

# Screening for *Chlamydia trachomatis* in Women 15 to 29 Years of Age: A Cost-Effectiveness Analysis

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**Background:** Clinical guidelines have traditionally advised annual *Chlamydia trachomatis* screening for women younger than 25 years of age.

**Objective:** To assess the cost-effectiveness of recently proposed strategies for chlamydia screening.

**Design:** State transition simulation model; cost-effectiveness analysis.

**Data Sources:** Published literature.

**Target Population:** Sexually active U.S. women 15 to 29 years of age.

**Time Horizon:** Lifetime.

**Perspective:** Modified societal.

**Interventions:** Four strategies targeted to 3 specific age groups (15 to 19 years, 15 to 24 years, and 15 to 29 years): 1) no screening, 2) annual screening for all women, 3) annual screening followed by 1 repeated test within 3 to 6 months after a positive test result, and 4) annual screening followed by selective semiannual screening for women with a history of infection.

**Outcome Measures:** Clinical events (for example, pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, and infertility), lifetime costs, quality-adjusted life expectancy, and incremental cost-effectiveness ratios.

**Results of Base-Case Analysis:** Annual screening in women 15 to 29 years of age followed by semiannual screening for those

with a history of infection was the most effective and cost-effective strategy. It consistently had an incremental cost-effectiveness ratio less than \$25 000 per quality-adjusted life-year (QALY) compared with the next most effective strategy. When the indirect transmission effects of a 10-year screening program on the probability of infection in uninfected women (that is, per-susceptible rate of infection) were considered, all strategies became more cost-effective.

**Results of Sensitivity Analysis:** Results were sensitive to the annual incidence of chlamydia, probability of persistent infection, screening test costs, and costs of treating long-term complications. Each variable was associated with threshold values beyond which screening became cost-saving. In probabilistic analysis, annual screening in women 15 to 29 years of age followed by semiannual screening for those with a history of infection had an incremental cost-effectiveness ratio less than \$50 000 per QALY in 99% of simulations.

**Limitations:** Uncertainty about the natural history of chlamydial infection and consideration of only the indirect transmission effects of *C. trachomatis* screening.

**Conclusions:** Annual *C. trachomatis* screening for all women 15 to 29 years of age and selective targeting of those with a history of infection for semiannual screening is very cost-effective compared with other well-accepted clinical interventions.

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See editorial comment on pp 570-572.

Genital infection with *Chlamydia trachomatis* is the most widespread bacterial sexually transmitted disease in the United States and is associated with annual costs that exceed \$2 billion (1–3). Women sustain the most severe consequences of untreated infection, including pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, and tubal infertility (1, 4). Since most chlamydial infections are asymptomatic, screening and early treatment are the most promising public health interventions to prevent serious sequelae (5–7). The availability of nucleic acid amplification technology to detect *C. trachomatis* that can be used on urine, as well as cervical and vaginal specimens (8–10), has enhanced the enthusiasm for screening by making it more feasible in nonclinical settings (11–13).

Although early guidelines advised annual *C. trachomatis* screening for all sexually active women younger than 25 years of age (14–16), reports of high recurrence rates have led to suggestions for more frequent testing in previously infected women (17–21). In fact, the Centers for Disease Control and Prevention (CDC) now advocates a follow-up test in women who have tested positive for *C. trachomatis*

(16). While annual *C. trachomatis* screening for sexually active adolescent and young adult women is cost-effective (22–24), the costs and clinical benefits of selectively targeting women with a history of chlamydial infection for more intensive screening have not been evaluated. Furthermore, most guidelines specifically target women between 15 and 25 years of age; however, recent reports of substantial risk in older women have prompted questions about the potential value of extending the upper age limit to 30 years (24–26). We sought to use the best available data in a decision analytic model to assess the cost-effectiveness of new *C. trachomatis* screening policies.

## METHODS

### Analytic Overview

We developed a computer-based mathematical model (by using DATA 4.0, TreeAge Software, Inc., Williamstown, Massachusetts) to simulate screening, diagnosis, and treatment of chlamydial infection in a representative cohort of sexually active U.S. women, incorporating infection

**Context**

Annual screening for *Chlamydia trachomatis* in sexually active women younger than 25 years of age is cost-effective, but the economic implications of more recent recommendations to expand screening to older women and to test more frequently in women with previous infection are unknown.

**Contribution**

The cost-effectiveness of annual screening in women 15 to 29 years of age followed by semiannual screening in those with previous infection is well within the range of other accepted health care interventions. In some scenarios, such as high-prevalence populations, screening was cost-saving.

**Implications**

Recently proposed screening recommendations for *Chlamydia trachomatis* are cost-effective.

—The Editors

severity, treatment setting, and risk for long-term complications. Strategies were 1) no screening; 2) annual screening for all women; 3) annual screening for all women followed by 1 repeated test within 3 to 6 months after a positive test result; and 4) annual screening for all women except those with a history of at least 1 infection, who are rescreened every 6 months. We evaluated the implications of targeting these strategies to 3 specific age groups (15 to 19 years, 15 to 24 years, and 15 to 29 years) in the base case and the possibility of extending the upper age limit of screening to 39 years in the sensitivity analysis. Model outcomes include intermediate events (for example, pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, and infertility) and long-term outcomes (for example, average per-person lifetime costs, life expectancy, and quality-adjusted life expectancy). Following the reference case recommendations of the Panel of Cost-Effectiveness in Health and Medicine (27), we measured the comparative performance of alternate strategies by using the incremental cost-effectiveness ratio (defined as the additional cost of a specific screening strategy divided by its additional clinical benefit compared with the next least expensive strategy). In addition to deterministic 1-way and 2-way sensitivity analyses, we conducted probabilistic sensitivity analyses by using a second-order Monte Carlo simulation. Finally, we analyzed the indirect effects of an effective screening program on the reduced force of infection (that is, the per-susceptible rate of infection). We reassessed the cost-effectiveness of alternative screening strategies by using a dynamic framework that permits the probability of infection in uninfected women to be a function of the number of infectious individuals in the population at that time.

