SUPPLEMENT ARTICLE

Screening and Treatment to Prevent Sequelae in Women with *Chlamydia trachomatis* Genital Infection: How Much Do We Know?

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Background. An important question for chlamydia control programs is the extent to which finding and treating prevalent, asymptomatic *Chlamydia trachomatis* genital infection reduces reproductive sequelae in infected women.

Methods. We reviewed the literature to critically evaluate evidence on the effect of chlamydia screening on development of sequelae in infected women.

Results. Two randomized controlled trials of 1-time screening for chlamydial infection—in a Seattle-area health maintenance organization and a Danish school district—revealed that screening was associated with an ~50% reduction in the incidence of pelvic inflammatory disease over the following year. However, both of these trials had methodological issues that may have affected the magnitude of observed screening benefits and might limit generalizability to other populations. A large, nonrandomized cohort of chlamydia screening among US Army recruits, although limited by lack of outpatient data, did not find a benefit of similar magnitude to the randomized trials. Methodological limitations restrict valid conclusions about individual benefits of screening using data from historical cohorts and ecological studies. We identified no trials directly evaluating the effect of chlamydia screening on subclinical tubal inflammation or damage, ectopic pregnancy, or tubal factor infertility and no studies addressing the effects of >1 round of screening, the optimal frequency of screening, or the benefits of screening for repeat infections.

Conclusions. Additional studies of the effectiveness of chlamydia screening would be valuable; feasible study designs may depend on the degree to which screening programs are already established. In addition, better natural history data on the timing of tubal inflammation and damage after *C. trachomatis* infection and development of more accurate, noninvasive tools to assess chlamydial sequelae are essential to informing chlamydia control efforts.

Routine screening for asymptomatic *Chlamydia trachomatis* genital infection among young, sexually active women is a fundamental component of chlamydia control in many countries [1, 2]. Thus, a critical question for chlamydia control programs is the extent to which finding and treating prevalent, asymptomatic chlamydial infections reduces the incidence of reproductive tract sequelae in infected women. Many uncertainties remain about the natural history of untreated *C. trachomatis* infection in leading to sequelae, as Haggerty et al discuss in this supplement [3]. One of the most important factors affecting the potential effectiveness of chlamydia control programs is the timing of tubal inflammation and damage relative to the acquisition of infection. This timing profoundly impacts the likelihood that infections can be identified and treated before development of short-term sequelae, such as symptomatic pelvic inflammatory disease (PID), and before development of tubal damage that may ultimately lead to long-term sequelae, such as tubal factor infertility and ectopic pregnancy. There is little doubt that *C. trachomatis* infection can lead to sequelae [4] and that chlamydial infection can be effectively treated with available

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antibiotics [5]. What is less clear, however, is the degree to which treatment given at various times during the natural course of infection can interrupt progression to sequelae.

The duration of genital *C. trachomatis* infection in the absence of treatment has not been completely elucidated [6], but available long-term studies suggest that a typical untreated chlamydial infection can last a year or longer [7, 8]. Thus, asymptomatic *C. trachomatis* infections may have been present for many months when detected by screening. By assuming that women acquire new chlamydial infections at a steady rate between screenings and that women are screened consistently at 1-year intervals, the mean duration of each chlamydia infection detected would be 6 months. With longer screening intervals, as frequently occurs in the United States [9], duration of infection could be greater. If acute PID and/or tubal damage primarily occur very soon after acquisition of *C. trachomatis* infection, screening will only affect that small proportion of the infected population who have recently acquired infection. Screening at less frequent intervals would result in even fewer women receiving benefit. If, however, tissue-damaging pathologic processes are mainly initiated later in the course of infection or continue to be elicited by ongoing infection over an extended period of time, screening would benefit a greater proportion of infected women.

In preparation for the April 2008 Chlamydia Immunology and Control Expert Advisory Meeting, we reviewed and critically evaluated evidence for the effectiveness of chlamydia screening in reducing the incidence of sequelae in screened women. We assessed this evidence in the context of achieving better understanding of chlamydial natural history and pathogenesis; thus, we focused primarily on the role of screening in interrupting progression to upper tract inflammation and sequelae in already infected women. We did not explore the effect of screening or other control efforts in reducing transmission of *C. trachomatis* in a population, which could prevent sequelae by preventing new incident chlamydial infections in women in the population. This evidence has recently been reviewed elsewhere [10]. Our goals were to assess what is known about screening and treatment to prevent sequelae in already infected women, to delineate remaining gaps in knowledge that have implications for chlamydia control programs, and to outline the most important research needs to fill those gaps.

METHODS

We conducted a search of the English-language literature from 1960 through March 2008 with use of the Medline computerized database of the US National Library of Medicine. The Medical Subject Headings and free text terms "chlamydia," "*Chlamydia trachomatis,*" and "chlamydia infections" (exploded) were combined with the terms "pelvic inflammatory disease," "salpingitis," "endometritis," "infertility," and "ectopic pregnancy" (exploded) and then limited to humans and persons ⩾13 years of age. The search excluded articles focused primarily on "*Chlamydophila pneumoniae.*" We also searched reference lists of articles to identify potential additional references.

We included original, prospective studies of chlamydia screening interventions in women that had any of the following primary outcomes: PID, infertility, or ectopic pregnancy. We also included registry-based retrospective cohort studies and ecological studies if they discussed one of the primary outcomes in relation to chlamydia testing. We did not include cross-sectional and case-control studies, nor did we include studies with a primary outcome of screening coverage, chlamydia prevalence or incidence, or adverse pregnancy outcomes other than ectopic pregnancy. We also excluded articles that assessed screening and outcomes after therapeutic abortion or other surgical instrumentation.

