many of the studies examining recurrent *C trachomatis* infections in young women included a single data source for determining infections such as testing done during clinic visits that depends on patients attending the same clinic^{9,10,12,16} or state-based surveillance reporting.^{13,17} In addition, some studies^{14,15} included a short follow-up of less than 1 year. These design characteristics may produce an underestimate of the frequency of recurrent *C trachomatis* infection.

From June 1998 to September 2001, we followed up 411 female adolescents in a longitudinal cohort study that included baseline and 6-, 12-, and 18-month follow-up visits using multiple data collection methods. These data collection methods included medical record reviews, urine-based tests for *C trachomatis* infection at each study visit, a review of state health department records of reported *C trachomatis* infections, and self-reported *C trachomatis* diagnoses obtained during structured face-to-face interviews at each study visit. Using these multiple data sources, we had information on *C trachomatis* diagnoses during 23 318 person-months, or a mean of 4.7 years per person. This provided a unique opportunity to ascertain a complete description of the frequency and patterns of recurrent *C trachomatis* infection in a vulnerable population.

METHODS

SETTING AND SAMPLE

This analysis used data from a cohort study that examined risks for STIs, including human immunodeficiency virus infection among pregnant and nonpregnant adolescents. The design and procedures of this study have been published previously¹⁸ and are briefly described herein. Participants were recruited from 10 public health clinics in 3 urban areas of Connecticut. This convenience sample was recruited by word of mouth, clinician referrals, and advertisements in the clinics. Eligibility criteria for participation at enrollment included being female, nulliparous, sexually active, aged 14 to 19 years, and human immunodeficiency virus–negative. By design, approximately half of the participants were pregnant at enrollment. Participants were enrolled from June 1998 to March 2000. The study protocol included baseline and 6-, 12-, and 18-month visits. Follow-up visits were conducted through September 2001. This study was approved by Yale University's Human Investigation Committee and by institutional review boards at all participating clinics. Written informed consent was obtained from all study participants; participation was voluntary and confidential. The consent forms obtained permission to review medical records and state health department reports. Participants were paid \$25 for each interview.

DATA COLLECTION

Urine-Based *C trachomatis* Screening

Per the study protocol, all participants were tested for *C trachomatis* infection at each study visit. This was performed using ligase chain reaction testing (Abbott Laboratories, Chicago, Ill). Urine samples were collected during each study visit, and ligase chain reaction testing was conducted at a central laboratory.

Self-reported Data

Structured face-to-face interviews were conducted with participants in English and in Spanish at each study visit. Interviews were administered by trained study staff who were not involved in the provision of clinical care at the sites and took approximately 60 to 90 minutes to complete. The survey instrument was pilot tested for cultural and age appropriateness among adolescents at the clinics from which the participants were recruited. Adolescents self-reported their *C trachomatis* infection history by answering the question "Have you been told by a nurse, doctor, or other health care provider that you had chlamydia?" If they said yes, they were asked for the date of the most recent diagnosis. At the baseline visit, the question asked about ever having had a chlamydia infection, covering the entire history of participants' sexually active lifetime. At follow-up visits, the question asked about the period since the last study visit.

Medical Record Reviews

Medical record reviews were conducted from January through September 2002 after all study visits had been completed and were available for 361 (87.8%) participants. Adolescents for whom medical records could not be obtained (n=50) were more likely to be Latina ($P=.02$); there were no other differences in measured characteristics. Trained study staff reviewed paper and computerized records from the recruitment sites, and information about positive *C trachomatis* test results was abstracted. Because participants often sought medical care at multiple clinics within their home city, we reviewed existing medical records for each participant from all participating clinics in that city. Medical records were reviewed for the period beginning with the participant's enrollment date or the first date available after her enrollment date and continuing until the last day of the record (which may have been later than her last study visit and up to September 2002).

State Health Department Reports

Chlamydia trachomatis is a reportable infection to state health departments using standardized case report forms. Positive *C trachomatis* test results that were reported to the Connecticut Department of Public Health were obtained for participants from June 1997 (1 year before the beginning of enrollment) through January 2002, when the review was completed. This information was obtained by providing the name, date of birth, and city of residence of study participants to staff in the sexually transmitted disease control program at the Connecticut Department of Public Health. Staff then returned information on all positive *C trachomatis* test results entered in their database for all study participants during the specified period.