**Model**

Health states in the model are defined to reflect important characteristics that affect prognosis, quality of life, and resource use. The time horizon incorporates a woman's entire lifetime and is divided into equal 6-month increments (that is, cycles) during which women transition from one health state to another. A cohort of 100 000 sexually active nonpregnant women enters the model at 15 years of age. In each cycle, uninfected women have an age-specific probability of developing an acute *C. trachomatis* infection that may be symptomatic or asymptomatic. We assume that women with symptomatic infections seek care and are treated according to the most recent CDC guidelines (16). Women with asymptomatic infection (or treatment failure) may be spontaneously cured, remain persistently infected (defined as a detectable infection for more than 6 months after the initial acute infection), or develop pelvic inflammatory disease. In our model, spontaneous cure refers to lower genital tract infection that, despite treatment failure or the absence of treatment, resolves spontaneously (does not progress to pelvic inflammatory disease or persist in the lower genital tract as subclinical infection) because of a successful immune response against the organism. A proportion of patients with pelvic inflammatory disease may develop long-term complications (such as infertility, ectopic pregnancy, and chronic pelvic pain), may remain chronically but asymptotically (subclinically) infected, or may be cured by effective treatment. Once cured of infection, a woman may subsequently become reinfected.

To estimate the effect of screening, the model distinguishes between detected and undetected acute infection. We assume that all eligible women are offered and adhere to screening in the base-case analysis, but we examine alternative assumptions in the sensitivity analysis. In a designated screening cycle, a woman with a positive test result moves temporarily to a detected state and is offered treatment (16). If a woman with a true-positive result returns for and adheres to treatment, she may be cured, although she will retain her history of infection. Women treated for acute infection are subject to the risk and costs of medication side effects. Women who develop long-term sequelae (such as chronic pelvic pain) are no longer considered part of the general screening cohort.

**Data**

**Table 1** presents selected model variables and their plausible ranges (1, 4, 6, 8, 9, 22, 28–63). When several estimates were available, we considered the strength of the study design, sample size, presence of control group, similarity of patient populations, and comparability of outcomes measurements. A wide plausible range was established for each variable by using the highest and lowest values reported in the literature.

The annual incidence of acute chlamydial infection varies widely depending on the age group, population, and

Table 1. Model Variables: Baseline Values and Ranges Used in Sensitivity Analyses\*

Variable	Base Case	Plausible Range	Reference
<b>Clinical</b>			
Acute chlamydial infection	0.06†	0.02–0.33	1, 28–33
Symptomatic	0.25	0.10–0.30	1, 4
Persistent acute chlamydial infection	0.30	0.00–0.70	37–39
Acute pelvic inflammatory disease	0.30	0.10–0.40	1, 4, 6
Symptomatic	0.40	0.15–0.40	4, 40, 41
Inpatient treatment	0.20	0.10–0.27	42–45
Pelvic inflammatory disease sequelae			
Chronic pelvic pain‡§	0.18	0.15–0.20	28, 41, 46, 47
Ectopic pregnancy§	0.09	0.05–0.10	28, 41, 46, 48
Tubal infertility‡§	0.20	0.10–0.23	28, 41, 46, 47
Infertility work-up	0.25	0.00–0.40	42, 49, 50
<b>Screening and treatment</b>			
Urine nucleic acid amplification test			
Sensitivity	0.90	0.65–0.96	8, 9
Specificity	0.99	0.99–1.00	8, 9
Effectiveness of treatment for acute infection	0.96	0.94–1.00	36
Adherence to azithromycin	0.80	0.75–0.90	34, 35
Azithromycin-related side effects	0.05	0.01–0.10	36, 49
Effectiveness of treatment for acute pelvic inflammatory disease¶	0.60		51–53
<b>Direct medical costs, \$</b>			
Urine nucleic acid amplification test	13	4–40	54–56
Treatment of acute urogenital chlamydial infection			
1 g of azithromycin	10	10–30	57, 58
Short clinic visit	26	11–44	59
Treatment of azithromycin-related side effects	49		49, 59
Treatment of acute pelvic inflammatory disease			
Outpatient	490	240–490	42, 43, 49, 60, 61
Inpatient	4715	4715–14 800	42, 43, 49, 60, 61
Treatment of pelvic inflammatory disease sequelae			
Chronic pelvic pain	1146	474–15 000	42, 43, 49, 60, 61
Ectopic pregnancy	4355	1300–14 300	42, 43, 49, 60, 61
Tubal infertility	5000	5000–8580	42, 43, 49, 60, 61
<b>Time costs, \$**</b>			
		<b>Net Working Days Lost</b>	
Acute urogenital chlamydial infection	36	0.5 d	22, 62, 63
Acute pelvic inflammatory disease			
Outpatient	513	7.1 d	22, 45, 62, 63
Inpatient	1084	15.0 d	22, 45, 62, 63
Pelvic inflammatory disease sequelae			
Chronic pelvic pain	684	9.5 d	22, 42, 43, 62
Ectopic pregnancy	1445	20.0 d	22, 42, 43, 62
Tubal infertility	321	4.5 d	22, 42, 43, 62
<b>Quality of life</b>			
	<b>Quality Weight††</b>	<b>Duration††</b>	
Symptomatic acute urogenital chlamydial infection	0.90	4 wk	
Symptomatic acute pelvic inflammatory disease	0.65	11 d	
Pelvic inflammatory disease sequelae			
Chronic pelvic pain	0.60	5 y	
Ectopic pregnancy	0.58	4 wk	
Tubal infertility‡‡	0.82	Until age 50 y	

\* Sensitivity analyses were conducted by using the range indicated for each variable. For probabilistic sensitivity analysis, we assumed a  $\beta$  distribution for all probabilities and utilities and a logit normal distribution for costs.

† Estimate applies to women 15 to 19 y of age, after which the probability of developing chlamydial infection decreases by 13% per year (31–33).

‡ Based on the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) randomized trial (47).

§ Based on a prospective cohort study of women with laparoscopically verified pelvic inflammatory disease (41).

|| Nucleic acid amplification test sensitivity represents the probability of a positive test result given lower genital tract infection, acute pelvic inflammatory disease, or pelvic inflammatory disease sequelae.