RESULTS

Our initial literature search yielded 875 unique citations. After review by an author (S.G.) for the aforementioned inclusion criteria, a total of 11 articles were selected for critical evaluation: 2 randomized controlled trials [11, 12] and 1 nonrandomized cohort study [13] that evaluated chlamydia screening interventions and clinical PID outcomes; 4 registry-based retrospective cohort studies evaluating chlamydia testing and long-term outcomes, including ectopic pregnancy [14–17] and infertility [17]; and 4 ecological studies of rates of chlamydia infection and either PID [18–20] or ectopic pregnancy outcomes (Table 1) [18, 21]. We identified no randomized or nonrandomized trials of the effect of chlamydia screening on subclinical tubal inflammation, tubal scarring, or the long-term outcomes of ectopic pregnancy and tubal factor infertility. We present the results according to study methods.

Randomized controlled trials. A randomized controlled trial by Scholes et al [12] is the study cited most widely, including by the US Preventive Services Task Force [22], as providing evidence for the individual benefits of screening. In this study involving 2607 young women at high risk in a Seattle-area health maintenance organization (HMO) population, a 1-time proactive approach of inviting women for chlamydia screening (64% were tested) significantly reduced the risk of subsequent PID by ~50% over the next year, compared with a control group not invited for testing (relative risk, 0.44; 95% confidence interval, 0.20–0.88). At the time of this review, these data remain the best available on the benefits of screening to prevent PID in infected women. However, some aspects of this trial raise questions as to whether the magnitude of observed benefits is generalizable and provides realistic expectations of benefit in real-world settings.

First, only 7% of the 36,547 women who were randomized

Table 1. Studies of the Individual Benefits of *Chlamydia trachomatis* Screening on Pelvic Inflammatory Disease (PID), Ectopic Pregnancy (EP), and Infertility

Reference (year)	Study design and setting	Population	Study methods	Outcome measures	Reported findings	Strengths	Limitations	Overall relevance and important messages
RCTs								
Scholes et al [12] (1996)	RCT of *C. trachomatis* screening to reduce PID; HMO in Seattle area (1990–1992)	Enrolled single, sexually active women aged 18–34 years who returned survey and had risk score ⩾3 (1 point for age <25 years, ⩾2 sex partners in 12 months, nulligravidity, or douching; 2 points for black race); 36,547 women randomized; 57% returned survey; 2607 (7% of randomized) had score ⩾3; 81% were aged 18–24 years; 22% of women were black	Randomly assigned to screening (1009 women invited to 1-time *C. trachomatis* testing by ELISA and/or culture) or control (1598 in usual care)	Outcome at 12 months: PID incidence, ascertained by self-report, inpatient diagnosis codes, pharmacy records, outpatient codes for PID and cervicitis, laboratory records; medical record review to confirm diagnosis; intention to screen analysis	Screening group: 64% tested, 7% (44) had *C. trachomatis* infection and were treated; controls: percentage tested not reported; outcomes: 42 PID cases; screening group: 9 cases (7 of 9 had been tested); controls: 33 cases; incidence of PID: 8 cases per 10,000 PM in screening group, 18 cases per 10,000 PM in the control group (RR, 0.44; 95% CI, 0.20–0.88; no change in RR after adjustment for baseline characteristics); 7 of 42 women with PID had positive *C. trachomatis*/*Neisseria gonorrhoeae* test results at time of diagnosis	Randomized controlled design; large sample size; intention to screen analysis	Randomized before enrollment and screening group preferentially called to submit survey and set up testing; only 7% of those randomized enrolled, and 1:1.6 instead of planned 1:2 screening to control ratio suggests randomization may have been compromised; Seattle HMO, women at high risk; thus, findings may not generalize to other populations	Study most frequently cited as evidence for the benefits of *C. trachomatis* screening, suggesting that a 1-time invitation for screening can prevent about half of subsequent PID cases; magnitude of PID prevented appears higher than what might be expected based on natural history studies; this and identified limitations, raise questions as to whether findings are generalizable and provide realistic expectations of benefit in real-world settings
Østergaard et al [11] (2000)	Cluster RCT of 17 high schools in Denmark (1997–1998), comparing invitation to home *C. trachomatis* testing with referral to clinic testing on *C. trachomatis* prevalence and PID	Mean age, 18 years; >95% white women	Students at schools randomly assigned to screening were offered 1-time home sampling (vaginal flush for women) for *C. trachomatis* NAAT (8 high schools, 2603 women) and students at control schools were given information and told could visit clinic for free *C. trachomatis* testing (9 high schools, 2884 women); included only sexually active students; boys also screened	Outcome at 1 year: PID incidence, ascertained by self-reported treatment or PID hospitalization, confirmed with pharmacy registry records (*C. trachomatis* prevalence results not presented here)	Less than half responded to first survey (48% in screening group and 38% in control group); ~75% were sexually active and enrolled; 2 groups similar; screening group: 867 (93%) of 928 enrolled women tested for *C. trachomatis* (5% positive); control group: 63 (8%) of 833 enrolled women tested for *C. trachomatis* (8% positive); ~45% lost to follow-up at 1 year; outcome: PID incidence at 1 year was 2.1% in screening group and 4.2% in control group (P = .045)	Randomized controlled design; differences in rates of testing in 2 groups allows evaluation of screening	Low initial participation, differential enrollment between groups, almost half lost to follow-up; outcome assessment nonblinded; PID outcome measured only by self-report and pharmacy records; findings from Danish high school students may not generalize to other populations	Substantial number of limitations, making it difficult to draw firm conclusions, but supports idea that 1-time proactive screening can reduce PID over the next year in high school students; magnitude of PID prevented appears higher than what might be expected based on natural history studies; this and identified limitations raise questions as to whether findings are generalizable and provide realistic expectations of benefit in real-world settings

