Background: Chlamydial infection is the most common sexually transmitted bacterial infection in the United States, with an estimated 3 million new cases annually. In 2001, the U.S. Preventive Services Task Force (USPSTF) recommended that clinicians screen all sexually active women at increased risk for infection for Chlamydia trachomatis.

Purpose: To summarize a systematic evidence review commissioned by the USPSTF in preparation for an update of its 2001 recommendation.

Data Sources: English-language articles identified in PubMed between July 2000 and July 2005. Additional articles were identified by bibliographic reviews and discussions with experts. A total of 452 articles were identified.

Study Selection: Explicit inclusion and exclusion criteria were used for each of 3 key questions. For studies of screening in nonpregnant women at increased risk, review was limited to randomized, controlled trials. For other groups, both randomized, controlled studies and nonrandomized, prospective, controlled studies were included.

Data Abstraction: Using standardized forms, staff of the Agency for Healthcare Research and Quality abstracted data on study design, setting, sample, randomization, blinding, results, and harms.

Data Synthesis: Only 1 new study met inclusion criteria. This poor-quality study of the effectiveness of screening for chlamydial infection among nonpregnant women at increased risk found that screening was associated with a lower prevalence of chlamydial infection and fewer reported cases of pelvic inflammatory disease at 1-year follow-up.

Limitations: No new evidence was found on screening in pregnant women, nonpregnant women not at increased risk, or men.

Conclusions: A systematic review found a small amount of new evidence to inform the USPSTF as it updates its recommendations regarding screening for chlamydial infection. There are large gaps in the evidence about screening men to improve health outcomes in women.


This article summarizes a full evidence update conducted for the USPSTF, which reviewed information published since the USPSTF 2001 review (9). This update focused on a search for direct evidence on the effect of screening asymptomatic individuals on health outcomes. The USPSTF reviewed the evidence to update its recommendations. (A description of how the Task Force devel-
In preparing for the review, the USPSTF identified 3 critical key questions for which they requested systematic evidence reviews. In addition, they identified several subsidiary questions for which they requested nonsystematic reviews to assist them with updating their recommendations and supporting materials. This article focuses on the results of the systematic review and concludes with a few highlights from the nonsystematic reviews.

Answers to the following key questions were pursued by means of a full-scale literature review.

1. Does screening for chlamydial infection in nonpregnant women reduce adverse health outcomes?
2. Does screening for chlamydial infection in pregnant women reduce adverse health outcomes?
3. Does screening for chlamydial infection reduce adverse health outcomes in men, reduce adverse health outcomes in women, or reduce the incidence of infection in women?

In this context, health outcomes of interest were defined as follows: PID, ectopic pregnancy, infertility, and chronic pelvic pain in nonpregnant women; chorioamnionitis, premature rupture of membranes, preterm labor, preterm delivery, spontaneous abortion, endometritis, and low birth weight in pregnant women; and epididymitis, urethritis, prostatitis, chronic prostatitis, reactive arthritis, and urethral strictures in men.

METHODS

Staff at the Agency for Healthcare Research and Quality conducted a systematic evidence review for each of the critical key questions.

Data Sources

The search strategy included a review of English-language articles identified from PubMed between July 2000 and July 2005. Additional articles were found through bibliographic reviews and discussion with experts. These searches identified 452 articles.

Study Selection

For key question 1, the review was limited to randomized, controlled trials of nonpregnant women at increased risk for infection. For nonpregnant women not at increased risk, the search was expanded to include both randomized, controlled trials and nonrandomized, prospective, controlled studies. For key questions 2 and 3 (screening in pregnant women and in men), the reviews were limited to randomized, controlled trials and nonrandomized, prospective, controlled studies.

Abstracts were reviewed by 2 staff members. All abstracts that were clearly within the scope of this review and those with potential or ambiguous relevance were retained. Eighteen articles were identified as potentially meeting these broad inclusion and exclusion criteria (Figure).