MEASURES AND STATISTICAL ANALYSIS

Recurrent infections were defined as a *C trachomatis* diagnosis by any source that occurred more than 30 days after a previ-

Table 1. Characteristics of 411 Members of the Convenience Sample*

Characteristic	Value
Age, y	
At enrollment (range)	17.3 ± 1.5 (14-19)
At first intercourse	14.5 ± 1.6
Race/ethnicity	
Black	166 (40.4)
Latina	149 (36.3)
Other	96 (23.4)
Pregnant at enrollment	
Yes	203 (49.4)
No	208 (50.6)
Lifetime No. of partners	
Mean	4.0 ± 4.4
Median (range)	2 (1-40)
Ever had <i>Chlamydia trachomatis</i> infection based on any source	216 (52.6)
Chlamydia diagnoses	
0	195 (47.4)
1	93 (22.6)
2	59 (14.4)
3	39 (9.5)
≥4	25 (6.1)
Range	0-10
Recurrence	
Rate per 1000 person-months	42.1
Had within 4 mo (n = 215)	66 (30.1)

*Data are given as mean ± SD or as number (percentage) unless otherwise indicated.

ous *C trachomatis* diagnosis by any source. Each participant's follow-up period was computed as follows. *Active follow-up* was defined as the period during which participants were actively followed up per the study protocol and were interviewed and screened for *C trachomatis* infection by the investigators at 6-month intervals for up to 18 months and was computed as the interval between the date of the first study visit and the date of the last study visit. *Passive follow-up* was defined as the period during which participants were not being actively interviewed and screened for *C trachomatis* infection by the investigators but during which other data collection methods would be expected to capture diagnoses. This included self-report of past diagnoses at the baseline visit and medical record and state health department reviews outside of the active follow-up period. The total follow-up time was the combined active and passive follow-up periods; data sources that overlapped in time for a given participant (eg, medical record review during the active follow-up period) were not double-counted in the total follow-up time.

The sample was described using summary statistics, including means, medians, ranges, frequencies, and proportions. The burden of recurrent infections was estimated by computing the proportion of female adolescents who had a recurrent diagnosis and by computing the proportion of all diagnoses that were recurrent infections. The rate of recurrent infections was estimated as the number of recurrent diagnoses divided by the amount of follow-up time after all initial diagnoses. The median time to recurrent infection and the proportion of women with recurrent infections within 4 months of the initial diagnosis (a recommended interval for rescreening¹⁹) were also estimated. Because age is often identified as a predictor of *C trachomatis* infection risk, estimates were stratified by age at first diagnosis (≤ 16 vs ≥ 17 years) for comparison. Age comparisons were made using the likelihood ratio χ^2 test for propor-

tions, the Tarone-Ware test statistic for comparing the survival distributions, and the z^2 test statistic for comparing rates (eg, for determining that the rate ratio is significantly different from 1).

RESULTS

Four hundred eleven young women were enrolled in this study. Characteristics of the sample are given in **Table 1**. Ninety-four percent of the sample had at least 1 follow-up visit at 6, 12, and/or 18 months after enrollment and, therefore, contributed time to the active follow-up period. The mean ± SD amount of active follow-up was 1.4 ± 0.4 years per participant, for a total of 6849 person-months. Passive follow-up time included the duration of sexual activity from the date of first sexual intercourse through the date of the enrollment visit, during which time *C trachomatis* diagnoses were ascertained by self-report; this mean ± SD amount of passive follow-up was 2.8 ± 1.8 years per participant, for a total of 13 818 person-months. Medical records data were also considered in calculating passive follow-up time; the mean ± SD interval contained in the medical records was 3.8 ± 2.6 years per participant for the 360 participants who had medical records reviewed, for a total of 16 358 person-months. State health department reports were available for the 5-year period from January 1997 (1 year before enrollment of study participants) through January 2002 (when data were abstracted) for all participants. However, because this surveillance system only included positive diagnoses and because we cannot know who was covered by this system for females who did not have a positive diagnosis, we did not use these dates to compute contributions to follow-up time except for females with a positive diagnosis. Using the earliest first date available (the age at first intercourse as self-reported at the baseline visit) and the latest last date available (the date of the last interview, the last date recorded in the medical record, or the last date of a diagnosis reported to the health department), the mean ± SD total follow-up time was 4.7 ± 1.9 years per participant, for a total of 23 318 person-months.

Two hundred sixteen participants (52.6%) were diagnosed as having a *C trachomatis* infection during the study period, and 123 participants (29.9% of the total sample and 56.9% of those with initial infections) were diagnosed as having recurrent *C trachomatis* infections (**Table 1**). Of 456 *C trachomatis* diagnoses made during the study period, 241 (52.9%) were recurrent infections (**Figure 1**). The rate of recurrent infections was 42.1 per 1000 person-months. The median time to recurrent infection was 5.2 months (**Figure 2**). None of these estimates differed significantly or substantially between the adolescents who were pregnant at baseline and those who were not (data not shown).