Cohort studies with untested control group								
Clark et al [13] (2002)	Nonrandomized cohort of 28,074 female US Army recruits in 1996–1997, assessing effect of *C. trachomatis* screening on PID-related hospitalizations through end of 1998	Overall, 80% aged <25 years, 36% of women were black	Nonrandomly assigned based on day of week to screening group (offered 1-time *C. trachomatis* testing by urine NAAT on Sundays at basic training intake, 80% volunteered (7053 screened and followed; another 6151 screened women excluded because not eligible for ongoing military health care) or control (not offered *C. trachomatis* testing if arrived at basic training on other days of week [*n* = 21,021])	Hospitalization via US Army administrative data, ICD-9 codes, all-cause and PID, EP, and infertility-related, comparing screened vs unscreened women; adjusted for age, race, education, and aptitude score	Screened group younger, higher aptitude score but less educated; *C. trachomatis* prevalence 9.1% in screened group; mean follow-up period of 1.5 years; outcome of PID hospitalization in screening group was 4.6 hospitalizations per 1000 PY and in control group was 5.1 hospitalizations per 1000 PY (RR, 0.94; 95% CI, 0.69–1.29); hospitalizations for PID, EP, or infertility was 7.2 hospitalizations per 1000 PY in screening group and 6.8 hospitalizations per 1000 PY in control group (RR, 1.10; 95% CI, 0.85–1.43); hospitalization for any reason was 199 hospitalizations per 1000 PY in screening group and 224 hospitalizations per 1000 PY in control group (RR, 0.94; 95% CI, 0.90–0.99); more pregnancy-related hospital stays in unscreened group	Large sample size, prospective collection of data	Nonrandomized, potentially important differences between groups; no intention to screen analysis; no outpatient data or validation of PID diagnosis	Although nonrandomized, this was a well-done study of non-health care–seeking women that raises the possibility that the benefits of screening may be difficult to measure in practice and dependent on population; although limited by lack of outpatient data, study suggests the effect of screening on PID may be weaker than that observed in the trial by Scholes et al [12] and Østergaard et al [11], despite high screening coverage
Low et al [17] (2005)	Historical cohort of women aged 15–24 years, Uppsala County, Sweden (1985–1989), followed up through 1999 for outcomes related to *C. trachomatis*	Total of 43,715 women, 52,731 *C. trachomatis* tests; 20,853 women never tested for *C. trachomatis,* 19,897 always *C. trachomatis* negative, 2965 ever *C. trachomatis* positive; no systematic screening, but 71% ever tested: 48% tested once, 22% tested twice, 30% tested ⩾3 times	Registry data linking *C. trachomatis* test history/results (1 laboratory; mostly culture) with hospital ICD-9 codes 1985–1999 using unique ID; also, outpatient diagnosis codes for 1993–1999	Cumulative incidence of PID, EP, infertility; HRs comparing outcomes by *C. trachomatis* testing status; adjusted for age, education, housing type, income, number of births, and census year	Among tested women, period prevalence of *C. trachomatis* was 12%; cumulative incidence by 35 years of age for PID, EP, and infertility was 3.9%, 2.3%, 4.1%, respectively, among all participants; 5.6%, 2.7%, and 6.7%, respectively, among *C. trachomatis*–positive women; 4.0%, 2.0%, and 4.7% respectively, among *C. trachomatis*–negative women; and 2.9%, 1.9%, and 3.1%, respectively, among women not tested; comparing *C. trachomatis*–positive with *C. trachomatis*–negative women, PID (aHR, 1.3; 95% CI, 1.0–1.6), EP (aHR, 1.3; 95% CI, 0.9–1.7), infertility (aHR, 1.3; 95% CI, 1.1–1.6); never tested women less likely than *C. trachomatis*–negative women to have PID or infertility diagnosis	Population-based cohort design with good record linkage, long follow-up, large sample size; includes women who were never tested for *C. trachomatis*	Most women had only 1–2 tests over 10–14 years; thus, undetected infections at other times were likely, especially among those with ⩾1 detected *C. trachomatis* infection; less sensitive tests used; could not control for sexual behavior, contraceptive use, etc; infertility outcome only available for women seeking treatment; unable to differentiate female and male factor infertility	Only registry study with an untested comparison group; shows that, outside a trial, women who have not been tested are likely to be different, and probably at lower risk of *C. trachomatis* than are those who have been tested; undetected, untreated infections at other times would tend to reduce observed impact of testing on later long-term sequelae; benefits of screening difficult to assess using these types of observational data; study suggests that women who have received a diagnosis of *C. trachomatis* infection are more likely to seek care for PID, EP, and infertility

