Repeat Infection With Chlamydia and Gonorrhea Among Females: A Systematic Review of the Literature

Christina B. Hosenfeld, MPH, Kimberly A. Workowski, MD,†‡ Stuart Berman, MD, SCM,† Akbar Zaidi, PHD,† Jeri Dyson, MD,§ Debra Mosure, PHD,† Gail Bolan, MD,* and Heidi M. Bauer, MD, MPH**

Abstract: Determining the magnitude of chlamydia and gonorrhea reinfection is critical to inform evidence-based clinical practice guidelines related to retesting after treatment. PubMed was used to identify peer-reviewed English language studies published in the past 30 years that estimated reinfection rates among females treated for chlamydia or gonorrhea. Included in this analysis were original studies conducted in the United States and other industrialized countries that reported data on chlamydia or gonorrhea reinfection in females. Studies were stratified into 3 tiers based on study design. Reinfection rates were examined in relation to the organism, study design, length of follow-up, and population characteristics. Of the 47 studies included, 16 were active cohort (Tier 1), 15 passive cohort (Tier 2), and 16 disease registry (Tier 3) studies. The overall median proportion of females reinfected with chlamydia was 13.9% (n = 38 studies). Modeled chlamydia reinfection within 12 months demonstrated peak rates of 19% to 20% at 8 to 10 months. The overall median proportion of females reinfected with gonorrhea was 11.7% (n = 17 studies). Younger age was associated with higher rates of both chlamydia and gonorrhea reinfection. High rates of reinfection with chlamydia and gonorrhea among females, along with practical considerations, warrant retesting 3 to 6 months after treatment of the initial infection. Further research should investigate effective interventions to reduce reinfection and to increase retesting.

Women are disproportionately affected by chlamydial and gonococcal infection in the United States, and account for over 50% of gonorrhea and 75% of reported chlamydia cases.[1] Both chlamydia and gonorrhea are associated with a variety of adverse reproductive health outcomes, including pelvic inflammatory disease (PID), ectopic pregnancy, tubal infertility, and perinatal infections.[2–4]

Reinfection with chlamydia or gonorrhea is associated with an increased risk of reproductive complications. Studies have shown that the ascension of chlamydia or gonorrhea into the upper genital tract is more common for reinfected women than for women experiencing their first infection.[2,4–7] Hillis et al found a 2-fold increased risk of ectopic pregnancy among women who had 2 chlamydial infections and 4.5-fold increased risk among women with 3 or more infections.[2] In this study, the risk of PID was similarly increased: 4-fold with 2 infections and 6.4-fold for 3 or more infections. Because most of the infections are asymptomatic in females, follow-up testing after treatment is paramount to detecting infection and preventing adverse reproductive health outcomes.

Because having a recent history of chlamydia or gonorrhea infection has been identified as a risk factor for infection, published guidelines suggest retesting after appropriate treatment.[8,9] The optimal interval between initial infection and a subsequent test, as well as whether retesting should be gender-specific, has not been well evaluated. In 2006, the Centers for Disease Control and Prevention recommended that clinicians consider advising all women with chlamydial or gonococcal infection to be retested approximately 3 months after treatment.[8] Although there is limited information on the benefit of retesting in men, the Centers for Disease Control and Prevention STD Treatment Guidelines and a recent review suggests such testing approximately 3 months after treatment.[8,10]

Our review of the literature examining chlamydia and gonorrhea reinfection was undertaken to provide the best estimate of reinfection rates in females and to inform evidence-based patient management recommendations for improving the quality of patient care to preserve reproductive health.

METHODS

We conducted a PubMed search for studies before April 2008 that estimated the rate of reinfection with gonorrhea or chlamydia among females. Queries included "repeat (gonorrhea or chlamydia)," "recurrent (gonorrhea or chlamydia)," "reinfection (gonorrhea or chlamydia)," "reinfection (gonorrhea or chlamydia)," and "rescreening (chlamydia or gonorrhea)." Searches were limited to articles published in English over the past 30 years. A total of 794 unduplicated publications were identified. Of the 794 publications, abstracts were reviewed by the authors for relevance to the topic; and 66

From the *California Department of Public Health, STD Control Branch, Richmond, California; †Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; ‡Division of Infectious Diseases, Emory University, Atlanta, Georgia; and §Division of Adolescent Medicine, University of Florida College of Medicine, Jacksonville, Florida.

Supported by Centers for Disease Control and Prevention (Comprehensive STD Prevention Systems and Infertility Prevention Project Grant Number 5H25/PS904362-17) and the California Department of Public Health.

Correspondence: Heidi M. Bauer, MD, MPH, STD Control Branch, California Department of Public Health, 850 Marina Bay Parkway, Building P, Second Floor, Richmond, CA 94804. E-mail: heidi.bauer@cdph.ca.gov.

Received for publication November 7, 2008, and accepted February 6, 2009.

DOI: 10.1097/OLQ.0b013e3181a2a933

publications were selected for detailed review. Further examination of bibliographies revealed 4 additional publications.

Included in this analysis were original studies conducted in the United States and other industrialized nations that reported a reinfection rate for chlamydia or gonorrhea in human females or provided sufficient data to calculate reinfection rates. Because the focus of the analysis was repeat infection rather than treatment failure, antibiotic efficacy studies, which generally have short-term follow-up, were not included in our analysis. Twenty-three studies were excluded because reinfection rates were not stratified by sex[11–21] or specific etiology (chlamydia or gonorrhea),[13,14,21–24] the publication was a nonpeer-reviewed letter,[25] data were duplicative of already published material,[26–28] reinfection rates could not be calculated using the data provided,[29–32] or initial infection was not laboratory-confirmed.[33] Specific study design, proportion of females retested, diagnostic test type used, length of follow-up, geographic region, and population demographics were not considered in the inclusion and exclusion criteria. To ensure high quality data, only peer-reviewed publications were included; conference abstracts and unpublished data were excluded. A total of 47 studies were included in the final analysis.

