

Management of *Chlamydia trachomatis* genital tract infection: screening and treatment challenges

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Abstract: *Chlamydia trachomatis* is a prevalent sexually transmitted infection that can lead to serious reproductive morbidity. Management and control of *C. trachomatis* is a challenge, largely due to its asymptomatic nature and our incomplete understanding of its natural history. Although chlamydia screening programs have been implemented worldwide, several countries have observed increasing rates of reported chlamydia cases. We reviewed the literature relating to the long-term complications of *C. trachomatis*, as well as screening strategies, treatment, and prevention strategies for reducing chlamydia in the population. Articles from 1950–2010 were identified through a Medline search using the keyword “*Chlamydia trachomatis*” combined with “screening”, “pelvic inflammatory disease”, “endometritis”, “salpingitis”, “infertility”, “ectopic pregnancy”, “urethritis”, “epididymitis”, “proctitis”, “prostatitis”, “reinfection”, “cost-effectiveness”, “treatment”, “vaccines”, or “prevention”. Progression of *C. trachomatis* varies, and recurrent infections are common. Currently, there is limited evidence on the effectiveness of chlamydia screening. Higher quality studies are needed to determine the efficacy of more frequent screening, on a broader range of sequelae, including infertility and ectopic pregnancy, in addition to pelvic inflammatory disease. Studies should focus on delineating the natural history of recurrent infections, paying particular attention to treatment failures. Furthermore, alternatives to screening, such as vaccines, should continue to be explored.

Keywords: *Chlamydia trachomatis*, sexually transmitted disease, chlamydia screening, chlamydia treatment

Introduction

Chlamydia trachomatis genital tract infections are prevalent worldwide and can cause serious reproductive morbidity.¹ In men, *C. trachomatis* is associated with nongonococcal urethritis and epididymitis.^{1–3} In women, chlamydia can lead to serious complications, including pelvic inflammatory disease (PID) and its subsequent sequelae, including ectopic pregnancy, infertility, and chronic pelvic pain.^{1,4–6} Chlamydial genital infections have also been reported to increase human immunodeficiency virus transmission and influence the development of human papilloma virus-induced adenocarcinoma.^{7,8} In addition, pregnant women infected with *C. trachomatis* put their children at risk for conjunctivitis and pneumonitis through mother to child transmission.⁹

The World Health Organization estimates that 92 million new cases of chlamydia occur worldwide every year.¹⁰ An estimated 3–4 million new cases occur every year in the US, 5 million in western Europe, and 16 million in Sub-Saharan Africa.^{10,11} Among men, chlamydia prevalence has been reported to be as high as 15%–20% in high-risk populations (such as those attending sexually transmitted disease clinics) and ranges

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from 3%–7% among asymptomatic populations.^{1,11,13–16} In women, chlamydia prevalence has been reported to range from 11.4% to greater than 20% in high-risk populations, and among asymptomatic patients has been reported to range from 3.0% in the general population to 9.5% among university students.^{1,12,14–19} Due to the burden of chlamydia, the US Centers for Disease Control (CDC) recommends annual screening for all sexually active women younger than 26 years.²⁰ Several countries have adopted similar screening programs or plan to implement programs that generally focus on identification and treatment, screening for asymptomatic infection, and partner notification.^{20–23}

In parts of the US and in other countries, there has recently been an increase in reported chlamydia cases.^{20,22–30} In part, these increasing rates may be attributed to the implementation of new screening practices, reporting of chlamydia cases, improvement in diagnostics with increased sensitivity, changes in sexual behavior, or changes in natural immunity. One explanation for the rising rates is the “arrested development” hypothesis, where aggressive screening and treatment actually blunts natural immunity to chlamydial infection, increasing reinfection.^{26,30} The validity of this hypothesis continues to be debated.^{28–32} Still, the increase in reported chlamydia cases has raised concern about the effectiveness of current screening programs. This review will examine the current management and screening practices, as well as the challenges in the control of chlamydia genital tract infections.