Cohort studies without untested control group								
Andersen et al [14] (2005)	Historical cohort of women aged <43 years testing for *C. trachomatis* in 1 county in Denmark (1984–1993); No systematic screening, test uptake not reported. tests done mainly for symptoms, before transcervical procedures, for partner notification, and opportunistic screening in some settings (eg, STD clinics)	13,693 women, 18,452 tests done before first pregnancy	Registry data using unique ID to link *C. trachomatis* test results (1 laboratory, all pre-NAAT) with pregnancy outcome by hospital diagnosis codes	EP incidence rate, HR comparing *C. trachomatis*–positive with *C. trachomatis*–negative women; excluded women with no pregnancy through 1 January 2003 (final, 6072 women); birth rate, HR for *C. trachomatis*–positive vs *C. trachomatis*–negative women; included women who did not become pregnant through age 43 years or 1 January 2003; adjusted for maternal age	*C. trachomatis* period prevalence 14%; nearly all patients received appropriate treatment; EP incidence rate lower in women with ⩾1 positive *C. trachomatis* test result: 0.35 cases/100 PY among *C. trachomatis*–positive women, 0.86 cases/100 PY among *C. trachomatis*–negative women (aHR, 0.55; 95% CI, 0.3–0.96); time to birth similar in both groups; birth rate among *C. trachomatis*–positive women was 5.84 births/100 PY and among *C. trachomatis*–negative women was 5.96 births/100 PY (aHR, 0.92; 95% CI, 0.84–1.00)	Population-based cohort design with good record linkage, >10 years of follow-up, large sample size	Rates among women never tested for *C. trachomatis* not evaluated; no systematic screening, less sensitive tests used; undetected infections at other times were likely in both groups, especially for those with ⩾1 detected *C. trachomatis* infection; could not control for sociodemographic factors, sexual behavior, contraceptive use, desire to conceive, etc	Study does not assess benefits of screening; undetected, untreated infections at other times (in either group) might affect interpretation; birth rate may be slightly lower in *C. trachomatis*–positive group, but do not know whether factors, such as desire to conceive, differed in the 2 groups; cannot necessarily extrapolate birth rates to infertility
Bakken et al [15] (2007)	Historical cohort of women born during 1970–1984 tested for *C. trachomatis* in 1 county in Norway (1990–2003); no systematic screening; reported testing rates high; ~80% of women tested, >50% had >1 test	20,762 women, 72,405 tests done before first pregnancy	Registry data linking *C. trachomatis* test results (1 laboratory, 51% NAAT) with inpatient and outpatient EP codes and births	EP incidence rate (HR comparing *C. trachomatis*–positive with *C. trachomatis*–negative women; evaluated whole group and limited to women with EP or birth in study period [n = 10,794]); birth rate (HR for *C. trachomatis*–positive vs *C. trachomatis*–negative women); censored at first birth or 31 December 2004; adjusted for parity and age at first *C. trachomatis* test	*C. trachomatis* period prevalence 18%; higher EP rates among *C. trachomatis*–positive women vs *C. trachomatis*–negative women in overall population and limited to those with pregnancies; dose response with number of positive *C. trachomatis* test results; among those with pregnancies: EP incidence among women with no positive test results was 0.29 cases/100 PY (reference), among women with 1 positive test result was 0.58 cases/100 PY (aHR, 1.8; 95% CI, 1.1–3.0), and among women with ⩾2 positive test results was 1.39 cases/100 PY (aHR, 3.4; 95% CI, 1.5–8.0); birth rate slightly higher among *C. trachomatis*–positive women (10.2 births/100 PY) than among *C. trachomatis*–negative women (9.6 births/100 PY; aHR, 1.07; 95% CI, 1.01–1.12)	Population-based cohort design with good record linkage, long follow-up, large sample size; more complete testing, more NAAT testing than other Scandinavian registry studies; inpatient and outpatient data a plus	Rates among women never tested for *C. trachomatis* not evaluated; no systematic screening, change in test technology over time; undetected infections at other times were likely in both groups, especially for those with ⩾1 detected *C. trachomatis* infection; could not control for sociodemographic factors, sexual behavior, contraceptive use, desire to conceive, etc	Study does not assess benefits of screening; compared with Danish study, higher risk of EP among those testing positive and treated for *C. trachomatis* infection; dose response suggests recurrent infection increases cumulative risk of EP; undetected, untreated infections at other times (in either group) might affect interpretation; as above, difficult to extrapolate birth rates to infertility