We categorized studies into "tiers" based on the research design and follow-up methods. "Active cohorts," or Tier 1 studies, were those that involved patient enrollment: randomized controlled trials and prospective cohort studies with active follow-up. Tier 2 studies were comprised of "passive cohorts," prospective or retrospective cohort studies with passive follow-up that did not require patient enrollment, did not have specific retesting intervals, but which collected data on the timing and results of subsequent tests. When reinfection rates were not provided by the original investigators, we calculated these rates for both active and passive cohort studies by dividing the number of females reinfected by the number of females retested after treatment for the initial infection. "Disease registry," or Tier 3 studies, included those that reported reinfection rates using case-based surveillance systems or clinic-based registries that did not contain information on patients who tested negative. For these studies, reinfection proportions were calculated by dividing the number of patients with a subsequent infection by the number of patients initially infected. At least 2 authors reviewed data from each study and verified reinfection rates.

Summary estimates of the median and range of reinfection rates were determined separately for chlamydia and gonorrhea. For studies that reported reinfection rates for sequential testing within the same study population at different time intervals, the reinfection rate based on the longest timeframe up to 12 month was included in the data analysis. For randomized trials in which reinfection was the outcome of interest and data were stratified by study arm, the reinfection rate based on the control conditions was included in the analysis. The Kruskal-Wallis and Mann-Whitney statistical tests were used to compare median reinfection rates among study tiers. To estimate the optimal timing for retesting patients treated for chlamydia or gonorrhea, we fitted a second degree (quadratic) regression model to the data with rate of reinfection as the dependent variable and time as the independent variable. This model was chosen because it provided the best fit based on standard model selection criteria. Model analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC); PROC REG was used to calculate regression coefficients, and PROC GPLOT was used to plot the data.

To examine which factors were associated with reinfection, summary rates were stratified by study tier, length of follow-up, proportion of females retested (Tiers 1 and 2 only), sample size, diagnostic test used, treatment regimen, and clinical setting. In addition, differential rates were examined among studies that included sufficient data on age, race or ethnicity, coinfection status, symptom status, partner management strategies, and sexual risk behavior.

RESULTS

A total of 47 studies were included in our analysis: 30 studies reported only chlamydia reinfection rates, 9 reported only gonorrhea reinfection rates, and 8 reported both chlamydia and gonorrhea reinfection rates. Of the 16 active cohort Tier 1 studies, 11 examined reinfection rates for chlamydia only and 5 examined reinfection for both chlamydia and gonorrhea (Table 1). Of 15 passive cohort Tier 2 studies, 13 examined reinfection rates for chlamydia only and 2 examined gonorrhea only (Table 2). Of the 16 disease registry Tier 3 studies, 6 measured reinfection rates for chlamydia only, 7 for gonorrhea only, and 3 for both chlamydia and gonorrhea (Table 3).

Overall, 37 studies took place in the United States and 10 studies were based in non-US populations. US-based studies included populations from at least 20 different states and 17 cities. The length of follow-up ranged from 2 months to 13 years. Although there was variability in the minimum time required for a second infection to be defined as a repeat infection, of those studies that specifically defined this timeframe, all but 2[34,35] defined reinfection as greater than 2 weeks after an initial positive.

Of the 38 studies reporting chlamydia reinfection rates, the proportion of females reinfected ranged from 0% to 32%, with a median proportion of 13.9%. Median rates of chlamydia reinfection varied somewhat by study design. Among Tier 1 studies, the median reinfection rate was 13.0%; Tiers 2 and 3 had median reinfection rates of 18.0% and 9.4%, respectively ($P = 0.19$). Rates of chlamydia reinfection were stratified by tier and modeled over time up to 36 months (Fig. 1). Modeled data from Tier 1 studies demonstrated a peak at 13 months with a reinfection rate of 20.9%; the rate at 3 months was 8.4% and the rate at 6 months was 14.7%. This peak was earlier and of similar magnitude to peaks associated with the Tier 2 or Tier 3 models; peak reinfection in Tier 2 studies (24.0%) occurred at 25 months, and reinfection for Tier 3 studies (16.2%) peaked at 36 months. Among Tier 1 and 2 studies, the length of follow-up ranged from 2 to 60 months after the initial chlamydial infection. Modeling chlamydia reinfection within 12 months demonstrated similar peak rates for Tier 1 and Tier 2 studies (18.6% at 10 months and 19.5% at 8 months, respectively). Although the proportion of those retested for chlamydia ranged from 23% to 100%, reinfection rates did not vary with the proportion retested.

Of the 17 studies reporting gonorrhea reinfection rates, the proportion of females reinfected ranged from 2.6% to 40%, with a median proportion of 11.7%. The median reinfection rate was 23.6% for Tier 1 studies, 15.8% for Tiers 2 studies, and 9.1% for Tier 3 studies ($P = 0.63$ for Tiers 1 and 2 compared with Tier 3). Given the relatively fewer data on gonorrhea reinfection, modeling gonorrhea reinfection by tier over a 36-month follow-up period did not result in reliable estimates of reinfection proportions (data not shown). Among Tier 1 and 2 studies, the length of follow-up ranged from 3 to 20 months after the initial positive. The proportion of females retested ranged from 38% to 77%; however, the reinfection rates did not vary by the proportion retested.

Patient demographics were associated with chlamydia and gonorrhea reinfection rates in several studies. Younger

TABLE 1. Chlamydia and Gonorrhea Reinfection in Active Cohort Studies (Tier 1)

Study Population	Test Type	Follow-Up Period	Definition of Reinfection	No. Enrolled Positives	Percentage Retested	CT Reinfection (%)*	GC Reinfection (%)*	Reference
Age: 16–24 yr Venue: general practice, family planning, and genitourinary medicine clinics Geography: United Kingdom Timeframe: 2002–2003	NAAT	6 mo 18 mo	≥28 d	592	70	**12.0** 18.7		LaMontagne et al[51]
Age: 15–39 yr Venue: Urban STD clinics (3) Geography: Multiple US cities Timeframe: 1999–2001	NAAT	3 mo†	≥14 d	CT only: 94 GC only: 39	CT: 89 GC: 77	**10.7**‡	**3.6**‡	Peterman et al[44]
Age: not provided Venue: clinics participating in case surveillance Geography: King County, WA Timeframe: 1998–2003	NAAT	4.2 mo	≥21 d	1047§	70§	**13.2**‖	**11.7**‖	Golden et al[38]
Age: 15–29 yr Venue: population-based home screening Geography: The Netherlands Timeframe: 2002–2003	NAAT	12 mo	Not reported	44	Not reported¶‖	**12.8**		Veldhuijzen et al[54]
Age: ≥14 yr Venue: STD clinic and emergency departments Geography: King County, WA Timeframe: 2001–2002	NAAT	6 mo	≥10 wk	38§	63§	**0.0**‡	**25.0**‡	Sparks et al[73]
Age: >18 yr Venue: municipal STD and other clinics Geography: San Francisco, CA Timeframe: 2000	NAAT	6 mo	Not reported	25	23	**8.0**		Bloomfield et al[48]
Age: 14–34 yr Venue: multiple clinics Geography: multiple US cities Timeframe: 1996–2000	NAAT	1 mo 4 mo	≥21 d	1889	81	7.4 **14.6**‖		Schillinger et al[53]
Age: 15–40 yr Venue: general practice clinics Geography: Amsterdam Timeframe: 1997–1999	NAAT	12 mo	≥28 d	72	56#	**0.0**		Van Valkengoed et al[74]
Age: 14–34 yr Venue: reproductive health, STD, adolescent medicine clinics Geography: multiple US cities Timeframe: not provided	Multiple	1 mo 4 mo	Not reported	1194	66	5.5 **12.7**		Whittington et al[55]