¶ Based on prospective, second-look laparoscopy studies among women hospitalized for pelvic inflammatory disease (51–53).

\*\* Time costs reflect the value of lost workdays because of screening, treatment, and disease.

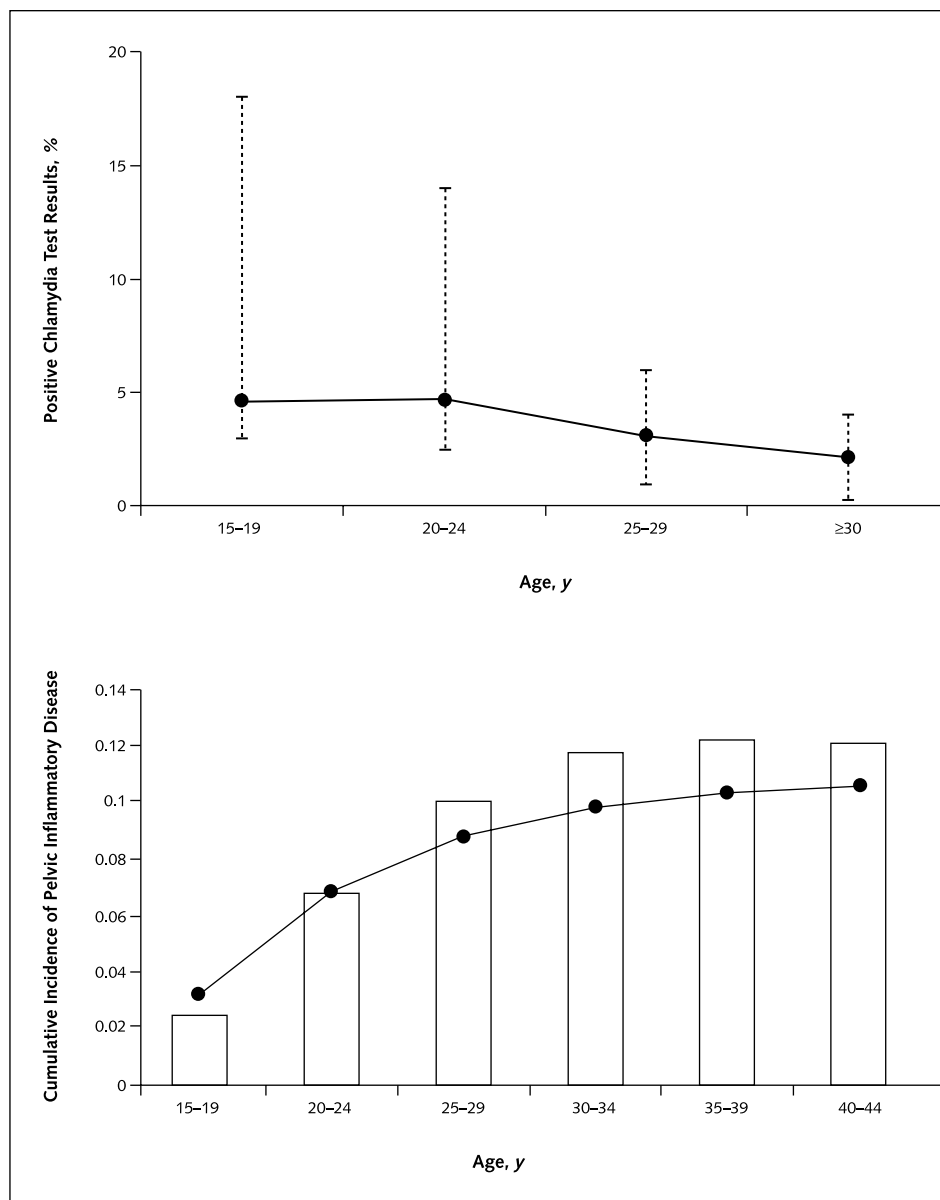
†† Quality weights and their duration were based on the Health Utility Index and obtained from a study commissioned by the Institute of Medicine (61).

‡‡ Estimate applies only to women who receive an infertility work-up.

clinical setting (1, 28–30). We assumed an annual incidence of 6% in women 15 to 19 years of age (28, 29), which was reduced by 13% per year beginning at age 20

years to reflect the age-related decrease in infection risk (31–33). We assumed that 80% of women who were notified of a positive test result (determined by using nucleic

Figure 1. Positive chlamydia screening test results and cumulative incidence of symptomatic pelvic inflammatory disease.



**Top.** The age-specific test positivity for *Chlamydia trachomatis* predicted by the model (circles) falls within the range reported by the Centers for Disease Control and Prevention Chlamydia Prevalence Monitoring Project data in 2000 (dotted line) (78). **Bottom.** The cumulative incidence of symptomatic pelvic inflammatory disease predicted by the model (circles) closely approximates data for self-reported pelvic inflammatory disease from the 1988 National Survey of Family Growth (NSFG) (bars) (79). The vertical columns are the range of values reported by the NSFG adjusted for the 85% of pelvic inflammatory disease that is estimated to be attributable to chlamydial infection (80).

acid amplification technology on a urine sample) would return for treatment (34, 35) and 96% of women treated with azithromycin would be cured, in accordance with a 1996 randomized, controlled trial comparing cure rates for *C. trachomatis* infection in persons treated with azithromycin versus doxycycline (36). We estimated that 30% of women with untreated or uncured acute chlamydial infection would remain persistently infected (37–39), 40% would be spontaneously cured of infection (38, 39), and 30% would develop acute pelvic inflammatory disease within 6 months of an initial infection (1, 4, 6). These

estimates translate to an average duration of infection of 0.93 year, which closely approximates the estimate of 0.96 year cited by Groseclose and colleagues (2) and Buhaug and colleagues (32). Women with a history of *C. trachomatis* infection have a relative risk for reinfection approximately twice that of women with first-time acute infection. In women 15 to 19 years of age, this translates to a reinfection risk of 12%, which is in agreement with values (9% to 13%) reported in published studies (18, 64). On the basis of studies of women with untreated *C. trachomatis* infection, 28% to 50% of women have positive results on

follow-up tests (range, 45 days to 16 months) (38, 39). Because of the potential for misclassification bias, the degree to which repeated test positivity represents persistent infection versus reinfection in these studies is uncertain, and we examined the effect of this uncertainty in a 2-way sensitivity analysis.