Hillis et al [16] (1997)	Historical cohort study of number of *C. trachomatis* infections and ensuing hospitalizations for EP and PID (PID results not presented here); Wisconsin (1985–1992); mandated annual risk-based screening in family planning clinics, universal screening in 2 STD clinics	11,000 women aged 10–44 years with ⩾1 *C. trachomatis* infection; women with ⩾3 infections: 97% aged <25 years; ~50% black, ~50% *N. gonorrhoeae* coinfection at first infection	*C. trachomatis* infections reported by public providers in Wisconsin *C. trachomatis* case registry 1985–1992 (all non-NAAT), linked by name, date of birth, and county with statewide hospital discharge ICD-9 database 1989–1994 (no information before 1989)	Compared EP hospitalizations among those with ⩾3 *C. trachomatis* infections (n = 644) with those with 2 *C. trachomatis* infections (n = 2044); random sample of women with 1 *C. trachomatis* infection (n = 8312); adjusted for *N. gonorrhoeae* infection, county, source of care	*C. trachomatis* period prevalence 11% (family planning), 13% (STD clinics). 98% of repeat *C. trachomatis* diagnoses ⩾30 days apart; percentage with EP hospitalization (1989–1994) for those with 1, 2, and ⩾3 infections was 0.13%, 0.49%, 1.4%, respectively, among all women, and 1.3%, 2.5%, and 4.8%, respectively, among women with pregnancy; compared with those with 1 *C. trachomatis* infection, elevated odds of EP among women with 2 infections (OR, 2.1; 95% CI, 1.3–3.4), ⩾3 infections (OR, 4.5; 95% CI, 1.8–5.3), *N. gonorrhoeae*/*C. trachomatis* coinfection (OR, 5.3; 95% CI, 1.9–15.0)	Population-based cohort design, large sample size	No comparison group (*C. trachomatis* negative or never tested); no person-time analysis; hospital discharge data likely to be fairly accurate for EP, but no data before 1989 and no outpatient data in later years; limited information on potential confounders	Study does not assess benefits of screening; the risk of EP among those without a past positive *C. trachomatis* test result or among those never tested unknown; dose response suggests recurrent infection increases cumulative risk of EP
Ecological studies								
Egger et al [21] (1998)	Ecological study of trends in rates of *C. trachomatis* infection and EP, Uppsala County, Sweden (1985–1995); 103,875 cervical samples and 51,630 pregnancies analyzed; no systematic screening; opportunistic testing reported to be intensive	Women aged 20–39 years (same population as [17])	Collected *C. trachomatis* test reports from single laboratory, hospital discharge ICD-9 codes	Rates of *C. trachomatis* diagnosis per 100 tests, rates of EP per 1000 pregnancies, by age group; Poisson regression used to examine association between risk of EP and current rates of *C. trachomatis* and rates of *C. trachomatis* from up to 5 years earlier	Overall *C. trachomatis* test positivity 5.4%; 1.8% of pregnancies were EP; both *C. trachomatis* and EP rates decreased markedly over time; among women aged 20–24 years, there was a strong correlation between EP rate and *C. trachomatis* rate in same year (r = 0.93; P < .001); among older women, the correlations were less pronounced, but more strongly associated with *C. trachomatis* rates 1 or 2 years earlier	Population-based ascertainment of EP rates during a period of intensive screening; large sample size, 10 years of data	Ecological design; thus, no conclusions can be drawn about causality; individual benefits of screening cannot be assessed; may be unmeasured confounders, such as intrauterine device use	Among young women, strong correlation between *C. trachomatis* and EP and concomitant decrease in rates supports *C. trachomatis* as cause of EP; decreases in *C. trachomatis* and EP occurred during same period as *C. trachomatis* control efforts, but also during same period as other potentially confounding factors (eg, increases in safer sex with HIV epidemic, better diagnosis and treatment of symptomatic *C. trachomatis* infection, decreases in *N. gonorrhoeae* infection
Hillis et al [18] (1995)	Ecological study of trends in *C. trachomatis* case and laboratory reports (1985–1991) and hospitalized PID and EP (1982–1991), Wisconsin; state *C. trachomatis* prevention program initiated in 1985, including *C. trachomatis* screening in family planning and STD clinics	…	Combined data from Wisconsin STD Surveillance System and public health laboratory databases, along with Wisconsin Hospital Discharge Database (before 1989, participation voluntary)	Reported *C. trachomatis* rates per 100,000 population, proportion of *C. trachomatis* tests positive for *C. trachomatis*, trends in PID and EP hospitalization rates	Among women aged 15–24 years, reported *C. trachomatis* infection rates increased sharply, then leveled off, but proportion of tests positive for *C. trachomatis* steadily decreased; among all women (aged 15–44 years), rates of PID hospitalization decreased by 31% during 1982–1985 and 33% during 1986–1991; EP rates increased by 14% during 1982–1985 and decreased by 20% during 1986–1990; no statistics reported for trends	Broad assessment of statewide trends in relation to implementation of an intensive *C. trachomatis* prevention program	Ecological design; thus, no conclusions can be drawn about causality; individual benefits of screening cannot be assessed; no outpatient data, especially important for PID; no statistics reported for trends	Decreases in proportion of *C. trachomatis* tests positive and in EP and PID rates occurred during same period as *C. trachomatis* control efforts, although PID rates appeared to be decreasing before *C. trachomatis* efforts started; other potentially confounding factors also occurred in same period (eg, increases in safer sex with HIV epidemic, better diagnosis, and treatment of symptomatic *C. trachomatis* infection); decreases in *N. gonorrhoeae* infections; change to outpatient management of PID

Kamwendo et al [19] (1996)	Ecological study of trends in PID hospitalizations, *N. gonorrhoeae*– and *C. trachomatis*–associated PID, and *N. gonorrhoeae* and *C. trachomatis* case report rates, Örebro, Sweden (1970–1994); public health officials began encouraging diagnosis and treatment of *C. trachomatis* around 1984, and *C. trachomatis* became a notifiable disease in 1988	…	Evaluated hospital records of patients with acute PID in Örebro for *N. gonorrhoeae*/*C. trachomatis* laboratory records: *N. gonorrhoeae* testing 1970–1994 (n = 2499), *C. trachomatis* testing 1981–1994 (n = 1030)	Proportion of PID with *C. trachomatis*/*N. gonorrhoeae*; PID incidence, using population statistics of hospital catchment area; *N. gonorrhoeae* and *C. trachomatis* incidence based on laboratory reporting	Proportion of PID with *C. trachomatis* decreased from 28% in 1985 to 8% in 1994; *N. gonorrhoeae* in 42% of PID in 1970, with decrease to 0% starting in 1980; PID incidence decreased consistently from a peak in 1975–1979 through 1990–1994 for the youngest age groups (15–19 and 20–24 years); PID relatively stable in oldest age groups (>30 years); *C. trachomatis* case report rates decreased 40%–60% during 1988–1994	Comprehensive assessment of acute PID hospitalizations and laboratory testing in a defined catchment area over 25 years	Ecological design; thus, no conclusions can be drawn about causality; individual benefits of screening cannot be assessed; no outpatient data, especially important for PID; no statistics reported for trends	Decreases in *C. trachomatis*, PID, and *C. trachomatis*–related PID occurred during same period as *C. trachomatis* control efforts, although PID rates appeared to be decreasing before *C. trachomatis* efforts started; other potentially confounding factors also occurred in same period (eg, increases in safer sex with HIV epidemic, better diagnosis, and treatment of symptomatic *C. trachomatis* infection); decreases in *N. gonorrhoeae* infections; change to outpatient management of PID
Chen et al [20] (2006)	Ecological study of trends in clinical encounters for PID in general practice and *C. trachomatis* case report rates, Australia (1998–2003); extent of *C. trachomatis* control efforts in a similar period not reported	…	Compared data from nationally representative survey of Australian general practices on patient encounters (502,100 encounters 1998–2003) with national *C. trachomatis* case report data	Rate of PID diagnosis per 10,000 female patient encounters, reported *C. trachomatis* rates per 100,000 population	Among women aged 15–34 years, PID encounter rates decreased from high of 39.9 cases/10,000 encounters in 1999–2000 to a low of 19.4 cases/10,000 encounters in 2001–2002; mean decrease of 3.6 cases/10,000 encounters per year (P = .02); no change in rate of PID encounters in women aged ⩾35 years; *C. trachomatis* case reports increased from a rate of ~50 cases/100,000 population in 1994 to ~180 cases/100,000 population in 2003; precise figures not reported	Use of outpatient PID data from nationally representative assessment	Ecological design; thus, no conclusions can be drawn about causality; individual benefits of screening cannot be assessed; only *C. trachomatis* case reports used, no information on test positivity; extent of *C. trachomatis* control efforts not reported	More recent study including outpatient data shows that PID rates appear to be decreasing in young women; unclear what has occurred in similar time with respect to *C. trachomatis* control activities, *C. trachomatis* prevalence, and incidence; *C. trachomatis* case reports may reflect increase in testing