(Continues)

TABLE 1. (Continued)

Study Population	Test Type	Follow-Up Period	Definition of Reinfection	No. Enrolled Positives	Percentage Retested	CT Reinfection (%)*	GC Reinfection (%)*	Reference
Age: ≥18 yr Venue: general practice clinics Geography: Ringkjobing County, Denmark Timeframe: 1997	NAAT	6 mo	>14 d	27	96%	**26.9**		Kjaer et al[63]
Age: 15–19 yr Venue: STD and adolescent health clinics Geography: Indianapolis, IN Timeframe: not provided	Culture	6 mo[†]	>28 d	CT: 226 GC: 116	CT: 58 GC: 48	**17.6**	**23.6**	Fortenberry et al[56]
Age: adolescents Venue: adolescent medicine clinics Geography: southeastern US city Timeframe: 1990–1992	Culture	20 mo	Not reported	216[§]	Not reported[¶‖]	**18.0**	**40.0**	Oh et al[61]
Age: adolescents Venue: family planning and STD clinics Geography: Marion County, IN Timeframe: not provided	Culture	6 mo	Not reported	209	54	**17.2**[‖]		Orr et al[75]
Age: mean age 21.5 yr Venue: student health clinic Geography: Seattle, WA Timeframe: not provided	NAAT, Culture	5 mo	>28 d	20	80	**6.3**		Workowski et al[76]
Age: 11–20 yr Venue: public health adolescent clinics Geography: Marion County, IN Timeframe: 1985–1990	IF	3 mo 6 mo 9 mo 12 mo	>4 d	407	70	8.6 9.0 12.3 **14.4**		Blythe et al[35]
Age: 14–19 yr Venue: adolescent clinic Geography: Sweden Timeframe: not provided	Culture	6 mo 12 mo	Not reported	53	93	14.3 **26.5**		Rahm et al[68]

*Reinfection rates in bold were used in the calculation of medians and models.
[†]Only data from the first follow-up visit included because unduplicated data for other visits was not reported.
[‡]Reinfection rate reflects data combined across randomized trial study arms.
[§]Data combined for gonorrhea and chlamydia patients.
[‖]Reinfection rate reflects data from the control arm of randomized trial.
[¶]Based on study design, all enrolled patients had at least one follow-up visit.
[#]Data combined for both women and men.
CT indicates chlamydia; GC, gonorrhea; NAAT, nucleic acid amplification test; IF, immunofluorescence.

TABLE 2. Chlamydia and Gonorrhea Reinfection in Passive Cohort Studies (Tier 2)

Study Population	Test Type	Follow-Up Period	Definition of Reinfection	Number of Enrolled Positives	Percentage Retested	CT Reinfection (%)*	GC Reinfection (%)*	Reference
Age: 12–20 yr Venue: school-based health centers Geography: Baltimore, MD Timeframe: 1996–2003	NAAT	12 mo	Not reported	1920	47	**26.3**		Gaydos et al[77]
Age: 16–24 yr Venue: National Job Training Program Geography: nationwide Timeframe: 1998–2005	Multiple	2 mo	Not reported	13,550	44	**5.6**		Joesoef et al[78]
Age: 15–24 yr Venue: not provided Geography: Sor-Trondelag County, Norway Timeframe: 1990–2003	Multiple	12 mo	Not reported	1819	58†	**8.6**		Bakken et al[79]
Age: not reported Venue: STD clinics Geography: Baltimore, MD Timeframe: 2003–2004	NAAT	3 mo	>14 d	119	38		**28.9**	Bernstein et al[47]
Age: not reported Venue: community-based prenatal program Geography: New Orleans, LA Timeframe: 1998–2000	DNA probe test	7.9 mo	Not reported	105	Not reported‡	**13.3**		Miller et al[67]
Age: 16–24 yr Venue: genitourinary medicine clinic Geography: Portsmouth, United Kingdom Timeframe: 1999–2002	NAAT	6 mo 12 mo 18 mo 36 mo	Not reported	861	26	6.7 **11.6** 14.7 20.5		Lee et al[64]
Age: not reported Venue: community-based prenatal program Geography: New Orleans, LA Timeframe: 1998–2000	DNA probe test	7.9 mo	Not reported	38	Not reported‡		**2.6**	Miller et al[80]
Age: not reported Venue: metro health clinic Geography: Denver, CO Timeframe: 1997–1999	NAAT	30 mo	Not reported	185	Not reported‡	**23.2**		Rietmeijer et al[45]
Age: 12–19 yr Venue: health management organization Geography: mid-Atlantic states Timeframe: 1998–1999	DNA probe test	24 mo	>30 d	983	74	**23.3**		Burstein et al[49]
Age: not reported Venue: public hospital prenatal clinic Geography: Atlanta, GA Timeframe: 1993–1994	Multiple	9 mo	>14 d	259	94	**32**		Allaire et al[66]

(Continues)

TABLE 2. (Continued)

Study Population	Test Type	Follow-Up Period	Definition of Reinfection	Number of Enrolled Positives	Percentage Retested	CT Reinfection (%)*	GC Reinfection (%)*	Reference
Age: 14–39 yr old Venue: family planning clinic Geography: New Orleans, LA Timeframe: 1993–1994	DNA probe test	36 mo	Not reported	256	70	**21.9**		Kissinger et al[58]
Age: not reported Venue: community-based prenatal program Geography: New Orleans, LA Timeframe: 1992–1996	DNA probe test	7.9 mo	Not reported	314	48	**16.8**		Miller[41]
Age: 15–19 yr Venue: family planning clinics Geography: multiple US cities Timeframe: 1988–1992 Region X Chlamydia Project	IF	60 mo	Not reported	3298	Not reported‡	**18**		Mosure et al[59]
Age: 13–21 yr Venue: teen health clinic Geography: Houston, TX Timeframe: 1985–1987	Culture	12 mo	Not reported	46	76	**11.4**		Chacko et al[81]
Age: 14–21 yr Venue: adolescent medicine clinic Geography: Oklahoma Timeframe: 1985–1987	DFA	24 mo	Not reported	563	57	**18.2**		Fortenberry and Evan[82]

*Reinfection rates in bold were used in the calculation of medians and models.
†Follow-up data combined for women and men.
‡Based on study design, all enrolled patients had at least one follow-up visit.
DFA indicates direct fluorescent antibody.