Data Extraction and Quality Assessment

Two reviewers independently reviewed the full articles of all identified studies to determine whether the articles met predetermined inclusion criteria. Additional reviewers were consulted for consensus building around 2 articles that were ultimately not included in this review. The 2 principal reviewers independently abstracted data by using standardized forms from included articles to determine study quality.

Role of the Funding Source

The work of the USPSTF is supported by the Agency for Healthcare Research and Quality.

RESULTS

Key Question 1

Does screening for chlamydial infection in nonpregnant women reduce adverse health outcomes?

Women at Increased Risk

In 2001, on the basis of a good-quality randomized, controlled trial by Scholes and colleagues published in 1996 (11), the USPSTF gave an A rating to their recommendation that clinicians routinely screen all sexually active women at increased risk for chlamydial infection. The study, conducted in a large managed care organization in Seattle, Washington, concluded that screening and treating young women at increased risk for chlamydial infection significantly reduced the incidence of PID after 1 year of follow-up (11).

Only 1 study (12) identified in the current systematic review met the inclusion criteria and addressed the effectiveness of screening for chlamydial infection among nonpregnant women at increased risk. In a cluster randomized trial, Ostergaard and colleagues (12) found that a 1-time, home-based screening intervention was associated with a lower prevalence of chlamydial infection and fewer re-

Key Summary Points

There is direct evidence that screening women at increased risk for chlamydial infection improves health outcomes.

There is no direct evidence that screening women not at increased risk for chlamydial infection improves health outcomes.

There is fair evidence that screening pregnant women can identify chlamydial infection and that treatment of chlamydial infection improves birth outcomes.

Evidence is insufficient to determine whether screening men for chlamydial infection improves health outcomes in women.
ported cases of PID at 1-year follow-up. As part of a larger study, the team randomly assigned 17 high schools in a Danish county to 1 of 2 groups. Students in schools selected to be in the intervention group were offered a single opportunity for home-based screening for chlamydial infection. Students in the control schools were given the same educational information and were encouraged to visit their physician for a free screening. Sexually active girls in both groups were offered the opportunity to receive follow-up in 1 year.

Ostergaard and colleagues found that the intervention was associated with a lower prevalence of chlamydial infection and fewer reported cases of PID at 1-year follow-up. Of 443 girls in the intervention group who participated in follow-up testing, 13 (2.9%) were found to have chlamydial infection and 9 (2.1%) reported receiving treatment for PID. Of 487 girls in the control group, 32 (6.6%) were found to have chlamydial infection and 20 (4.2%) reported receiving treatment for PID. Both of these differences were found to be statistically significant. Given the differences in initial screening rates between the groups (93.4% of the intervention group vs. 7.6% of the control group), the USPSTF chose to include this study as an example of a trial of screening versus not screening. The effect of baseline screening in the control group would be expected to decrease the ability of the intervention to demonstrate a difference between screening and not screening. This factor gives additional weight to the study findings.

Although universal screening was offered, Ostergaard and colleagues targeted high school–age female adolescents, who are defined by the USPSTF as being at increased risk for chlamydial infection because of their age alone. The overall initial prevalence rate of chlamydial infection among those screened was 5.0%. The USPSTF thus considered this to be a trial of screening women at increased risk and not a trial of the effect of universal screening. The study was deemed to be of poor quality because of an unaccounted loss of participants in both groups for follow-up screening. Whereas 93.4% participants in the intervention group and 100% of those in the control group agreed to follow-up screening, only 51.1% in the intervention group and 58.5% in the control group actually participated in follow-up screening. The researchers did not provide sufficient information to assess the effects that this loss may have had on the results of the study.