Because chlamydia prevalence has substantially decreased in regions with large-scale screening programs (65, 66), we analyzed the indirect effects of an effective 10-year screening program on the reduced force of infection. For this analysis, the probability of infection in uninfected women (that is, per-susceptible rate of infection) is considered to be a function of the number of infectious individuals in the population at that time, in addition to a woman's age and history of infection. We assumed that all asymptomatic, acute lower genital tract infections in women that are detected and subsequently cured with antibiotics represent averted episodes of transmission to men and their sex partners. For men and women, we assumed that the number of averted transmitted infections is also a function of the average number of sexual partners per year, the transmission probability of chlamydial infection per partnership, and the proportion of future partners already infected with *C. trachomatis*.

We used national survey data to determine the age-specific estimates for the average number of male sex partners per woman per year (range, 1.19 to 1.57) and female sex partners per man per year (range, 1.29 to 1.69) (67, 68). The probability of *C. trachomatis* transmission among sexual partners has been reported to be 45% from women to men and 56% from men to women (69), although some investigators have estimated the transmission probability per partnership to be 68% for transmission from men to women and vice versa (70, 71). Because of the considerable uncertainty associated with these variables, such as the probability of transmission per sexual contact, the average number of sexual partners (and the heterogeneity of those partnerships and sexual behavior), the average duration of the infectious period, and the fraction of asymptotically infected persons, that collectively contribute to assumptions about the indirect benefits of a screening program, each variable was varied widely in the sensitivity analysis (72).

**Table 1** shows the direct medical costs for screening and treatment (54–59). Screening costs include those for test kits, laboratory supplies, and labor time for collection and processing (54–56). We used urine-based nucleic acid amplification tests for screening in the base case because of their high acceptance among adolescents (11) and feasibility in nonclinical settings (11–13). Adopting a modified societal perspective for the base case, we included the costs of time lost from work (22, 42, 43, 45, 61–63) for women in the cohort but did not include the averted costs (direct and indirect) associated with transmitting *C. trachomatis* to men and neonates. To assess the potential effect on our estimated lifetime costs of screening, we included these costs in a sensitivity analysis (1, 22, 35, 61, 62, 70, 71, 73–75). All costs were inflated

to 2000 U.S. dollars by using the medical care component of the Consumer Price Index (76).

We derived quality weights for health states (that is, utilities) related to chlamydial infection and sequelae from a study commissioned by the Institute of Medicine (61); these were varied widely in sensitivity analysis. We applied population-based age- and sex-specific quality weights to all other health states (77).

### Role of the Funding Source

The funding source had no role in the design, conduct, or reporting of this study or in the decision to submit the manuscript for publication.

## RESULTS

Before evaluating alternative screening strategies, we sought to validate the model by comparing projected outcomes with independent data not used for initial variable estimation. The model predicts age-specific test positivity for chlamydial infection within a plausible range of values reported by family planning clinics in 50 U.S. states participating in the 2000 CDC Chlamydia Prevalence Monitoring Project (78) (**Figure 1, top**). The projected cumulative incidence of symptomatic acute pelvic inflammatory disease is also similar to published estimates for self-reported pelvic inflammatory disease (79) adjusted for the proportion attributable to chlamydial infection, which is estimated to be 85% (80) (**Figure 1, bottom**).

**Table 2** shows the outcomes for a hypothetical cohort of 100 000 women at risk for chlamydial infection who are screened by using alternative strategies. Relative to no screening, screening for *C. trachomatis* prevents 11% to 42% of all pelvic inflammatory disease and its sequelae, depending on the frequency and duration of the screening program. The most effective strategy is to screen all sexually active women between 15 and 29 years of age annually and to rescreen those with infection every 6 months (that is, semiannually). The least effective strategies are those that assign 1 screening frequency to all women, regardless of previous infections, and restrict routine screening to women 15 to 19 years of age (data not shown). As expected, since the health consequences of chlamydia are largely morbidity rather than mortality, the effect of screening on life expectancy is negligible.

### Cost-Effectiveness Analysis

Without screening, average lifetime costs are \$340 per woman, mostly attributable to pelvic inflammatory disease and its sequelae. The additional lifetime costs associated with screening program implementation vary from \$48 to \$107 per woman. Costs attributable to pelvic inflammatory disease and its sequelae progressively shift to those associated with screening and treatment as screening efforts are intensified (**Figure 2**).

The most efficient and cost-effective screening strategies are those that modified screening frequency in women

**Table 2. Projected Costs, Health Outcomes, and Incremental Cost-Effectiveness of Alternative Approaches to Screening for Chlamydial Infection in 100 000 Women\***

Screening Strategy	Total Cases of Chronic Pelvic Pain, <i>n</i>	Total Cases of Tubal Infertility, <i>n</i>	Total Cases of Ectopic Pregnancy, <i>n</i>
No screening	3437	3882	1743
Annual screening (age 15–24 y): 1 frequency for all women	2573	2915	1308
Annual screening (age 15–24 y): 1 repeated test 3–6 mo after positive result	2509	2843	1276
Modified annual screening (age 15–24 y): every 6 months if previously infected	2372	2688	1206
Annual screening (age 15–29 y): 1 frequency for all women	2300	2608	1170
Annual screening (ages 15–29 y): 1 repeated test 3–6 mo after positive result	2217	2514	1128
Modified annual screening (age 15–29 y): every 6 months if previously infected	2003	2274	1020

\* QALE = quality-adjusted life expectancy; QALY = quality-adjusted life-year.