TABLE 3. Chlamydia and Gonorrhea Reinfection in Disease Registry Studies (Tier 3)

Study Population	Test Type	Follow-Up Period	Definition of Reinfection	No.of Enrolled Positives	CT Reinfection (%)*	GC Reinfection (%)*	Reference
Registry: STD surveillance database Geography: Alberta, Canada Timeframe: 1991–2003	Multiple	156 mo	>14 d	2549		**8.2**	De et al[50]
Venue: STD clinics Geography: multi-center US sites Timeframe: 1997–1999	Multiple	12 mo	>1 mo	CT: 2841 GC: 2423	**4.8**	**5.0**	Newman et al[42]
Venue: city health department clinics Geography: Baltimore, MD Timeframe: 2001 and 2002	NAAT	24 mo	>14 d	3226		**9.9**	Bernstein et al[36]
Registry: county disease surveillance system Geography: San Diego County, CA Timeframe: 1995–2001	Multiple	12 mo	≥30 d	4747		**4.1**	Gunn et al[60]
Venue: public STD clinics Geography: Baltimore, MD Timeframe: 1994–1998	Not provided	57.5 mo	≥3 mo	1717		**7.1**	Mehta et al[52]
Registry: Defense medical surveillance system Geography: Active duty service members Timeframe: 1994–1998	NAAT	67 mo	Not reported	5935	**9.4**		Barnett and Brandage[57]
Age: 12–60 yr Venue: family planning, STD, school-based clinics Geography: Baltimore, MD Timeframe: 1994–1996	NAAT	33 mo	>30 d	817	**20.4**		Burstein et al[43]
Age: 10–44 yr Registry: state disease surveillance system Geography: Washington Timeframe: 1993–1998	Multiple	72 mo	>30 d	32,698	**14.8**		Xu 2000 et al[46]
Venue: STD clinic Geography: Step County, NC Timeframe: 1992–1994	Culture	17 mo	>14 d	181		**8.3**	Fox et al[65]
Venue: middle school-based health centers Geography: Baltimore, MD Timeframe: 1996–1997	NAAT	13 mo	≥30 d	19†	**26.9**	**21.1**	Burstein et al[62]
Registry: county disease surveillance system Geography: San Francisco, CA Timeframe: 1989–1993	Multiple	60 mo	≥30 d	CT: 6996 GC: 3893	**15.1**	**19**	Ellen et al[37]
Age: 10–44 yr Registry: state disease surveillance system Geography: Wisconsin Timeframe: 1985–1992	Multiple	24 mo 84 mo	Not reported	11,000	**1.3** 24.4		Hillis et al[2]
Age: 10–44 yr Venue: family planning, STD, public health Geography: Wisconsin Timeframe: 1985–1990	Multiple	12 mo 72 mo	≥30 d	38,866	**3.9** 17.7		Hillis et al[39]

(Continues)

TABLE 3. (Continued)

Study Population	Test Type	Follow-Up Period	Definition of Reinfection	No.of Enrolled Positives	CT Reinfection (%)*	GC Reinfection (%)*	Reference
Registry: laboratory data Geography: Gothenburg, Sweden Timeframe: 1979–1980; 1983–1984	Culture	15 mo	Not reported	2181	**7.2**		Ramstedt et al[83]
Venue: Native American medical center Geography: Anchorage, AK Timeframe: 1979–1980	Multiple	18 mo	≥7 d	102		**30.4**	Blackwood[34]
Venue: genitourinary medicine clinics Geography: Sheffield, UK Timeframe: 1976–1979	Not provided	12 mo	Not reported	1711		**17.4**	Kinghorn 1982 et al[40]

*Reinfection rates in bold were used in the calculation of medians and models.
†Data combined for gonorrhea and chlamydia patients.

age was consistently statistically associated with a higher risk for reinfection. Because of variations in the populations studied, these higher risk groups were identified as "younger" women,[34,36–38] women under 20 years of age,[39–42] and women under 26 years.[2,43–46] Several studies that did not identify statistical significance still noted a trend of increased reinfection in younger participants.[47–55] The relationship between race or ethnicity and reinfection varied by study. Non-Hispanic blacks had a significantly higher risk of chlamydia reinfection in some studies;[2,37,39,42,44,46,56] however, other studies found no association with reinfection,[35,38,41,45,57–59] despite a high proportion of black participants in several of these studies.[35,41,57–58] Among the 10 gonorrhea studies that assessed the correlation of non-Hispanic black race with reinfection, blacks were found to be at increased risk for reinfection in 7 studies.[37,40,42,44,50,56,60] Of the studies that did not find a statistically significant relationship between race and gonorrhea reinfection, 2 of 3 study populations were over 80% black.[36,47]

Of the 8 studies that examined the role of coinfection on reinfection estimates, 6 identified a statistically significant association. Five studies demonstrated that coinfection with gonorrhea increased reinfection with chlamydia,[2,38–39,46,61] and 3 studies demonstrated that coinfection with chlamydia increased the risk of gonorrhea reinfection.[38,40,61] The reason for initial testing and the presence of symptoms were not consistently associated with higher rates of reinfection. In all studies, routine screening in the absence of symptoms identified the majority of infections. Of the 7 studies that provided data on the reasons that females returned for a subsequent test,[39,43,46,51,62–64] only 1 study distinguished between the initial and subsequent visit.[64]