Methods

Our primary literature search was conducted with Medline to identify randomized clinical trials, from 1950 through 2010, which examined the effectiveness of *C. trachomatis* screening in reducing reproductive morbidity. The term “*Chlamydia trachomatis*” was combined with “screening”, “pelvic inflammatory disease”, “endometritis”, “salpingitis”, “infertility”, or “ectopic pregnancy”. Citations were limited to human studies involving nonpregnant women. Postabortion and transcervical instrumentation studies were excluded. This search yielded three randomized clinical trials examining the effectiveness of chlamydia screening to reduce PID (see Table). The same key words, excluding “screening”, were used to identify articles examining chlamydial complications in women. In a separate search, “*Chlamydia trachomatis*” and “reinfection” were combined with “pelvic inflammatory disease”, “endometritis”, “salpingitis”, “infertility”, or “ectopic pregnancy”. A new search with keywords “*Chlamydia trachomatis*” and “urethritis”, “epididymitis”, “proctitis”,

or “prostatitis” was used to identify articles examining chlamydial complications in men. Other searches included the keywords “*Chlamydia trachomatis*” and “cost-effectiveness”, “treatment”, “vaccines”, or “prevention”. We also cross-referenced articles to identify additional references.

Symptoms, complications, and long-term reproductive outcomes

Chlamydial genital tract infections in men

Chlamydial genital tract infections are asymptomatic in approximately 50% of men.^{33,34} If symptoms are present they are generally mild,^{35,36} compromising early identification, which may lead to nongonococcal urethritis.^{1–3,37–39} Urethral infection with *C. trachomatis* can ascend from the lower genital tract and cause inflammation of the epididymis, a structure on the back of the testicle where sperm is stored, a condition known as epididymitis.^{40–43} Approximately 45%–85% of men with epididymitis have had prior *C. trachomatis* infections and/or gonococcal infections.^{40,41,44} *C. trachomatis* is also associated with proctitis and inflammation of the rectal mucosa in both lymphogranuloma venereum (LGV, systemic *C. trachomatis* infection caused by serovars L1–L3), and non-LGV strains (genital infection caused by serovars B and D–K).¹ Once rarely identified in industrialized nations, reports of LGV proctitis among men who have sex with men have recently been increasing throughout Europe, North America, and Australia.⁴⁵ Because symptoms of LGV proctitis are nonspecific and unfamiliar to many physicians in industrialized countries, diagnosis may be delayed.⁴⁵

Chlamydial infections may also cause prostatitis, although this relationship has not been completely delineated. *C. trachomatis* has been detected in up to 30% of prostatic or semen secretion samples and in 2.2% to 33% of prostate tissue samples collected from prostatitis patients.^{46–56} In contrast, a medical record-based retrospective cohort study of 17,764 US Air Force males did not find any significant associations between *C. trachomatis* and the development of prostatitis (hazard ratio [HR] 1.16, 95% confidence interval [CI] 0.82–1.62).⁵⁷ Furthermore, two studies using transperineal biopsy of the prostate, suggested to be the best method for reducing contamination from the lower genital tract,⁵⁸ failed to isolate *C. trachomatis* from any of their biopsy patients.^{58,59} There are several possible reasons for the discrepant findings among these studies, including different study populations, varying definitions of prostatitis, and different *C. trachomatis* diagnostic methods. Furthermore, semen samples, prostatic secretions, and some prostate tissue

Table Randomized trials examining the effectiveness of screening in preventing pelvic inflammatory disease in nonpregnant women