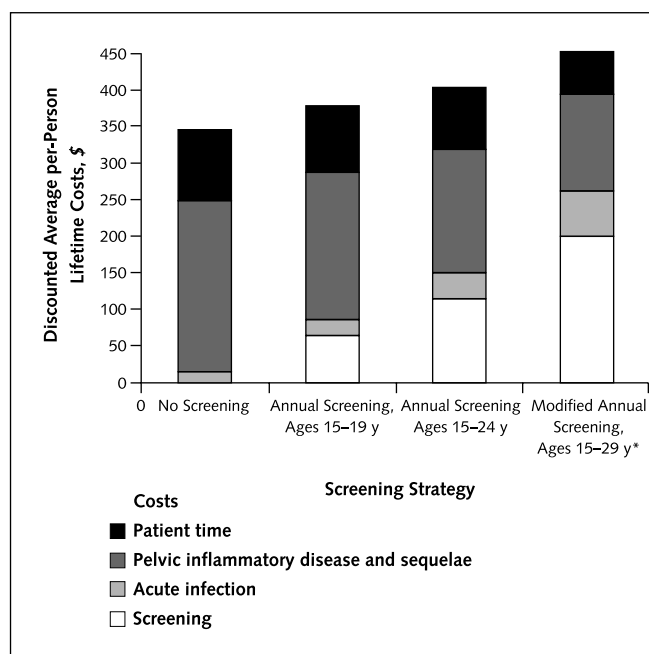
† The difference in cost divided by the difference in QALE or life expectancy for each strategy compared with the next best strategy. All strategies are assumed to be equally available.

‡ Major outcomes include pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy, or tubal infertility.

§ This strategy is more costly and less effective than modified annual screening: every 6 months if previously infected.

with previous infections (Table 2). These strategies are generally more effective and cost-effective (that is, dominant) than strategies that use a single frequency of screening and those that use 1 repeated test after an identified infection. Compared with annual screening for all women 15 to 24 years of age, a modified strategy in which women between 15 and 24 years of age are screened annually and those with documented infection are screened every 6

months is more effective and costs \$2830 per quality-adjusted life-year (QALY). In comparison, this same strategy applied to women 15 to 29 years of age is even more effective and costs \$7490 per QALY. Results unadjusted for health-related quality of life show much higher cost-effectiveness ratios, ranging from \$394 000 to \$1 183 000 per life-year (Table 2).

**Figure 2. Average per-person lifetime costs for selected screening strategies.**

The costs attributable to pelvic inflammatory disease and its sequelae progressively shift to those associated with screening and treatment as screening efforts are intensified. \*Every 6 months if previously infected.

### Sensitivity Analysis

Figure 3 depicts the results of a series of deterministic sensitivity analyses focusing on a modified strategy of annual screening in women 15 to 29 years of age followed by screening every 6 months in those with a history of *C. trachomatis* infection. Provided the annual incidence for acute infection does not decrease by more than 32% per year beginning at age 20 years, the incremental cost-effectiveness ratio associated with screening was consistently below \$50 000 per QALY (compared with the next best strategy), a commonly cited cost-effectiveness threshold for well-accepted preventive health care interventions (81).

We identified several important thresholds at which annual screening in women 15 to 24 years of age becomes cost-saving: 1) Annual incidence of acute infection is greater than 11.4% in women younger than 20 years of age (base-case value, 6%), 2) probability of persistence exceeds 49% (base-case value, 30%), 3) direct medical costs associated with screening are less than \$7.50 (base-case value, \$13), and 4) average per-person lifetime cost of treating complications of pelvic inflammatory disease is greater than \$1955 (base-case value, \$1139). A modified strategy of annual screening in women 15 to 24 years of age followed by screening women with a history of *C. trachomatis* infection every 6 months becomes cost-saving when the annual risk for acute infection is more than 15% or the

Table 2—Continued

Average Discounted Lifetime Costs, \$	Average Discounted QALE, y	Average Discounted Life Expectancy, y	Incremental Cost per Major Outcome Averted, \$†‡	Incremental Cost per QALY, \$†	Incremental Cost per Life-Year Saved, \$†
340	27.2805	27.35089	—	—	—
388	27.3007	27.35101	2090	2350	394 000
395	27.3021	27.35101	Dominated\$	Dominated\$	Dominated\$
400	27.3051	27.35103	2390	2830	635 000
418	27.3054	27.35103	Dominated\$	Dominated\$	Dominated\$
432	27.3072	27.35104	Dominated\$	Dominated\$	Dominated\$
447	27.3115	27.35107	4880	7490	1 183 000

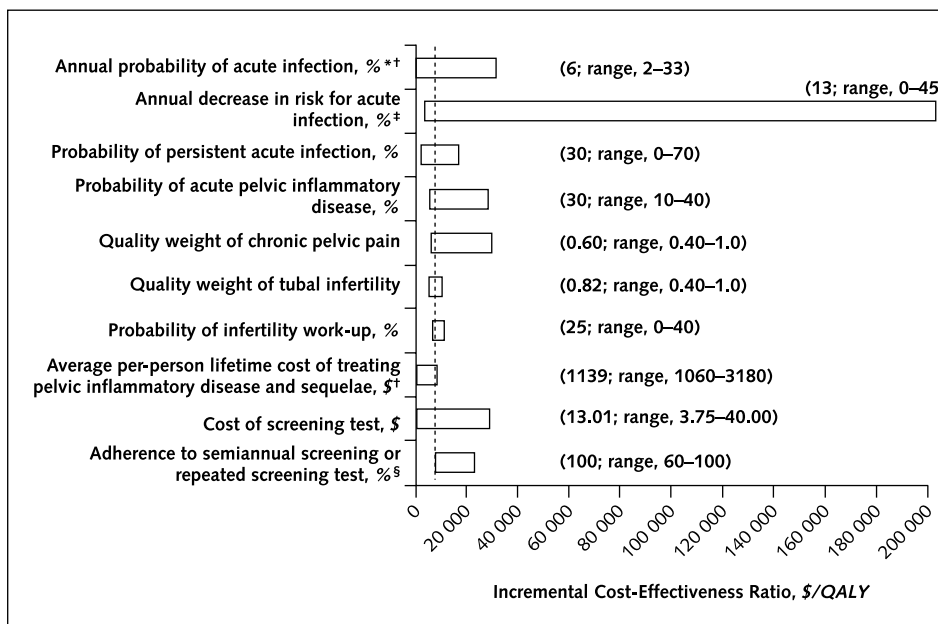
average lifetime cost of pelvic inflammatory disease–related complications is greater than \$2110.