Innovative and effective partner treatment strategies were generally associated with lower rates of reinfection. Expedited partner therapy (EPT) significantly decreased chlamydia reinfection estimates in 1 randomized control trial[58] and gonococcal reinfection estimates in another randomized control trial.[38] In 2 randomized trials, EPT was associated with lower rates of chlamydia reinfection, however, the results were not statistically significant.[38,53]

Study characteristics that were not associated with chlamydia or gonorrhea reinfection rates included study sample size, diagnostic test type, treatment regimen, geographic area, timeframe, and clinic type. Clinic type was examined for studies conducted within a single type of venue; however, this comparison among STD,[38,42,44,47,52,65] family planning,[58–59] and private or managed care clinics[49] demonstrated no appreciable differences in reinfection rates. In addition, studies that presented information about the behavioral factors of the study populations, including new or multiple partners[30,35,38–40,43–45,47,50–52,55–56,59,61,68] and history of STD,[39–40,43,45,47,52] showed no consistent relationship between these factors and risk of reinfection. Of note, several studies did not stratify risk factor analyses by sex[36,38,44–45,47,49–50,54,60] or by organism.[38,42,56]

CONCLUSION

Our synthesis of studies of chlamydia or gonorrhea reinfection in females demonstrated consistently high rates of repeat chlamydia or gonorrhea infection and provided direct evidence to support clinical guidelines. Combined with the recent review demonstrating high reinfection rates in men,[10] our analysis of reinfection rates in females provides substantial evidence to support retesting for chlamydia and gonorrhea among both women and men 3 to 6 months after treatment. Although peak rates for data censored at 12 months follow-up

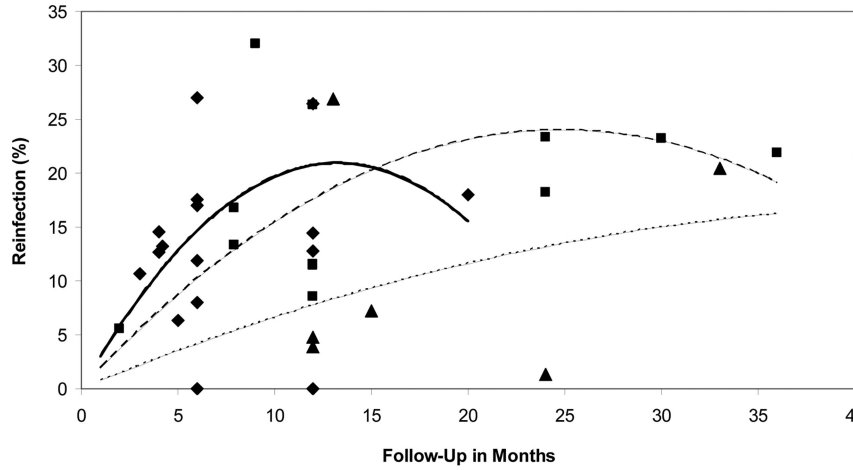

Figure 1. Observed and modeled chlamydia reinfection rates in females over 36 months, by study tier. Diamond (♦): active cohort studies (Tier 1) observed reinfection rates. Square (■): passive cohort studies (Tier 2) observed reinfection rates. Triangle (▲): disease registry studies (Tier 3) observed reinfection rates. Solid line: tier 1 modeled reinfection rates. Dashed line: tier 2 modeled reinfection rates. Dotted line: tier 3 modeled reinfection rates.

occurred after 6 months, retesting before 6 months may prevent the development of complications. Despite some variability in reinfection rates, retesting would likely benefit all patients irrespective of age, race or ethnicity, symptom status, partner treatment, and sexual risk behavior. It is also important to note that retesting is distinct from a test of cure, which is not recommended unless compliance is in question, symptoms persist, reinfection is suspected, or the patient has chlamydia and is pregnant.[8]

Establishing the ideal timeframe for retesting is challenging. Currently, retesting of women with chlamydia or gonorrhea is recommended 3 months after completion of treatment.[8] Early testing allows prompt identification and treatment of infections acquired shortly after treatment, but fails to identify infections acquired later. Although a more extended timeframe may maximize the number of infections identified, this delay may allow infection to persist and compromise subsequent reproductive health. Another consideration is the practicality of retesting, as several studies demonstrated that less than 30% of initially infected females were retested.[48,64] Retesting at 3 to 6 months was supported by tier 1 modeling data that estimated the rate of reinfection at 6 months to be 14.7%, which exceeded the median for tier 1 studies (13.0%) and approached the higher median observed for tier 2 studies (18.0%).

Although the optimal timeframe for retesting may be influenced by whether reinfections are persistent or recurrent, distinguishing between these possibilities has been challenging. Using chlamydia genotyping methods, Blythe et al found a high rate of discordance between the initial and repeat infections among females studied.[35] Although useful in distinguishing new infections, genotyping is less useful in identifying persistent infection, since the genotype of the organism acquired from an untreated partner is likely to be the same as the initial infection. A few studies have found evidence that treatment failure may play an important role in persistent chlamydial infection.[38,55,69] Further adding to the challenge of establishing the optimal retesting timeframe is the relative lack of data on the rate of or time until the development of complications.

Although several studies demonstrated higher reinfection rates among younger women, the reinfection rate among women over age 25 years exceeded 10% in several studies.[34,41,53] Further, our assessment demonstrated similarly high rates of reinfection for a variety of clinical settings including STD clinics, family planning clinics, and managed care organizations. While there is evidence that some approaches to partner treatment, including EPT, reduce reinfection, risk of such reinfection is still substantial.[38,53,58] Ensuring that women of all ages return for a subsequent test 3 to 6 months after treatment will likely prevent adverse reproductive health outcomes. Studies in prenatal settings, which found chlamydia reinfection rates of 13% to 32%, support current recommendations that pregnant women at increased risk, including those recently treated for chlamydia or gonorrhea, should be retested during the third trimester to prevent maternal postnatal complications and infection in the infant.[8] Effective strategies for improving retesting rates may include patient counseling, flagging medical charts, making advance appointments, and/or retesting reminders by telephone, mail, text messaging, or email.

Surprisingly, reinfection rates observed for active (Tier 1) and passive (Tier 2) cohort studies did not vary by the proportion of females retested. One might expect higher rates of reinfection among women who return to clinic without prompting, especially if they have symptoms, are nonadherent to treatment, or have known re-exposure to an untreated partner. If this was the case, reinfection rates would be expected to decline as a greater proportion of women are retested. Instead, observed findings support interventions to maximize the number of patients retested, since this strategy is likely to identify the largest number of infections.