A study by Clark and colleagues (13) was closely reviewed by the USPSTF. Although this study did not meet the criteria for the systematic review because it was a non-randomized trial of screening women at increased risk, it is presented here as a good-quality study that contributes to our understanding of screening for chlamydial infection. Clark and colleagues conducted a nonrandomized cohort study examining hospitalization rates after screening for chlamydial infection in female military recruits (13). A total of 7053 women were screened and treated for chlamydial infection over 2 years on arrival at basic training. A group of 21,021 women who were not screened on arrival were followed as a comparison group. Eighty percent of the women studied were younger than age 25 years, and the overall prevalence rate of chlamydial infection among the women screened was 9.1%. The average duration of follow-up for both cohorts was more than 1.5 years. Results were adjusted for age, race, education, and entrance aptitude score. The investigators found a slight decrease in the adjusted relative risk for hospitalization overall (0.94 [95% CI, 0.90 to 0.99]). The investigators noted a lower adjusted relative risk for hospitalization for PID, but this difference was not statistically significant (0.94 [CI, 0.69 to 1.29]). The relative risk for hospitalizations for chlamydia-related sequelae (PID, infertility, or ectopic pregnancy) was nonstatistically higher in the screened group than in the unscreened group (1.10 [CI, 0.85 to 1.43]).

The intervention and control groups differed significantly in terms of age, education, and entrance aptitude scores: The screened group was slightly younger and had lower educational levels and aptitude scores than the control group. Both groups were about 35% African American. The study examined military hospitalizations only and did not capture civilian hospital use by either group. In addition, the investigators could not include outpatient treatment for PID or other sequelae. Although the research team adjusted for major known demographic confounders, the trial is a nonrandomized study in groups with significant differences. The time frame for this study may not have been adequate to detect the full consequences of the long-term effects of chlamydial infection, but the findings nonetheless remind us that dramatic benefits from a single screening test may not be significant or may not be captured in a specific evaluation project.

Figure. Study flow diagram.
Women Not at Increased Risk

In 2001, the USPSTF found no direct trials of screening women not at increased risk for chlamydial infection that reported health outcomes. It found fair evidence for each link in the analytic framework, noting that there was fair evidence that screening women not at increased risk would find additional cases of chlamydial infection. The USPSTF found little evidence of potential harms of screening. However, given the low prevalence of chlamydial infection in this population, the USPSTF made no recommendation for or against routinely screening asymptomatic women not at increased risk for chlamydial infection. The USPSTF concluded that the potential benefits of screening women not at increased risk may be small and consequently may not justify the potential harms of screening.

The current systematic review found no new direct trials of screening for chlamydial infection among women not at increased risk.

Key Question 2

Does screening for chlamydial infection in pregnant women reduce adverse health outcomes?

In 2001, the USPSTF found fair evidence that screening asymptomatic pregnant women can detect chlamydial infection and that treatment of chlamydial infection during pregnancy improves health outcomes for both the mother and infant. The USPSTF concluded that the potential benefits outweighed the potential harms of screening pregnant women and recommended that clinicians routinely screen all asymptomatic pregnant women age 25 years or younger, and other pregnant women at increased risk, for chlamydial infection. The USPSTF considered the potential net benefits of screening pregnant women who are not at increased risk to be small, leading it to make no recommendation for or against screening pregnant women not at increased risk for chlamydial infection.

Evidence reviewed for this report revealed no new randomized, controlled studies or nonrandomized, prospective, controlled studies addressing this topic.

Key Question 3

Does screening for chlamydial infection reduce adverse health outcomes in men, reduce adverse health outcomes in women, or reduce the incidence of infection in women?

In 2001, the USPSTF noted that the benefits to men of treating asymptomatic infection are small, because long-term sequelae are rare and treatment of symptomatic infection is effective. However, the USPSTF noted the potential for significant benefit if screening in men can, in fact, decrease the incidence of infection in women. Finding no evidence to support this hypothesis, the USPSTF concluded that the evidence was insufficient to make a recommendation regarding screening men for chlamydial infection.