NOTE. Data from the Prevention of Pelvic Infection (POPI) trial, an additional randomized controlled trial (RCT) of *C. trachomatis* screening to prevent PID, were published too late to be included in this review but are now available [32]. aHR, adjusted hazard ratio; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; HMO, health maintenance organization; HR, hazard ratio; ICD-9, *International Classification of Diseases, Ninth Revision;* NAAT, nucleic acid amplification test; OR, odds ratio; PM, person-months; PY, person-years; RR, relative risk; STD, sexually transmitted disease.

were ultimately enrolled. Women aged 18–34 years who were registered with the HMO were randomized to screening and control groups and then sent a survey to determine study eligibility based on a risk score (Table 1). The authors reported more aggressive contacting of survey nonresponders from the intervention group to expedite testing appointments after eligibility determination. This may have resulted in the observed 1:1.6 ratio instead of the expected 1:2 ratio between the intervention and control groups, introducing the possibility of selection bias. It is not clear how such a selection bias might affect estimation of screening benefits, but randomization may have been compromised.

Second, by applying the rate of PID in the control group to person-months in the intervention group, we would expect 21 cases of PID, but only 9 cases were observed. Thus, 12 cases of PID were apparently prevented by treating 44 women, suggesting that at least 27% of the infections identified by screening would have progressed to diagnosed PID without any intervention. This figure appears substantially higher than findings from other studies of asymptomatic populations undergoing screening who were followed up untreated for 12 months [3, 8]. In addition, *C. trachomatis* has been implicated in ~30% of acute PID cases [23]; thus, even if all chlamydia-associated cases of PID were prevented by screening, a 50% decrease is larger than what might be expected on the basis of previous studies.

Østergaard et al [11] conducted a cluster randomized trial of 17 high schools in a Danish county, in which students in intervention schools were offered 1-time screening of home-collected specimens for *C. trachomatis* and students in control schools were given referral information about clinic-based testing. Less than half of the students returned eligibility surveys. Because 93% of participating students in the intervention group had *C. trachomatis* testing performed, compared with only 8% of control students, the effect of screening could be evaluated. Female students were followed up in 1 year, and incident PID was assessed by self-report, with confirmation by pharmacy records. Outcome assessment was unblinded, and almost 50% of students were lost to follow-up; thus, this study had a substantial number of limitations. Nonetheless, it had findings similar to those from the trial by Scholes et al [12]. The 1-time screening approach in the Danish study was associated with a halving of PID occurrence over 1 year (4.2% vs 2.1%; $P = .045$). Testing of 867 female students and detection of 43 infections prevented 9 reported cases of PID among the 443 interviewed students at follow-up. Unlike Scholes et al [12], Østergaard et al [11] also screened boys attending the same schools, and this may have had an impact on community transmission, preventing some new infections and reinfections that could have also led to PID.

Cohort studies. An impact of the magnitude found in these 2 randomized controlled trials should be easy to detect. However, a large cohort study of chlamydia screening in female US Army recruits by Clark et al [13] did not reproduce these findings. In this study, a total of 7053 women participating in a screening program on Sundays at a basic training intake center were tested and treated for *C. trachomatis* infection, and 21,021 women who arrived on different days were not. These women were followed up for hospitalizations over a mean of 1.5 years with use of US Army coded administrative data. There were no significant differences between the screened and unscreened groups in hospitalization rates for chlamydia-related outcomes (PID, infertility, or ectopic pregnancy). This study was not randomized and was limited by lack of outpatient data, which is a large concern because, at the time of the study, most PID cases were treated in the outpatient setting [24]. However, it does raise the issue that the positive effects of screening may be difficult to ascertain and dependent on the population, and suggests the effect may be weaker than that observed by Scholes et al [12], at least in some populations.