There were a number of limitations to the summary estimates and analysis of predictors of reinfection. Differences in study design, length of follow-up, and definition of outcome presented challenges in assessing chlamydia and gonorrhea reinfection in females. Compared to Tier 1 studies with active follow-up, reinfection rates identified in Tier 2 and 3 studies would be expected to be less valid estimates of the true incidence in the populations assessed. In particular, Tier 3 studies undoubtedly underestimate true reinfection rates; since data on the proportion of females retested were not reported, the denominator was the number of infected individuals initially reported. To compensate for the effects that study design may

have had on reinfection rates, studies were grouped into tiers for a stratified analysis. Increasing the study duration would be expected to be associated with increasing reinfection proportions. In addition, it is not known when the reinfection was actually acquired, only when the test was performed and infection identified. We attempted to minimize the effects of varying follow-up lengths on rates of reinfection by analyzing reinfection within a 12-month timeframe. The bias associated with incomplete retesting is difficult to predict since women with infection may have sought care elsewhere, decreasing observed rates of reinfection, or women may have been retested because they suspected they might be infected, leading to an overestimate of reinfection. Finally, in evaluating factors associated with reinfection, reports may have been biased in favor of statistical associations and several studies did not provide stratified estimates by sex or organism.

Our systematic review has provided substantial evidence for high chlamydia and gonorrhea reinfection rates among females across a variety of study populations and clinic settings. Because repeat infections confer an elevated risk for PID and other complications, retesting women treated for chlamydia or gonorrhea should be a priority. If a patient does not return for retesting, providers should retest at the next clinical visit, regardless of whether the patient believes that her sex partners were treated. Further, given the consistent and substantial rate of reinfection in the 47 studies reviewed, the value of continued documentation of high reinfection rates is questionable. Rather, investigators should focus on developing and evaluating interventions to prevent reinfection and to increase retesting. While several studies have demonstrated effective behavioral interventions to prevent incident infection,[70–71] few studies of innovative methods for retesting have been published[72] and few studies examined interventions to prevent reinfection.[38,53,58] If effective, such clinical interventions may well reduce the risk of PID, ectopic pregnancy, and other adverse reproductive health outcomes.

REFERENCES

1. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance, 2006. Atlanta, GA: US Department of Health and Human Services; 2007.
2. Hillis SD, Owens LM, Marchbanks PA, et al. Recurrent chlamydial infections increase the risks of hospitalization for ectopic pregnancy and pelvic inflammatory disease. Am J Obstet Gynecol 1997; 176(1 pt 1):103–107.
3. Scholes D, Stergachis A, Heidrich FE, et al. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. N Engl J Med 1996; 334:1362–1366.
4. Westrom L, Joesoef R, Reynolds G, et al. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. Sex Transm Dis 1992; 19:185–192.
5. Brunham RC, Maclean IW, Binns B, et al. *Chlamydia trachomatis*: Its role in tubal infertility. J Infect Dis 1985; 152:1275–1282.
6. Paavonen J, Eggert-Kruse W. *Chlamydia trachomatis*: Impact on human reproduction. Hum Reprod Update 1999; 5:433–447.
7. Patton DL, Wolner-Hanssen P, Cosgrove SJ, Holmes KK. The effects of *Chlamydia trachomatis* on the female reproductive tract of the *Macaca nemestrina* after a single tubal challenge following repeated cervical inoculations. Obstet Gynecol 1990; 76:643–650.
8. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2006. Morb Mortal Wkly Rep 2006; 55(RR-11):35–49.
9. US Preventive Services Task Force. Screening for chlamydial infection: US Preventive Services Task Force recommendation statement. Ann Intern Med 2007; 147:128–134.
10. Fung M, Scott KC, Kent CK, et al. Chlamydial and gonococcal reinfection among men: A systematic review of data to evaluate the need for retesting. Sex Transm Infect 2007; 83:304–309.
11. Beller M, Middaugh J, Gellin B, et al. The contribution of reinfection to gonorrhea incidence in Alaska, 1983 to 1987. Sex Transm Dis 1992; 19:41–46.
12. Brooks GF, Darrow WW, Day JA. Repeated gonorrhea: An analysis of importance and risk factors. J Infect Dis 1978; 137: 161–169.
13. Brunham RC, Pourbohloul B, Mak S, et al. The unexpected impact of a *Chlamydia trachomatis* infection control program on susceptibility to reinfection. J Infect Dis 2005; 192:1836–1844.
14. Gift TL, Malotte CK, Ledsky R, et al. A cost-effectiveness analysis of interventions to increase repeat testing in patients treated for gonorrhea or chlamydia at public sexually transmitted disease clinics. Sex Transm Dis 2005; 32:542–549.
15. Klausner JD, Barrett DC, Dithmer D, et al. Risk factors for repeated gonococcal infections: San Francisco, 1990–1992. J Infect Dis 1998; 177:1766–1769.
16. McEvoy BF, Le Furgy WG. A 13-year longitudinal analysis of risk factors and clinic visitation patterns of patients with repeated gonorrhea. Sex Transm Dis 1988; 15:40–44.
17. Michelson KN, Thomas JC, Boyd C, et al. *Chlamydia trachomatis* infection in a rural population: The importance of screening men. Int J STD AIDS 1999; 10:32–37.
18. Noble RC, Kirk NM, Slagel WA, et al. Recidivism among patients with gonococcal infection presenting to a venereal disease clinic. Sex Transm Dis 1977; 4:39–43.
19. Richey CM, Macaluso M, Hook EW. Determinants of reinfection with *Chlamydia trachomatis.* Sex Transm Dis 1999; 26:4–11.
20. Thomas JC, Schoenbach VJ, Weiner DH, et al. Rural gonorrhea in the southeastern United States: A neglected epidemic? Am J Epidemiol 1996; 143:269–277.
21. Thomas JC, Weiner DH, Schoenbach VJ, et al. Frequent reinfection in a community with hyperendemic gonorrhoea and chlamydia: Appropriate clinical actions. Int J STD AIDS 2000; 11:461–467.
22. Champion JD, Shain RN, Korte JE, et al. Behavioural interventions and abuse: Secondary analysis of reinfection in minority women. Int J STD AIDS 2007; 18:748–753.
23. Gunn RA, Fitzgerald S, Aral SO. Sexually transmitted disease clinic clients at risk for subsequent gonorrhea and chlamydia infections: possible 'core' transmitters. Sex Transm Dis 2000; 27:343–349.
24. Orr DP, Johnston K, Brizendine E, et al. Subsequent sexually transmitted infection in urban adolescents and young adults. Arch Pediatr Adolesc Med 2001; 155:947–953.
25. Herieka E, Schober P, Dhar J. *Chlamydia trachomatis* reinfection rate: A forgotten aspect of female genital chlamydia management. Sex Transm Infect 2000; 77:223.
26. Bakken IJ, Skjeldestad FE, Lydersen S, et al. Births and ectopic pregnancies in a large cohort of women tested for *Chlamydia trachomatis.* Sex Transm Dis 2007; 34:739–743.
27. Kissinger P, Clayton JL, O'Brien ME, et al. Older partners not associated with recurrence among female teenagers infected with *Chlamydia trachomatis.* Sex Transm Dis 2002; 29:144–149.
28. Magnus M, Schillinger JA, Fortenberry JD, et al. Partner age not associated with recurrent *Chlamydia trachomatis* infection, condom use, or partner treatment and referral among adolescent women. J Adolesc Health 2006; 39:396–403.
29. Bunnell RE, Dahlberg L, Rolfs R, et al. High prevalence and incidence of sexually transmitted diseases in urban adolescent females despite moderate risk behaviors. J Infect Dis 1999; 180: 1624–1631.
30. Burstein GR, Gaydos CA, Diener-West M, et al. Incident *Chlamydia trachomatis* infections among inner-city adolescent females. JAMA 1998; 280:521–526.
31. Shain RN, Perdue ST, Piper JM, et al. Behaviors changed by intervention are associated with reduced STD recurrence: The importance of context in measurement. Sex Transm Dis 2002; 29:520–529.
32. Shain RN, Piper JM, Holden AE, et al. Prevention of gonorrhea and chlamydia through behavioral intervention: Results of a two-year controlled randomized trial in minority women. Sex Transm Dis 2004; 31:401–408.