The current systematic review identified no randomized, controlled studies or nonrandomized, prospective, controlled studies of screening men for chlamydial infection and the ability of screening programs to reduce the incidence of infection among women.

Contextual Questions

The full evidence update report includes information on the following contextual questions.

1. Has the epidemiology of chlamydial infection in the United States changed in significant ways since 2001, including in groups at increased risk?
2. What are the harms of screening for chlamydial infection?
3. Are screening tests for chlamydial infection accurate?
4. What is the optimal screening frequency?
5. Does chlamydial infection increase the risk for infection with HIV?
6. What is the cost-effectiveness of screening for chlamydial infection?

Limited nonsystematic reviews were conducted for the subsidiary questions. Literature reviews for subsidiary questions included review articles and topic-specific searches of MEDLINE. Articles reviewed during the critical key question reviews were tagged if they addressed a subsidiary key question. Recommendations for sentinel articles were also sought from content experts. The purpose of these searches was to provide updated context for recommendations rather than to serve as evidence for changes in the recommendations. The results of these searches may be viewed in the full report at www.preventiveservices.ahrq.gov. Selected highlights from the report are included below.

Epidemiology

The review found that the epidemiology of chlamydial infection in the United States has not changed in significant ways in recent years. Age remains the strongest predictor of risk in both men and women. Among women, the highest rates of infection are reported among those 15 to 19 years of age, followed by those 20 to 24 years of age. Other associated risk factors include both behavioral and demographic factors, including having multiple sexual partners, having a new sexual partner or an infected sexual partner, inconsistently using barrier contraceptives, and having a history of previous or coexistent sexually transmitted infections (STIs) (7). The incidence of chlamydial infection continues to be higher in many African-American and Hispanic communities.

Harms of Screening

Several new qualitative studies have examined the adverse effects associated with a diagnosis of chlamydial infection.

A 2003 paper addressed the psychosocial impact of the diagnosis of chlamydial infection through a qualitative study using semistructured interviews with 17 Scottish women with recently diagnosed chlamydial infection. The researchers found that these women perceived that testing
and diagnosis of chlamydial infection were associated with negative stereotypes, such as contamination and delinquency, and they perceived a social stigma attached to their diagnosis. The women expressed concern over the meaning of their diagnosis to their future fertility and had significant anxiety about the attitudes of their male partners. They also were concerned about notifying both current and past partners (14).

As part of a large trial of screening for chlamydial infection in England, Pimenta and colleagues (15) conducted in-depth interviews with more than 400 women who completed screening. Overall, participants were accepting of the screening program, and most found screening beneficial. Participants with positive test results commonly reported “feeling dirty, [feeling] ashamed at passing on the infection, and [sensing others’] suspicion about where the infection originated.” The investigators reported that for some women, this led to “tension and suspicion within relationships,” but no long-term repercussions within relationships were identified (15).

A qualitative study of 12 heterosexual men and 12 heterosexual women with recently diagnosed chlamydial infection identified significant differences in their responses to diagnosis. The women reported feeling anxious about their future reproductive health, feared stigmatization, and blamed themselves for contracting chlamydial infection. The men generally reported less concern and were less willing to disclose their condition to sexual partners. Some of the men, according to the investigators, blamed their partners for their infection and avoided accepting responsibility for themselves. The female participants experienced blame and denial of the infection on the part of their male partners. The women also reported concern about potential threats to their relationships. The investigators concluded that a culture of the “blameless male and stigmatized female” continues to persist around the issue of STIs. They note that avoidant attitudes and behaviors among men should be accounted for in STI screening and treatment programs (16).