Of 215 young women having an initial diagnosis and available age information (1 participant had a missing date of birth), 112 were 16 years or younger at the time of initial diagnosis, and 103 were 17 years or older (**Table 2**). Recurrent infections were diagnosed in 69 (61.6%) of the younger adolescents and in 54 (52.4%) of the older adolescents. The median time to recurrent infection was 5.9 months among the younger adolescents and 4.8 months

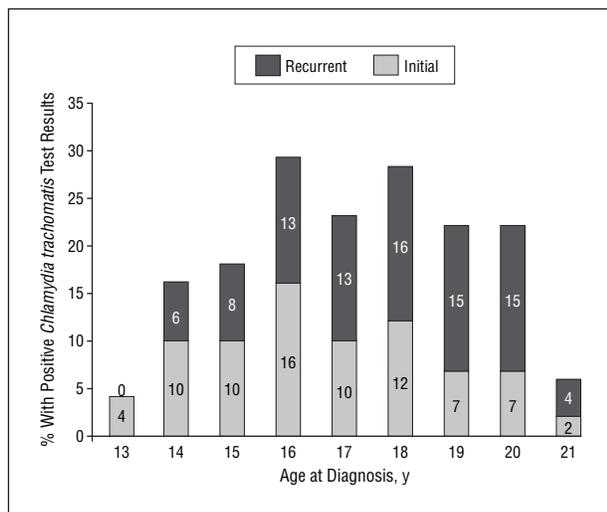


Figure 1. Burden of initial and recurrent infections by age at diagnosis.

among the older adolescents. The proportions in each group who had a recurrent infection within 4 months of the initial infection were 33.0% and 28.2%, respectively, among younger and older adolescents; the rates were 40.6 and 44.9 per 1000 person-months, respectively. None of these differences by age were statistically significant.

COMMENT

In this study, we used multiple data sources to examine recurrent *C trachomatis* infections in a cohort of young women who were followed up for more than 23 000 person-months to provide a comprehensive estimate of the frequency and patterns of recurrent *C trachomatis* infection. Our results suggest that the frequency of recurrent *C trachomatis* infection among young women seeking health care is consistent with and possibly higher than previously published estimates. Our observed rate of recurrent infections, 42.1 per 1000 person-months, is higher than the rates reported among other samples of young women by LaMontagne et al²⁰ (20.0 per 1000 person-months, reported as 24.0 per 100 person-years and converted by us for comparability) and by Whittington et al¹⁵ (33.0 per 1000 person-months). Estimated rates among different populations are generally lower as well and have been reported as 24.1 per 1000 person-months (reported as 28.9 per 100 person-years and converted by us for comparability) among women of a broader age range (mean age, 29.6 years) in one study¹² and as 28 per 1000 person-months in a population of men and women in another study.¹⁶ Our observed median time to reinfection, 5.2 months, is shorter than the median of 7.6 months reported by Burstein et al⁹ among a population of women younger than 25 years, although it is not substantially different from estimates in similar but not directly comparable studies that report the mean time to recurrent *C trachomatis* infection²¹ and the median time to recurrent *C trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* infections combined.²² Furthermore, we estimated that 52.9% of all diagnoses were re-

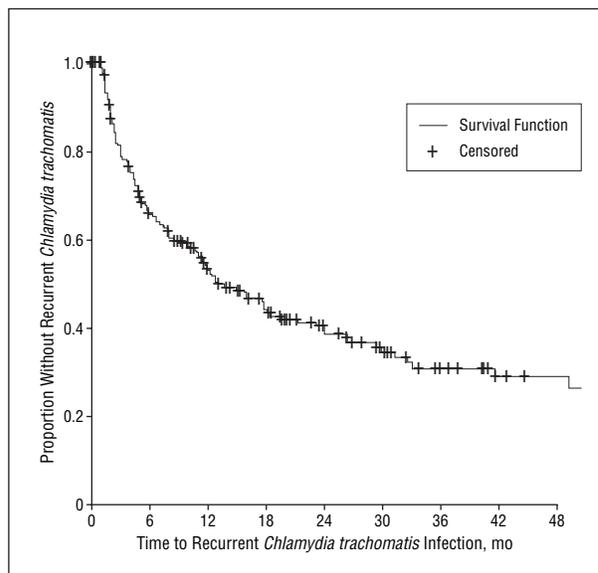


Figure 2. Time to recurrent infection.