33. Niccolai LM, Hochberg AL, Ethier KA, et al. Burden of recurrent *Chlamydia trachomatis* infections in young women: Further uncovering the "hidden epidemic". Arch Pediatr Adolesc Med 2007; 161:246–251.
34. Blackwood LG. Repeated infections with *Neisseria gonorrhoeae* in a population of Alaska natives. Sex Transm Dis 1982; 9:89–92.
35. Blythe MJ, Katz BP, Batteiger BE, et al. Recurrent genitourinary chlamydial infections in sexually active female adolescents. *J Pediatr* 1992; 121:487–493.
36. Bernstein KT, Curriero FC, Jennings JM, et al. Defining core gonorrhea transmission utilizing spatial data. Am J Epidemiol 2004; 160:51–58.
37. Ellen JM, Hessol NA, Kohn RP, et al. An investigation of geographic clustering of repeat cases of gonorrhea and chlamydial infection in San Francisco, 1989–1993: Evidence for core groups. J Infect Dis 1997; 175:1519–1522.
38. Golden MR, Whittington WL, Handsfield HH, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. N Engl J Med 2005; 352:676–685.
39. Hillis SD, Nakashima A, Marchbanks PA, et al. Risk factors for recurrent *Chlamydia trachomatis* infections in women. Am J Obstet Gynecol 1994; 170:801–806.
40. Kinghorn GR, Pryce D, Morton RS. Repeated gonorrhea in Sheffield: The size of the problem, epidemiologic significance, and personal characteristics of repeaters. Sex Transm Dis 1982; 9:165–169.
41. Miller JM Jr. Recurrent chlamydial colonization during pregnancy. Am J Perinatol 1998; 15:307–309.
42. Newman LM, Warner L, Weinstock HS. Predicting subsequent infection in patients attending sexually transmitted disease clinics. Sex Transm Dis 2006; 33:737–742.
43. Burstein GR, Zenilman JM, Gaydos CA, et al. Predictors of repeat *Chlamydia trachomatis* infections diagnosed by DNA amplification testing among inner city females. Sex Transm Infect 2001; 77:26–32.
44. Peterman TA, Tian LH, Metcalf CA, et al. High incidence of new sexually transmitted infections in the year following a sexually transmitted infection: A case for rescreening. Ann Intern Med 2006; 145:564–572.
45. Rietmeijer CA, Van Bemmelen R, Judson FN, et al. Incidence and repeat infection rates of *Chlamydia trachomatis* among male and female patients in an STD clinic: Implications for screening and rescreening. Sex Transm Dis 2002; 29:65–72.
46. Xu F, Schillinger JA, Markowitz LE, et al. Repeat *Chlamydia trachomatis* infection in women: Analysis through a surveillance case registry in Washington State, 1993–1998. Am J Epidemiol 2000; 152:1164–1170.
47. Bernstein KT, Zenilman J, Olthoff G, et al. Gonorrhea reinfection among sexually transmitted disease clinic attendees in Baltimore, Maryland. Sex Transm Dis 2006; 33:80–86.
48. Bloomfield PJ, Steiner KC, Kent CK, et al. Repeat chlamydia screening by mail, San Francisco. Sex Transm Infect 2003; 79: 28–30.
49. Burstein GR, Snyder MH, Conley D, et al. Adolescent chlamydia testing practices and diagnosed infections in a large managed care organization. Sex Transm Dis 2001; 28:477–483.
50. De P, Singh AE, Wong T, et al. Predictors of gonorrhea reinfection in a cohort of sexually transmitted disease patients in Alberta, Canada, 1991–2003. Sex Transm Dis 2007; 34:30–36.
51. Lamontagne SD, Baster K, Emmett L, et al. Incidence and reinfection rates of genital chlamydial infection among women aged 16–24 years attending general practice, family planning and genitourinary medicine clinics in England: A prospective cohort study by the Chlamydia Recall Study Advisory Group. Sex Transm Infect 2007; 83:292–303.
52. Mehta SD, Erbelding EJ, Zenilman JM, et al. Gonorrhoea reinfection in heterosexual STD clinic attendees: Longitudinal analysis of risks for first reinfection. Sex Transm Infect 2003; 79: 124–128.
53. Schillinger JA, Kissinger P, Calvet H, et al. Patient-delivered partner treatment with azithromycin to prevent repeated *Chlamydia trachomatis* infection among women: A randomized, controlled trial. Sex Transm Dis 2003; 30:49–56.
54. Veldhuijzen IK, Van Bergen JE, Gotz HM, et al. Reinfections, persistent infections, and new infections after general population screening for *Chlamydia trachomatis* infection in the Netherlands. Sex Transm Dis 2005; 32:599–604.
55. Whittington WL, Kent C, Kissinger P, et al. Determinants of persistent and recurrent *Chlamydia trachomatis* infection in young women: Results of a multicenter cohort study. Sex Transm Dis 2001; 28:117–123.
56. Fortenberry JD, Brizendine EJ, Katz BP, et al. Subsequent sexually transmitted infections among adolescent women with genital infection due to *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Trichomonas vaginalis.* Sex Transm Dis 1999; 26:26–32.
57. Barnett SD, Brundage JF. Incidence of recurrent diagnoses of *Chlamydia trachomatis* genital infections among male and female soldiers of the US Army. Sex Transm Infect 2001; 77:33–36.
58. Kissinger P, Brown R, Reed K, et al. Effectiveness of patient delivered partner medication for preventing recurrent *Chlamydia trachomatis. Sex Transm Infect* 1998; 74:331–333.
59. Mosure DJ, Berman S, Kleinbaum D, et al. Predictors of *Chlamydia trachomatis* infection among female adolescents: A longitudinal analysis. Am J Epidemiol 1996; 144:997–1003.
60. Gunn RA, Maroufi A, Fox KK, et al. Surveillance for repeat gonorrhea infection, San Diego, California, 1995–2001: Establishing definitions and methods. Sex Transm Dis 2004; 31:373–379.
61. Oh MK, Cloud GA, Fleenor M, et al. Risk for gonococcal and chlamydial cervicitis in adolescent females: Incidence and recurrence in a prospective cohort study. J Adolesc Health 1996; 18:270–275.
62. Burstein GR, Waterfield G, Joffe A, et al. Screening for gonorrhea and chlamydia by DNA amplification in adolescents attending middle school health centers. Opportunity for early intervention. Sex Transm Dis 1998; 25:395–402.
63. Kjaer HO, Dimcevski G, Hoff G, et al. Recurrence of urogenital *Chlamydia trachomatis* infection evaluated by mailed samples obtained at home: 24 weeks' prospective follow up study. Sex Transm Infect 2000; 76:169–172.
64. Lee VF, Tobin JM, Harindra V. Re-infection of *Chlamydia trachomatis* in patients presenting to the genitourinary medicine clinic in Portsmouth: The chlamydia screening pilot study - three years on. Int J STD AIDS 2004; 15:744–746.
65. Fox KK, Thomas JC, Weiner DH, et al. Longitudinal evaluation of serovar-specific immunity to *Neisseria gonorrhoeae.* Am J Epidemiol 1999; 149:353–358.
66. Allaire AD, Huddleston JF, Graves WL, et al. Initial and repeat screening for *Chlamydia trachomatis* during pregnancy. Infect Dis Obstet Gynecol 1998; 6:116–122.
67. Miller JM Jr, Maupin RT, Mestad RE, et al. Initial and repeated screening for gonorrhea during pregnancy. Sex Transm Dis 2003; 30:728–730.
68. Rahm VA, Odlind V, Pettersson R. *Chlamydia trachomatis* in sexually active teenage girls. Factors related to genital chlamydial infection: A prospective study. Genitourin Med 1991; 67:317–321.
69. Somani J, Bhullar VB, Workowski KA, et al. Multiple drug-resistant *Chlamydia trachomatis* associated with clinical treatment failure. J Infect Dis 2000; 181:1421–1427.
70. Shain RN, Piper JM, Newton ER, et al. A randomized, controlled trial of a behavioral intervention to prevent sexually transmitted disease among minority women. N Engl J Med 1999; 340:93–100.
71. Kamb ML, Fishbein M, Douglas JM Jr, et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: A randomized controlled trial. Project RESPECT Study Group. JAMA 1998; 280:1161–1167.
72. Malotte CK, Ledsky R, Hogben M, et al. Comparison of methods to increase repeat testing in persons treated for gonorrhea and/or chlamydia at public sexually transmitted disease clinics. Sex Transm Dis 2004; 31:637–642.
73. Sparks R, Helmers JR, Handsfield HH, et al. Rescreening for gonorrhea and chlamydial infection through the mail: A randomized trial. Sex Transm Dis 2004; 31:113–116.
74. van Valkengoed IG, Morre SA, van den Brule AJ, et al. Follow-up, treatment, and reinfection rates among asymptomatic *Chla-*