Accuracy of Screening Tests

The USPSTF 2001 systematic review on chlamydia screening found that nucleic acid amplification tests (NAATs) had higher sensitivities and specificities than older antigen detection tests and higher sensitivities than culture. However, the USPSTF did not at that time provide clinical guidance on which tests should be used. In 2002, the CDC recommended that NAAT’s be used for screening both women and men (17). It reached this conclusion on the basis of a systematic review that included, in addition to many of the studies considered by the USPSTF, a large multicenter study on screening technologies. In 2005, Cook and colleagues (18) presented a systematic review of noninvasive testing for chlamydial infection in which overall high sensitivities and specificities were found for polymerase chain reaction and other NAATs from both genital and urine samples.

Chlamydial Infection and HIV

There is broad consensus in the literature that, as with other inflammatory STIs, chlamydial infection facilitates the transmission of HIV infection in both men and women. Sexually transmitted infections increase both the infectivity of persons with HIV infection and the susceptibility of those with STIs to HIV infection (19, 20).

The prevalence of chlamydial infection among men who have sex with men has not been studied widely outside of HIV care settings. In addition, tests other than culture, which are not widely available, have not been cleared by the U.S. Food and Drug Administration for use with rectal or pharyngeal specimens.

Research Gaps and Emerging Issues

The systematic review uncovered no evidence on the effect of screening men to reduce the prevalence of infection in women, but our understanding of the ability of screening and treatment of a high-risk group to reduce community prevalence of an STI may be informed by a study in a South African mining community (21). A research team conducted 2 cross-sectional samples of male miners in a mining town, where more than 90% of the miners live in single-sex hostels near the mines. The intervention consisted of the establishment of a mobile STI clinic for female sex workers and other local women with multiple sex partners. Women enrolled at the clinic were encouraged to return for monthly visits and were treated presumptively with azithromycin at each visit. For women who returned to the clinic, rates of gonorrhea and chlamydial infection decreased with each visit. At the end of the intervention, the rate of gonorrhea among miners decreased from 10.9% to 6.2% ($P < 0.001$) and that of chlamydial infection decreased from 6.6% to 3.5% ($P = 0.005$). Community records also showed that the miners significantly decreased their number of visits to local medical facilities for STI care.

Similar results were found in a study presented at a meeting of the International Society for Sexually Transmitted Disease Research in Ottawa, Ontario, Canada, in 2003 (22). Researchers reported that chlamydial infection among women decreased by 50% at a health center serving a population in which men who had been screened and treated for chlamydial infection while incarcerated resided. If this type of research continues, future recommendations regarding screening for chlamydial infection in men may have an evidence base.

Another area lacking research is that of the potential harms associated with screening for chlamydial infection. In 2005, the CDC began a study to examine the psychosocial effect of a positive diagnosis of chlamydial infection (Walsh C. Personal communication, 2005).

Discussion

The evidence base supporting screening for chlamydial infection has not expanded greatly since the USPSTF made its first recommendation regarding screening in 2001.
Table 1 summarizes the combined evidence from the 2001 USPSTF systematic review and the current update. The evidence is strongest regarding screening in nonpregnant women at increased risk for infection. The effectiveness of screening men for chlamydial infection to reduce the incidence of infection and its sequelae in women remains a large gap in our current understanding of screening for chlamydial infection.