Table 2. Recurrence and Age at Initial Diagnosis Among 215 Participants With an Initial Diagnosis of *Chlamydia trachomatis* Infection and Available Age Information*

Variable	Age at Initial Diagnosis, y		P Value
	≤16 (n = 112)	≥17 (n = 103)	
Had recurrence	69 (61.6)	54 (52.4)	.17
Time to recurrence, median, mo	5.9	4.8	.32
Had recurrence within 4 mo	37 (33.0)	29 (28.2)	.44
Recurrence rate per 1000 person-months	40.6	44.9	.45

*Data are given as number (percentage) unless otherwise indicated.

current infections, which is higher than the estimate of 26% reported by Rietmeijer et al.¹² Although some differences may be due to variations in populations or study designs, the consistency with which we found a greater burden of recurrent infections and our method of using multiple data sources suggest that these may be real differences.

Our results indicate that enhanced efforts to prevent recurrent *C trachomatis* infections in young women are urgently needed. An important window of opportunity exists at the time of an initial diagnosis to prevent recurrent infections. Prevention counseling or behavioral interventions should be delivered to young women at the time of a *C trachomatis* diagnosis. For example, because some women may be reinfected by nonmonogamous partners, patients may benefit from interventions that focus on educating young women about misperceptions of risk in relationships such as the assumption of monogamy. Furthermore, promotion of sustained condom use and enhanced communication skills about sensitive topics such as a *C trachomatis* diagnosis will be important for young women in sexual partnerships. Finally, innovative partner treatment strategies, including patient-delivered therapy, have received growing recognition as

ways to increase partner treatment. The process of providing medication to infected patients to deliver directly to their sex partners can increase treatment rates for partners who are unlikely to seek treatment on their own in a timely manner. A growing body of research is increasingly demonstrating its effectiveness in preventing recurrent infections.²³⁻²⁵ However, these studies have not explicitly evaluated outcomes of or barriers to patient-delivered therapy among adolescents; therefore, issues that may be especially pertinent for this population such as anxiety about consequences in relationships or difficult communication about sensitive topics will need to be addressed.

Treatment guidelines published by the Centers for Disease Control and Prevention¹⁹ include a recommendation to clinicians to advise all women with *C trachomatis* infections to be retested at approximately 3 months after treatment. The results of our study underscore these treatment guidelines. Although this strategy may not decrease the risk or burden of recurrent *C trachomatis* infections, it can reduce the overall burden of *C trachomatis* infection in the population through early detection and treatment and do so in a focused manner by screening a population that is likely to be infected.

Although other investigators have identified younger age during adolescence as a significant predictor of recurrent *C trachomatis* infection compared with older age during adolescence,^{13,17} our data suggest that all adolescents are at similar risk because the burden of recurrent infections was not different between those with an initial diagnosis at 16 years or younger vs at 17 years or older. Therefore, behavioral and other interventions and re-screening for all young women with *C trachomatis* infection regardless of age will be important. Indeed, investigations have found a higher incidence of recurrent infections among younger women as a whole (eg, ≤ 25 vs >25 years).⁹

This study has some limitations. First, ascertainment of infections was not constant during all years of follow-up. The active follow-up constituted approximately 30% of the total follow-up period (6849 of 23 318 person-months). When not in the active follow-up period, participants were not necessarily being routinely screened for *C trachomatis* infection. This limitation would result in an underestimate of the frequency of recurrent infections. However, the passive follow-up is a relative strength in this study in that it provides an opportunity to capture information on study participants who were lost to the active follow-up. It also extends the mean amount of follow-up by several years for each study participant, providing greater case ascertainment and evaluation of the patterns over time. A second limitation of this study that would result in an underestimate of recurrent infections is that, if a participant self-reported multiple past infections at a single study visit, she was only asked for the date of the most recent diagnosis. In these instances, we only counted the single infection for which we had the date of diagnosis because we could not confirm duplications in other sources without dates for the other diagnoses. Third, we lacked treatment data in this study for the initial diagnosis and information about the resumption of sexual activity after the initial diagnosis. Although we only considered diagnoses that were more than

30 days apart as recurrent infections to reduce the possibility of classifying the same infection as a recurrent infection, we cannot rule out the possibility that persistence or treatment failures resulted in the same infection being diagnosed more than 30 days apart.

Strengths of this study are the combination of the data collection methods that used investigator-initiated screening and the extended follow-up periods that included existing data sources. Although each source may not capture all diagnoses for several reasons,¹⁸ each also has the potential to capture diagnoses missed by the other sources, thereby providing a complete ascertainment of diagnoses. In conclusion, recurrent *C trachomatis* infections comprise a substantial health burden among young women, possibly higher than previously recognized in this vulnerable population.

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