Screening for Chlamydia and Gonorrhea

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The first large randomized clinical trial (RCT) to study the effect of screening asymptomatic women for Chlamydia trachomatis infection was conducted in the early 1990s in a managed care organization in the US Pacific Northwest.1 The investigators measured the incidence of symptomatic pelvic inflammatory disease (PID) diagnosed in clinic or hospital settings in 2607 women aged 18 to 34 years who were followed up for 1 year. To the surprise of many skeptics, the trial, despite a relatively small number of verified PID cases, demonstrated a significant reduction in PID among the women screened compared with usual care, with absolute rates of 8 per 10 000 woman-months vs 18 per 10 000 woman-months, respectively.6

These findings, coupled with emerging data that chlamydia screening and resultant treatment might be associated with reduced incidence of adverse reproductive health outcomes (including ectopic pregnancy, as well as PID), prompted the first discussions of incorporating routine screening into women’s primary care. With the advent of more sensitive, noninvasive urine chlamydia testing in the mid-1990s, and later, self-collected vaginal swabs, options to operationalize routine screening substantially increased. In 1996, the US Preventive Services Task Force (USPSTF) first recommended chlamydia screening for women at increased risk,2 consistent with earlier recommendations from 1993 from the US Centers for Disease Control and Prevention (CDC).3

In this issue of JAMA, the USPSTF updates its 2014 screening guidance for chlamydia and gonorrhea in women and men with a new Recommendation Statement4 and an updated Evidence Review.5 According to the Recommendation Statement, “The USPSTF recommends screening for chlamydia in all sexually active women 24 years or younger and in women 25 years or older who are at increased risk for infection. (B recommendation) The USPSTF recommends screening for gonorrhea in all sexually active women 24 years or younger and in women 25 years or older who are at increased risk for infection. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for chlamydia and gonorrhea in men. (I statement)”4

These recommendations are timely, given that the most recent CDC report on sexually transmitted infection (STI) surveillance noted that chlamydia and gonorrhea rates in the US in 2019 were at a 20-year high, with overall rates of 553 cases per 100 000 population and 188 per 100 000, respectively.6 The main contribution of the extensive review by the USPSTF5 is to extend the evidence base for chlamydia and gonorrhea screening, including 1 new RCT of chlamydia screening. That trial, the Australian Chlamydia Control Effectiveness Pilot trial (ACCEPt),7 compared chlamydia screening with usual care in 180 355 men and women aged 16 to 29 years in 130 rural Australian primary care clinics. Screening was associated with reduced risk of hospital-diagnosed PID (unadjusted risk ratio [RR], 0.6 [95% CI, 0.4 to 1.0]; absolute risk, 0.24% for screening vs 0.38% for usual care), but was not significantly associated with reduced risk of clinic-diagnosed PID (RR, 1.1 [95% CI, 0.7 to 1.8]); 0.45% vs 0.39%) or clinic-diagnosed epididymitis (RR, 0.9 [95% CI, 0.6 to 1.4]; 0.26% vs 0.27%). The findings may have been predictable, in that the bar might have been set too high to detect the value of routine screening, especially among men, who rarely (<1%) develop epididymitis from urethral chlamydial infection, and for whom the main benefit of screening is likely to accrue to prevent onward transmission to vulnerable sex partners.

Widespread implementation of routine chlamydia screening over the last 2 decades has coincided with improvement...
in the epidemiologic trajectory of reproductive health among
women as measured by reduced rates of hospitalizations and
outpatient visits for PID and ectopic pregnancy, although a
direct causal relationship has been questioned. Equally im-
portant, the inclusion of chlamydia screening in preventive
health care for young women helped normalize a conversa-
tion around sexual health that had previously been absent.
However, the evidence base comprehensively addressed by the
USPSTF and the resultant recommendations leave several
questions unanswered.

First, the validity of evidence based on any randomized
clinical trial rests on the specificity of its primary end point.
By any measure, the clinical diagnosis of PID is fraught with
imprecision. Moreover, the majority of reproductive tract dam-
age caused by C trachomatis in women is due to asymptom-
atic infection. Accordingly, it may be time to consider the
inclusion of a more diverse menu of biologically based assess-
ments of upper reproductive tract infection that incorporate
comprehensive measures of infection and pathogenesis into
considerations of screening efficacy. In 2019, the CDC con-
vened a scientific meeting to discuss STI-related PID and its
sequelae. A recently published overview of the meeting noted
several challenges to making an accurate diagnosis of PID, in-
cluding an increasing recognition of the role of facultative and
anaerobic bacteria, Mycoplasma genitalium, and enteric patho-
gens, and the broadly oversensitive nature of clinical diagnos-
tic criteria designed to ensure that PID is not underrecog-
nized and undertreated. The availability of noninvasive
biomarkers, including blood microarray analyses or multi-
plex PCR of lower genital tract sampling, may advance this ef-
fort, but will require considerable study.