When we included the averted costs (direct and indirect) associated with transmitting *C. trachomatis* infection to men and neonates, the average discounted lifetime costs associated with each screening strategy is reduced by \$44 with the modified annual screening strategy (age 15 to 24 years) and by \$70 with the modified annual screening

strategy (age 15 to 29 years), although the rank ordering of strategies does not change (Table 3).

In 2-way sensitivity analysis, we simultaneously varied probability of persistent infection (0%, 15%, 30%, and 45%) and relative risk for reinfection (1.0, 2.0, and 3.0) compared with the probability of an initial infection (Figure 4). Various assumptions about persistence and recurrence produce results for age-specific chlamydial test posi-

Figure 3. Sensitivity analysis.



The effect of varying selected model variables on the estimated incremental cost-effectiveness ratio for the strategy of annual screening in women 15 to 29 years of age followed by semiannual screening for those with a history of infection. Values in parentheses are the baseline values for each variable and the plausible range used in sensitivity analysis. The bars indicate the variability of the cost-effectiveness ratio caused by changes in the value of the indicated variable, all other variables being held constant. The dotted vertical line indicates the incremental cost-effectiveness ratio under baseline assumptions. \*Applies to women younger than 20 years of age. †Associated with a threshold value beyond which this strategy is cost-saving, relative to no screening. ‡Applies to women 20 years of age or older. §Applies to women with a history of chlamydial infection. QALY = quality-adjusted life-year.

tivity and symptomatic acute pelvic inflammatory disease that are consistent with published data, but these assumptions substantially affect the cost-effectiveness of alternative screening strategies. For example, when persistence and recurrence are low, strategies in which all women are screened annually are cost-effective, reflecting the relative efficiency of a single screening frequency when risk for continued or subsequent infection is low. In contrast, if the relative risk for recurrence is at least 2.0 (relative to an initial infection) and risk for persistence is at least 15%, strategies that assign a single screening frequency to all women are dominated by modified strategies that assign a 6-month screening schedule to women with previous infections.

In a second-order Monte Carlo (probabilistic) analysis, all variables were varied simultaneously for 1000 simulations to estimate the proportion of runs in which each strategy achieves an incremental cost-effectiveness ratio less than \$25 000 per QALY and less than \$50 000 per QALY. For the modified annual screening strategy (age 15 to 29 years), the incremental cost-effectiveness ratio is less than \$25 000 per QALY in 94% of simulations and less than \$50 000 in 99% of simulations. When the upper age limit for screening is extended to 39 years, the incremental cost-effectiveness ratio is less than \$50 000 per QALY in less than 50% of simulations.

#### Indirect Benefits of a 10-Year Screening Program

Using a dynamic framework, we analyzed the indirect effects of a 10-year screening program. When the probability of infection in uninfected women (that is, per-susceptible rate of infection) is a function of the number of infectious individuals in the population at that time, the model predicts decreases in chlamydia prevalence similar to data observed from areas with long-standing screening programs sponsored by the CDC and public health departments (1, 5, 65, 66, 82, 83) (Figure 5). As expected, model predictions after 8 and 9 years tend to underestimate the reduction in prevalence due to other indirect effects of

screening (that is, increased condom use and decrease in sexual activity or number of sexual partners), which were not included in the validation analysis.

In comparison to the base case, when indirect effects secondary to screening are included, the rank order of screening strategies does not change. The modified strategy in which women 15 to 29 years of age are screened annually and those with documented infection are screened every 6 months remains the most effective strategy and becomes even more cost-effective. The incremental cost-effectiveness ratio associated with this strategy decreases from \$7490 in the base case to \$4670 per QALY, compared with the same strategy applied to women 15 to 24 years of age. Relative to no screening, the strategies of annual screening and modified annual screening in women 15 to 24 years of age become cost-saving.

#### DISCUSSION

Over a wide range of plausible assumptions, annual screening in women 15 to 29 years of age followed by semiannual screening for those with a history of infection was the most effective strategy and consistently had an incremental cost-effectiveness ratio well below \$50 000 per QALY gained compared with the next most effective strategy. In comparison, restricting screening to only adolescents (age 15 to 19 years) was less cost-effective. Similarly, the CDC's currently recommended strategy of annual screening followed by a repeated test for women with positive results (16) was less effective and less cost-effective than a strategy in which women with a history of infection were screened every 6 months. This reflects the fact that a period of increased risk, whether attributable to persistence or recurrence, extends beyond the 6-month period after initial infection. Given the lack of empirical data on the risk profile of individual women over time, we did not evaluate thresholds of repeatedly negative chlamydial test results, which might permit reversion to an-

**Table 3. Projected Costs and Complications Prevented in Men and Neonates with Alternative Screening Strategies in 100 000 Women\***

Screening Strategy	Total Averted Cases of Urethritis, nt	Total Averted Cases of Epididymitis, n‡	Total Averted Cases of Neonatal Conjunctivitis, n§	Total Averted Cases of Neonatal Pneumonia, n§	Average Averted Discounted Lifetime Costs, \$
Annual screening (age 15–24 y): 1 frequency for all women	30 606	153	947	474	32
Modified annual screening (age 15–24 y): every 6 mo if previously infected	41 519	208	1314	657	44
Modified annual screening (age 15–29 y): every 6 mo if previously infected	68 165	341	2829	1415	70

\* Averted costs and complications are relative to the strategy of no screening.