The 2 randomized controlled trials and the study by Clark et al [13] used symptomatic, clinically diagnosed PID as the study outcome. No randomized trials have directly evaluated the effect of chlamydia screening on ectopic pregnancy and infertility, conditions that may not be observed for several years, in part because young women's use of contraception to prevent unplanned pregnancy delays their diagnosis. Three historical cohort studies in Scandinavian countries and a study in Wisconsin used clinical and population registers to link *C. trachomatis* testing records with data on long-term complications [14–17]. These studies, the findings of which are summarized in Table 1, yield useful information on the risk of long-term complications in women with at least 1 diagnosed and treated *C. trachomatis* infection but provide little insight on the role of screening in preventing these complications.

Only one of the historical cohort studies, the Swedish study by Low et al [17], had information about a comparison group of women who had never been tested for chlamydia. This group had lower rates of PID and infertility diagnoses than did women who were tested, including women who only had negative chlamydia test results. This highlights the fact that, outside a randomized trial, women who have not been tested are likely to be different and probably at lower risk of chlamydial infection, compared with those who have been tested. Another methodological issue affecting interpretation of these studies relates to undetected infections. The intensity of *C. trachomatis* testing and control has been greater in the 3 Scandinavian countries in which the cohort studies were done than in most other European countries [2]. Nonetheless, data reported in the Norwegian and Swedish studies show that most women had only 1–2 tests performed over a 10–14-year period [15, 17]; therefore, there is a high likelihood of undetected infections at other

times. Because *C. trachomatis* is associated with high rates of repeat infection [25, 26], women with 1 detected chlamydial infection are particularly likely to have had ⩾1 other undetected, untreated infection. This would tend to reduce the observed impact of testing on subsequent long-term sequelae. All in all, it is difficult to make an unbiased assessment of the benefits of screening using these types of observational data.

Ecological studies. Ecological studies have been cited as showing the effectiveness of screening programs, based on coincident decreases in chlamydia and chlamydia-related outcomes observed in regions that were the earliest to initiate chlamydia control efforts (Table 1) [18, 19, 21]. During the 1980s and early 1990s, when chlamydia control activities were being implemented, rates of identified chlamydial infection decreased in conjunction with rates of PID [18, 19] and ectopic pregnancy [18, 21]. However, in some areas, PID rates appeared to be decreasing before the chlamydia control programs started [18, 19], and many factors, such as decreases in the number of gonorrhea infections, increases in safer sex with the human immunodeficiency virus (HIV) epidemic, and better diagnosis and treatment of symptomatic *C. trachomatis* infection, occurred at a similar time. Since the late 1990s in Australia, outpatient clinical encounter rates for PID have continued to decrease among young women, whereas rates of reported chlamydia cases have increased substantially [20]. Similar findings have been observed in British Columbia [27]. Chlamydia control programs may well be contributing to ongoing decreases in chlamydia-associated sequelae, but ecological studies cannot be used to determine causality.

DISCUSSION

Summary of existing data. Only a few studies have evaluated the direct benefits of screening for *C. trachomatis* genital infection. Two randomized controlled trials of 1-time screening for chlamydial infection—in a Seattle-area HMO and a Danish school district—revealed an ~50% reduction in the incidence of PID among screened women in the following year. However, both of these trials had methodological issues that may have affected the magnitude of observed screening benefits in the populations evaluated and that might limit the generalizability of these findings to real-world settings. A large, nonrandomized cohort of chlamydia screening among US Army recruits did not find a substantial reduction in the number of hospitalizations for PID. Data from historical cohorts have methodological limitations that restrict the capacity to make valid conclusions about the benefits of screening. Ecological studies have generally supported the effectiveness of chlamydia control programs in decreasing population-wide sequelae. However, because of coincident temporal changes in behavior, clinical practices, and rates of other infections, no firm conclusions can be drawn about the role of chlamydia screening in reducing complications, and it is impossible to assess benefit on an individual level.

Gaps in knowledge. At present, it is unknown whether findings similar to those observed in the randomized controlled trials reviewed here would be found in other populations possibly at lower risk, and it is also unclear whether the screening efforts implemented in these trials apply to screening programs currently in place. Perhaps most important, major gaps in knowledge include whether screening and treatment of asymptomatic, prevalent infection can prevent long-term sequelae, such as infertility and ectopic pregnancy—the outcomes we most want to prevent. Most of the studies we reviewed evaluated only 1-time screening, and there is little understanding of the overall benefits to an individual of >1 round of screening, the optimal frequency of screening, or the benefits of screening for recurrent infections [10]. In addition, the relative benefits of different types of screening approaches to prevent sequelae have not been evaluated. Finally, development of optimal screening strategies is limited by gaps in knowledge related to the natural history of *C. trachomatis* infection. For example, understanding the benefits of screening for infertility prevention depends in part on whether the pathologic processes leading to symptomatic PID (the main outcome in available trials) are the same as those leading to long-term outcomes. The effectiveness of a screening strategy also depends on the risk and timing of tubal damage relative to acquisition of infection and the mean duration of infection in the targeted population. Inaccurate measurement of the outcomes of chlamydial infection hampers our ability to evaluate screening strategies in both research and nonresearch settings.