Second, the authors of the updated evidence-based review noted
limitations in the quality and applicability of some of the
included studies. The absence of new information about
gonorrhea screening and the more recent high-quality RCT fo-
cused on chlamydia screening highlight the need for invest-
ment in STI clinical trials designed to measure screening effi-
cacy and effectiveness using clinically relevant and well-
deﬁned outcomes for key populations at risk of infection.
Current understanding of the role of Neisseria gonorrhoeae in
upper reproductive tract pathology is limited relative to C tra-
chomatis, particularly given global declines in gonorrhea-
associated PID and the lack of a nonhuman primate model.

Third, even though the USPSTF recommendations apply to “all asymptom-
atic, sexually active adolescents and adults, including pregnant persons,” the specific recom-
mandations are stratified into 2 groups: “men” and “women” based on the evidence that reported screening outcomes by biological sex (ie, male/female) rather than gender identity. Concepts of gender identity have changed appreciably in the decades since these guidelines were introduced, and current guidelines should be relevant for individuals who define themselves as female but may be biologically male, and for those who define themselves as male but may be biologically female. These scenarios are not uncommon. While the updated 2021 CDC STI Treatment Guidelines include mention of screening in trans-
gender and gender-diverse persons, the USPSTF guidelines indicate that the recommendations are stratified by “men” and “women,” although the net benefit estimates are driven by biological sex (ie, male/female) rather than gender identity.

However, the Recommendation Statement does acknowledge the issues related to the guidelines and gender identity and suggests that “[p]ersons should consider their sex at birth and current anatomy (especially presence of a cervix/vagina) and consult with their own clinician, if necessary, to determine which recommendation best applies to them.” Like all pathogens, STIs infect vulnerable tissue, including urethral, endocervical, rectal, and pharyngeal mucosa, in people across the spectrum of gender identity. A more broadly relevant approach would be to develop evidence-based guidelines for screening people who identify as nonbinary, but to be inclusive when developing patho-
gen-specific guidelines in general or, at a minimum, to specifi-
cally refer to cis-gender women or men. The USPSTF identified the need for studies to “better understand the benefits and harms of screening specific populations at risk such as men who have sex with men, members of the LGBT+ community, and persons with nonbinary gender identity.”

Fourth, men who have sex with men (MSM) are experi-
cing historic high rates of gonorrhea (5166 cases per 100 000) and most infections occur at the pharynx or rectum (extragenital sites). In 2019 CDC data, the rate of gonorrhea infection was substantially higher among MSM compared with men who reported having sex only with women, with absolute rates in the latter group of 123 cases per 100 000. The updated evidence review summarizes research that includes MSM populations. However, the term MSM is behaviorally determined and describes specific sexual exposures that may confer risk at a given time; it does not necessarily accord with sexual identity as a gay man or sexual orientation as homosexual. Thus, current guidelines that address men (as the USPSTF does) should consider STI risk conferred while having sex as a man, whether with men, women, or both. Comprehensive screening guidelines for common STIs like chlamydia and gonorrhea could incorporate the limited evidence base for MSM, whether it is regular practice or not. The same approach could be applied to women who have sex with women, who may be at risk for acquiring chlamydia, particularly if they are also have sex with men.

The USPSTF guidelines are powerful agents of change and influence a wide spectrum of health-based metrics, from quality assurance measures to criteria for financial reimbursement. The latest version of the guidelines for screening for chlamydia and gonorrhea appropriately focuses on the available evidence base, prioritizing high-level clinically based data. However there has also been recent progress in understanding of the pathogenesis and microbial etiology of upper reproductive tract infection in women; the role C trachomatis and N gonorrhoeae have in facilitating HIV acquisition and transmission at the urethra, rectum, and cervix; and the sexual networks that support the current resurgence of STIs in the US, especially in the absence of adequate management of exposed sex partners. Considering these critical advances in the evolution of clinic-based screening guidelines is a work in progress; the dialogue among basic scientists, clinical trial investigators, and public health professionals to inform the next version of updated USPSTF chla-
mydia and gonorrhea screening guidelines should start now.
ARTICLE INFORMATION

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Correction: This article was corrected on September 16, 2021, to fix the year of the initial USPSTF recommendation; wording in 3 other paragraphs; and the correct citation for reference 2.

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REFERENCES