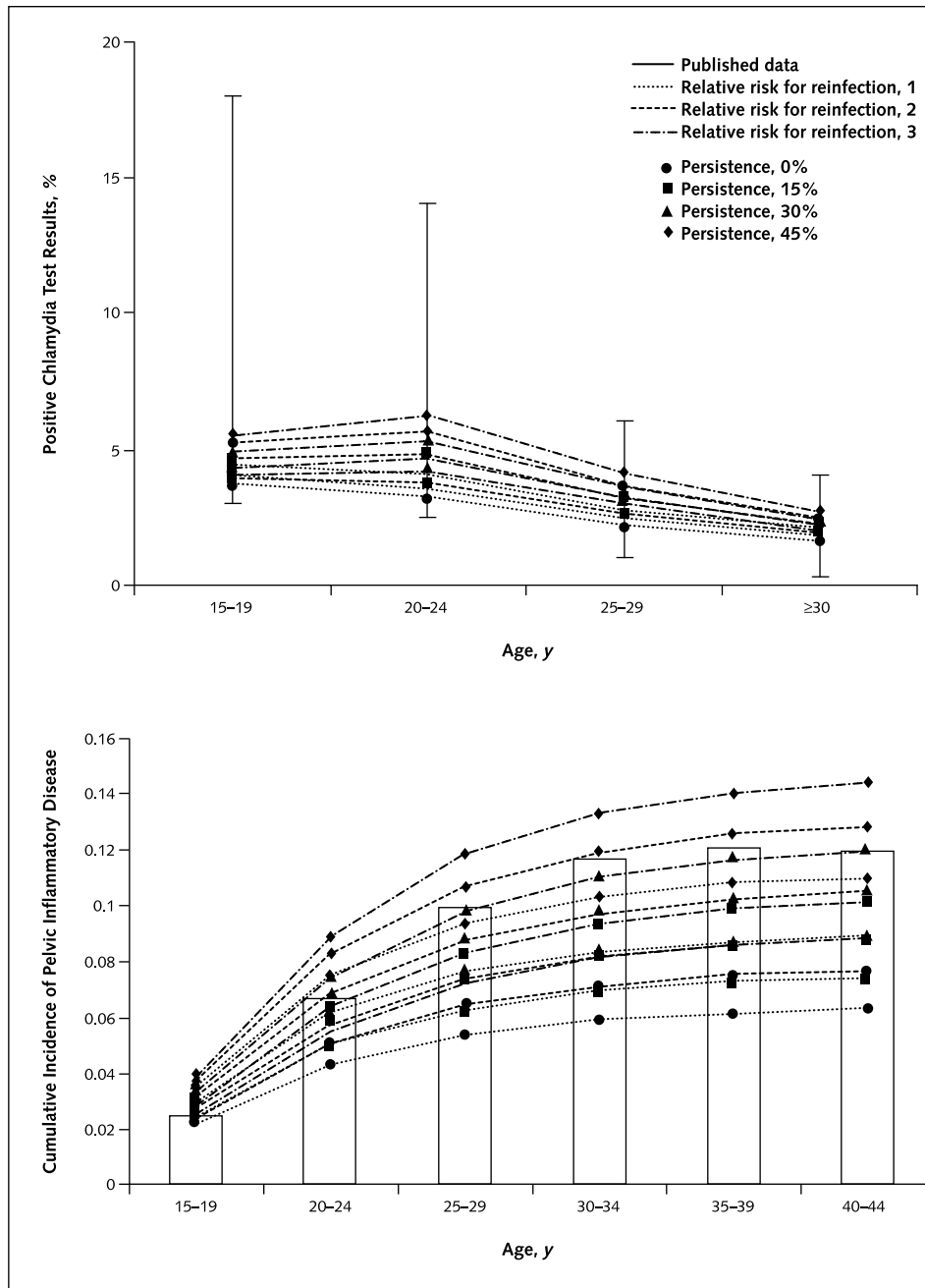
† Calculated as a function of number of infections detected through screening, the transmission probability of chlamydial infection, the average number of male sexual partners per year, and the proportion of future partners already with chlamydial infection (68, 69).

‡ Assumes epididymitis develops in 1% of men with untreated urethritis (73).

§ Estimated as a function of the number of infections detected by screening, the age-specific probability of a live birth, and the assumption of a 30% and 15% risk for neonatal conjunctivitis and pneumonia among infected mothers (74, 75).

|| Includes direct medical costs associated with neonatal conjunctivitis, neonatal pneumonia, epididymitis, and symptomatic urethritis. Time costs were valued for urethritis and epididymitis only (1, 22, 61, 62).

Figure 4. Two-way sensitivity analyses simultaneously varying the probability of persistent infection (0%, 15%, 30%, and 45%) and the relative risk for recurrent infection (1.0, 2.0, and 3.0).



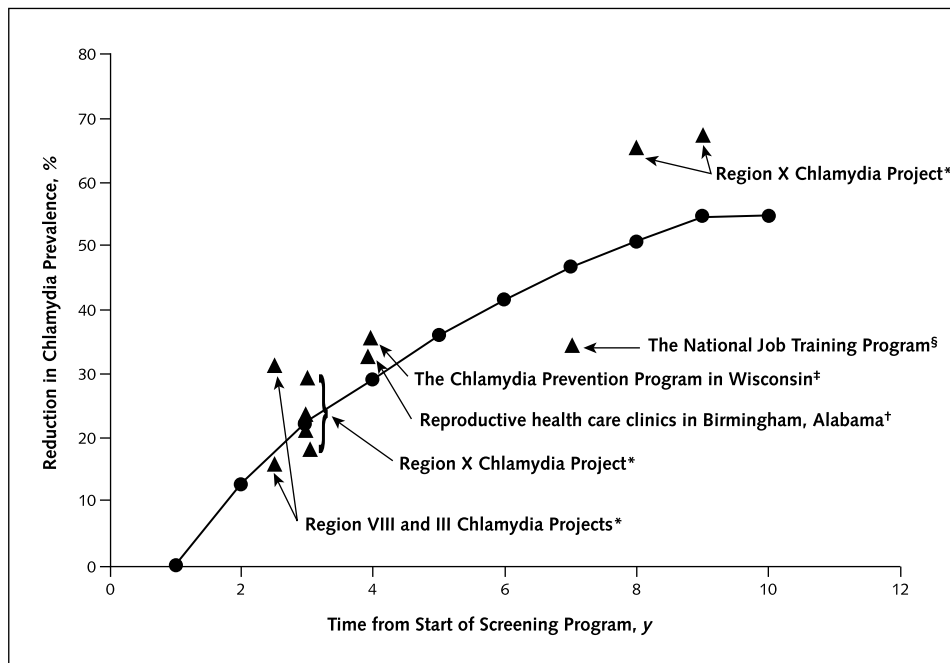
Many scenarios produce results for age-specific test positivity (*top*) and cumulative incidence of symptomatic pelvic inflammatory disease (*bottom*) that are within the range of published data from the Centers for Disease Control and Prevention Chlamydia Prevalence Monitoring Project in 2000 (78) and the National Survey of Family Growth (79), respectively.

nual screening. To guide future recommendations, additional studies must define the duration of risk for repeated chlamydial infection.