mydia trachomatis cases in general practice. Br J Gen Pract 2002; 52:623–627.
75. Orr DP, Langefeld CD, Katz BP, et al. Behavioral intervention to increase condom use among high-risk female adolescents. J Pediatr 1996; 128:288–295.
76. Workowski KA, Lampe MF, Wong KG, et al. Long-term eradication of *Chlamydia trachomatis* genital infection after antimicrobial therapy. Evidence against persistent infection. JAMA 1993; 270:2071–2075.
77. Gaydos CA, Wright C, Wood BJ, et al. *Chlamydia trachomatis* reinfection rates among female adolescents seeking rescreening in school-based health centers. Sex Transm Dis 2008; 35:233–237.
78. Joesoef MR, Weinstock HS, Johnson RE. Factors associated with recurrent chlamydial infection and failure to return for retesting in young women entering national job training program, 1998–2005. Sex Transm Dis 2008; 35:368–371.
79. Bakken IJ, Nordbo SA, Skjeldestad FE. *Chlamydia trachomatis* testing patterns and prevalence of genital chlamydial infection among young men and women in central Norway 1990–2003: A population-based registry study. Sex Transm Dis 2006; 33:26–30.
80. Miller JM, Maupin RT, Nsuami M. Initial and repeat testing for chlamydia during pregnancy. J Matern Fetal Neonatal Med 2005; 18:231–235.
81. Chacko MR, Smith PB, McGill L. Recurrent chlamydial cervicitis in young women at a family planning clinic. Adolesc Pediatric Gynecol 1989; 2:149.
82. Fortenberry JD, Evans DL. Routine screening for genital *Chlamydia trachomatis* in adolescent females. Sex Transm Dis 1989; 16:168–172.
83. Ramstedt K, Forssman L, Johannisson G. Contact tracing in the control of genital *Chlamydia trachomatis* infection. Int J STD AIDS 1991; 2:116–118.