Table 2. Outcomes of Screening 10 000 Asymptomatic Women for Chlamydial Infection*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk for Chlamydia trachomatis Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Epidemiologic</td>
<td></td>
</tr>
<tr>
<td>Prevalence, %</td>
<td>0.1</td>
</tr>
<tr>
<td>New cases, n</td>
<td>10</td>
</tr>
<tr>
<td>Expected PID in untreated C. trachomatis rate†</td>
<td>0.3</td>
</tr>
<tr>
<td>Expected cases of PID in untreated women without screening, n</td>
<td>3</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.90</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.99</td>
</tr>
<tr>
<td>True positive</td>
<td>9</td>
</tr>
<tr>
<td>False negative</td>
<td>1</td>
</tr>
<tr>
<td>False positive</td>
<td>100</td>
</tr>
<tr>
<td>Total positive</td>
<td>109</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>8.25</td>
</tr>
<tr>
<td>Effect of therapy</td>
<td></td>
</tr>
<tr>
<td>Adherence to azithromycin therapy</td>
<td>0.80</td>
</tr>
<tr>
<td>C. trachomatis infection treated†</td>
<td>7.2</td>
</tr>
<tr>
<td>C. trachomatis infection cured with treatment</td>
<td>0.96</td>
</tr>
<tr>
<td>Cases of C. trachomatis infection cured</td>
<td>6.9</td>
</tr>
<tr>
<td>Cases of C. trachomatis infection not cured</td>
<td>0.3</td>
</tr>
<tr>
<td>Total cases of C. trachomatis infection after screening and treatment§</td>
<td>1.3</td>
</tr>
<tr>
<td>PID</td>
<td></td>
</tr>
<tr>
<td>Expected cases with screening, n</td>
<td>0.39</td>
</tr>
<tr>
<td>Cases avoided by screening, n</td>
<td>2.6</td>
</tr>
<tr>
<td>Number needed to screen to avoid 1 case of PID</td>
<td>3846</td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
</tr>
<tr>
<td>Expected cases resulting from C. trachomatis infection–related PID, n</td>
<td>0.08</td>
</tr>
<tr>
<td>Cases avoided by screening, n</td>
<td>0.52</td>
</tr>
<tr>
<td>Number needed to screen to avoid 1 case of infertility</td>
<td>19 231</td>
</tr>
</tbody>
</table>

* Assumptions made in this table, which are derived from a review of the literature by Hu and colleagues (24), include that 80% of women with a positive result on chlamydia testing will be contacted and will receive and take azithromycin; 90% of women treated with azithromycin will be cured of infection; and 20% of women who experience PID will become infertile. PID = pelvic inflammatory disease.
† Data from reference 1.
‡ True-positive rate multiplied by 0.8.
§ Persons with a false-negative rate plus persons in whom infection is not cured.
There is an emerging literature about the potential harms of screening in qualitative studies examining the implications of a positive chlamydia test result. These studies find significant anxiety and concern for the future of intimate relationships after a positive diagnosis of chlamydial infection.

This review identified no studies investigating screening intervals for chlamydial infection. Therefore, there is no direct evidence to guide decisions about repeated screening in those who have already been screened, regardless of the outcome. Studies in this area will make a major contribution to improving the evidence base for screening programs.

Table 2 shows hypothetical outcomes of a screening program for chlamydial infection that are based on assumptions from recent studies. It shows the results that might be expected from screening programs among non-pregnant women with underlying prevalence rates of chlamydial infection, including 0.1% (women not at increased risk), 1.0% (women age 25 to 29 years who are not otherwise at increased risk), 5.0% (sexually active female adolescents), and 10.0% (women at significant increased risk, such as military recruits). The positive predictive value increases from 8% to 91%, whereas the number needed to screen to prevent 1 case of PID decreases from 3800 to 38 between the groups with the lowest and highest prevalence rates.

Despite this evidence, many, if not most, women are not receiving this recommended preventive health service. The National Committee for Quality Assurance noted in their 2005 report that although there has been modest and steady improvement in the rates of screening women for chlamydial infection, in 2004 the screening rate was 32.6% among women age 16 to 20 years in commercial health plans and 45.9% among women enrolled in Medicaid managed care plans (23). For women age 21 to 25 years, the rates were 31.7% in commercial plans and 49.0% in Medicaid plans (23). In an editorial accompanying an article by Hu and colleagues (24) on the cost-effectiveness of screening for chlamydial infection, Stamm acknowledges that “actual practice falls far short of recommended practice” (25). The author suggests that before screening programs are expanded to men or to women with lower prevalence rates of chlamydial infection, “sexually active women 15 to 24 years of age ... should have the highest priority for screening” (25).

From the Agency for Healthcare Research and Quality, Rockville, Maryland.

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References

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