The age-specific incidence of chlamydial infection was a critical contributor to the cost-effectiveness of alternative strategies. When the annual incidence in adolescents (age 15 to 19 years) exceeded 11.4%—consistent with some reports from sexually transmitted disease clinics and inner

cities (20, 21)—annual screening in women 15 to 24 years of age was cost-saving. In our analysis of the indirect transmission effects of a 10-year screening program on the probability of infection in uninfected women (per-susceptible rate of infection), all strategies became more cost-effective. The incremental cost-effectiveness ratio of the modified annual screening strategy in women 15 to 29 years of age decreased by about 40% and screening strategies applied to

Figure 5. Reduction in future chlamydia prevalence.



The reduction in future chlamydia prevalence predicted by the model (circles) approximates data reported in areas with broad-based screening programs sponsored by the Centers for Disease Control and Prevention (CDC) and public health departments (triangles). \*Data from CDC-sponsored, regional screening programs participating in the National Infertility Prevention Program (1, 5, 65). †Data from women attending reproductive health care clinics in Birmingham, Alabama, between 1995 and 1998 (82). ‡Data from the Chlamydia Prevention Program in Wisconsin (1987–1991) (83). §Data from women participating in the National Job Training Program from May 1990 to June 1996 (66).

women 15 to 24 years of age became cost-saving. Given these results, implementing a modified annual screening strategy to the more restrictive age range of 15 to 24 years may be reasonable if budgetary constraints are severe. These results should be interpreted with caution, however, since considerably more assumptions were made about the heterogeneity of sexual behavior and nature of partnership in this analysis than in the base case.

Similar to other studies, we found that extending routine screening beyond the age range currently recommended by the CDC and U.S. Preventive Services Task Force to include women 25 to 29 years of age would provide substantial additional benefits (84). The results of our base-case analysis and sensitivity analyses support extending the screening age range as a cost-effective use of societal resources. These results are also supported by data from the 2000 CDC Chlamydia Prevalence Monitoring Project, which indicate that in approximately two thirds of states, the prevalence of chlamydial infection in women 25 to 29 years of age was 3% or more (78). However, fewer data are available on age-related prevalence in women 30 to 39 years of age, and estimates for older women have often been aggregated (78). Consideration of what we know about infectious disease dynamics in an effective sexually transmitted disease prevention program would predict an increase in the average age of infection. This phenomena, most often reported after successful immunization programs, may also support extending the screening age range.

As better data on the age-related prevalence in older women and the temporal changes in average age of infection with screening become available, we should reevaluate recommendations about the upper age limit of screening.

The cost of screening tests and the average per-person lifetime cost of pelvic inflammatory disease were also key factors in the cost-effectiveness of alternate screening strategies and were associated with threshold values beyond which screening became cost-saving. As noninvasive screening becomes more widely used, the large-scale purchase of these tests may result in substantial price reductions. However, as the management of pelvic inflammatory disease and ectopic pregnancy shifts increasingly toward outpatient treatment, cost-effectiveness ratios associated with screening interventions may increase.

Our study has several limitations. First, the limitations associated with our primary data sources are our study's limitations as well. There is considerable uncertainty about the natural history of chlamydial infection, especially the relative magnitude of reinfection and persistent infection. Our results suggest that a better understanding of the degree to which repeated test positivity within 1 year after an acute infection represents persistent infection versus reinfection is a major priority for the design of effective and cost-effective chlamydial control strategies.

Second, we developed our model primarily to evaluate the cost-effectiveness of new screening guidelines, for example, selectively targeting women with a history of chla-

mydial infection for more frequent screening. As such, we developed the state transition model with very detailed natural history and screening modules that required stratification of several health states to capture the heterogeneity in age-related probabilities of initial, recurrent, and persistent infection. To fully integrate a dynamic transmission model into this framework would be computationally difficult and, by necessity, would require a more simplistic approach to the costing analysis. Therefore, we conducted a separate analysis linking a dynamic framework to our state transition model to incorporate the indirect transmission effects of a 10-year screening program. As other studies have reported (85), static models that do not include indirect effects on the incidence of infection in susceptible members of the cohort will provide a reasonably close approximation to a dynamic model if the outcome of interest is incidence of infection in 1 birth cohort, the basic reproductive rate of infection is high, the target population of the intervention is the general population, and very few or very many persons in the cohort undergo the intervention—these characteristics are representative of our analysis. Furthermore, because such cohort models nearly always underestimate the cost-effectiveness of the intervention (in this case, screening), if screening is deemed to be cost-effective by using this framework, use of a dynamic model would not change the decision (85). Although incorporating indirect effects on the incidence of infection in susceptible members of the cohort led to an overall improvement in the cost-effectiveness of screening strategies, we found that this did not alter our general conclusions.

Third, we based our analysis on published performance data for nucleic acid amplification tests, including data on the ligase chain reaction test. While the latter is no longer widely available, comparisons of several nucleic acid amplification tests suggest that performance characteristics are similar (8, 9). Fourth, our analysis does not include screening women for both gonorrhea and chlamydia. Recent data support substantial racial and ethnic disparities in the prevalence of both chlamydial and gonococcal infections (86); future policy analyses should formally consider interventions to reduce these disparities. Finally, better data are needed on the quality-of-life effect of pelvic inflammatory disease and their sequelae. These data are critical to refine estimates of cost-effectiveness since most consequences from chlamydial infection are in the form of morbidity rather than mortality.

In conclusion, a program that screens all women 15 to 29 years of age annually and selectively targets women with a history of infection for semiannual screening will provide substantial clinical benefit and is highly cost-effective. Research priorities most likely to influence future screening guidelines should address the relative contribution of persistence and recurrence to rates of test positivity, determine the relative risk for acute pelvic inflammatory disease and long-term sequelae associated with persistent and recurrent

infection, and obtain better age-related estimates of chlamydial infection in women older than 30 years of age.

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