Implications. Direct evidence about the effectiveness of finding and treating prevalent, asymptomatic chlamydial infection in preventing adverse sequelae clearly has major implications for chlamydia control efforts. Sequelae of chlamydial infection in a population can be prevented either by curing existing infections before they progress to PID and/or tubal damage or by preventing new *C. trachomatis* infections [28]. How a chlamydia control program should be structured, therefore, depends on the relative effectiveness of screening in reducing sequelae in infected women, compared with interrupting transmission and, thereby, reducing incidence in the population. Chlamydia screening has often been perceived as providing its main benefit through identification of women with chlamydial infection early enough to treat them and prevent progression to sequelae in those individuals [22]. This is the type of benefit that was evaluated in the trial by Scholes et al [12]. Until recently, cost-effectiveness analyses evaluating chlamydia screening as a way to prevent PID were structured around halting disease progression in already infected women rather than using screening as a tool to decrease transmission and prevent new infections in a population [29, 30]. A program

focused primarily on reducing the number of sequelae in infected women makes the most sense if women with asymptomatic, prevalent infections still receive a substantial amount of benefit from treatment (ie, if tubal inflammation and damage would continue to be elicited beyond the time that a typical infection is detected by screening). However, if screening has little impact on preventing sequelae in infected women, because tubal damage, if it is to occur, happens relatively soon after the infection is acquired, control programs must focus primarily on reducing incidence of new chlamydial infection in the population. A program to reduce incidence of new infection in a population through interruption of chlamydia transmission might put greater emphasis, for example, on treatment of sex partners. Thus, more-precise estimates of the benefits of chlamydia screening to an individual infected woman may lead to consideration of new ways to optimally restructure chlamydia control programs to reduce adverse outcomes of chlamydial infection in a population.

Next steps and research needs. Additional studies of the effectiveness of detecting and treating asymptomatic, prevalent chlamydial infection in preventing sequelae would be useful. For countries that do not currently have an active chlamydia screening program in place as the standard of care, randomized controlled trials to better delineate the individual benefits of screening [12] could be done and would be valuable. Before the National Chlamydia Screening Programme was fully established in England, a randomized controlled trial of 1-time chlamydia screening among college-aged women was conducted and recently completed [31]. Published data from the trial were released too late for inclusion in this review but are available now [32]. Ideally, screening studies would collect data in a way that does not focus solely on prevention of PID in screened individuals, but also includes an assessment of community-wide benefits. Screening a group of women could reduce transmission in a population and, thus, prevent new infections, with their own attendant risk of sequelae, in women in the whole population.

Countries considering implementation of chlamydia screening programs have the opportunity to use randomization approaches, such as the stepped wedge design, to systematically evaluate the effects of screening, as is currently being done in the Netherlands [33]. In areas where screening for *C. trachomatis* infection is already recommended, assessments of the benefits of screening may be more challenging. However, additional creative approaches that make comparisons according to changes in screening intensity and coverage would add insight. Community randomization to evaluate the benefits of enhanced chlamydia screening efforts is currently being undertaken in Australia and provides an opportunity to collect valuable information (J. Hocking, personal communication). However, potential methodological problems need to be anticipated, including underlying baseline differences in community chlamydia prevalence, achieving high screening coverage, testing and treatment of sex partners, and accurate, unbiased ascertainment of outcomes.

A better understanding of the natural history of *C. trachomatis* infection is also essential to improving and informing chlamydia control efforts [3]. Ideally, natural history studies would help better clarify the incidence and timing of PID and tubal damage leading to long-term sequelae after untreated chlamydial infection. Such assessments would need to be done in different populations, including asymptomatic women with prevalent infection who have no indication for testing other than screening. Because it would be unethical to withhold treatment from a woman with known diagnosed infection and it is impossible to know when an infection was acquired when detected by screening, evaluations of the natural history of chlamydia will be difficult. However, studies that provide insight on some aspects of natural history may still be possible [34, 35]. Prospective studies that have obtained genital specimens for other reasons (eg, human papillomavirus natural history studies or vaccine trials and HIV prevention trials) should be explored as opportunities for better understanding chlamydia natural history, provided that study participants have given consent to test stored specimens and that chlamydia screening has been offered in accordance with standards of care. Additional natural history data on repeat infections would also be useful [3], because these could help assess the importance of rescreening efforts. Ultimately, we would benefit from more-specific information about when treatment needs to be provided to prevent sequelae and whether treatment of long-standing prevalent infection has a tangible impact on complications. Better data on natural history would be helpful in modeling, shaping, and evaluating screening strategies in the context of a comprehensive chlamydia control program; such data would inform targeting of screening, the optimal frequency of screening, and resource allocation for screening women versus managing sex partners.

A critical component of research addressing chlamydia natural history and the impact of chlamydia screening is our ability to accurately measure the sequelae of *C. trachomatis* infection. We desperately need better, noninvasive tools to measure the complications of chlamydial infection. Diagnosis of acute PID is notoriously subjective, insensitive, and nonspecific [23, 36]. Infertility has multiple causes and may not be recognized for years after a chlamydial infection has caused tubal damage, because the affected woman may not have tried to become pregnant. Ectopic pregnancy is a more clear-cut diagnosis than is PID and infertility and could be more easily used in linking with administrative inpatient and outpatient data to assess outcomes. However, ectopic pregnancy is an uncommon outcome and its timing also depends on efforts or behaviors associated

with becoming pregnant. Thus, ideally, we need tools not only to more accurately assess the sequelae observed as end-products (eg, PID, ectopic pregnancy, and infertility) but also to detect the intervening pathophysiologic processes leading to or predictive of those sequelae. More proximal, noninvasive markers of tubal damage would be extremely valuable for natural history and screening intervention studies and for candidate vaccine trials [37]. In addition, having the ability to predict individuals at increased risk of sequelae or reinfection could lead to targeting strategies that identify those who need, for example, more frequent screening or more intensive follow-up of sex partners. Thus, a better understanding of the immunologic, host, and organism factors underlying pathogenesis and sequelae and a search for relevant clinical markers could ultimately help guide targeted screening and control efforts [38, 39].

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