| Author/year | Study population | Methods | Randomization | Results |
|---------------------------------|---|---|---|--|
| Oakeshott et al ⁹² | 2529 sexually active female students, aged 16–27 years, recruited from 20 universities in London, UK. | Participants provided self-collected vaginal samples at baseline and completed a questionnaire on sexual health. CT was diagnosed using TMA. After one year, participants completed a questionnaire about possible symptoms of PID and sexual behavior over the past year. Medical records were collected for 17% and three doctors blinded to study group and CT status at baseline allocated reported PID cases into probable, possible, or no PID, using the CDC guidelines and Hager's criteria. | 98.6% (2529/2563) were randomly allocated for immediate CT screening and treatment (1259) or deferred screening (1186; vaginal samples analyzed after one year) using random number tables. 94% (2377/2529) were followed up after one year. | Incidence of PID was 1.3% (15/1191) for screened group and 1.9% (23/1186) for controls (RR 0.65, 95% CI 0.34–1.22). 9.5% (7/74) of CT positive women at baseline in control group developed PID. 1.6% (1/63) of CT positive women in screening group developed PID (RR 0.17, 95% CI 0.03–1.01). |
| Østergaard et al ¹²¹ | 1700 sexually active female high school students from Denmark, aged ≥15 years. | Intervention group received a home sampling kit at baseline and questionnaire. Those who were CT-positive (diagnosed by TMA) were referred for treatment. The control group received the same questionnaire with an offer of free testing at a local clinic or doctor's office. Home sampling kits were sent at follow-up to determine CT incidence. Follow-up questionnaire collected information on treatment or hospitalization for PID during the past year. Medical records were sought through the central Danish register for prescriptions related to PID. | 5487 female high school students were randomized (1:1) by simple redeeming to a home sampling group (2603) or a usual care group (2884). 43% (2351/5487) responded to the baseline questionnaire. Among sexually active females 55% (930/1700) were followed for 1 year. | Incidence of PID was 2.1% in the intervention group and 4.2% in the control group ($P = 0.045$). |
| Scholes et al ¹²⁰ | 2607 sexually active female HMO enrollees aged 18–34 years from Washington State, US. | Self-administered questionnaires were mailed to single HMO enrollees to determine those at high risk of CT (based on age, race, gravidity, and sexual partner in the past 12 months). Emphasis was placed on contacting nonresponders who were assigned to the screening group. In the screening group swabs were tested for CT by ELISA. Specimens collected by cytobrush were tested by chlamydia cell culture. Control group (usual care) saw their providers as needed. Both groups received a follow-up questionnaire at 12 months and were asked about diagnosis of PID. Outpatient and inpatient databases were used to identify those participants with a diagnosis of PID. Medical records of those with possible cases of PID were reviewed by blinded abstracters to determine PID status (based on signs, symptoms, and laboratory findings). | 57% (20,836/36,547) responded to the initial questionnaire and 85% (17,725) of responders were ineligible. Of the 13% eligible (2607), 1009 were randomly assigned (authors did not give randomization method) to the screening group and 1598 to the usual care group. 64% (645/1009) of women in the screening group were tested for CT. 76% were followed-up at 12 months. | Databases identified 57 participants diagnosed with PID. Medical records showed a clinical diagnosis of PID in 37 participants. Additional 5 were identified in chart review. 9 confirmed cases of incident PID in the screening group and 33 in the usual care group (RR 0.44, 95% CI 0.20–0.90). |

Abbreviations: CT, *Chlamydia trachomatis*; TMA, transcription mediated amplification; PID, pelvic inflammatory disease; CDC, Centers for Disease Control; RR, relative risk; CI, confidence interval; HMO, health maintenance organization; ELISA, enzyme-linked immunosorbent assay.

samples (such as transrectal biopsy or transurethral resection) can be contaminated by the lower genital tract, making it difficult to identify *C. trachomatis* directly in the prostate.

The debate over the role of *C. trachomatis* in male upper genital tract pathology has also raised questions about the impact of chlamydial infection on male fertility. Indeed, studies examining the relationship between *C. trachomatis* and male factor infertility have also been inconclusive,^{57,60–65} and few high quality prospective studies exist. Still, the risk of transmission to female partners leading to PID, ectopic pregnancy, or infertility^{1,4–6} is of great concern. Furthermore, reinfection rates in males have been reported to be approximately 11.3%, which is similar to reinfection rates in women.⁶⁶ Because reinfection in women may be associated with increased risk of reproductive morbidity, there is concern over the risk of transmission to female partners following repeated infections.

Chlamydial genital tract infections in women

Although *C. trachomatis* generally runs an asymptomatic course in approximately 80% of women,³⁴ it is associated with serious reproductive morbidity. *C. trachomatis* can infect the columnar epithelial cells of the endocervix and cause cervicitis,^{1,67,68} and is also associated with urethritis.^{69,70} Although chlamydial cervicitis is often asymptomatic, it does cause mucopurulent discharge in about 37% of women and hypertrophic ectopy (an area of ectopy that is edematous and bleeds easily) in 19% of women.¹ However, there are no specific genital symptoms that are correlated with chlamydial infection of the cervix for diagnosis.¹

Lower genital chlamydial infection can ascend to the upper genital tract, leading to serious complications. There are several ways *C. trachomatis* may be able to ascend into the upper genital tract. First, *C. trachomatis* has been shown in vitro to be able to attach to spermatozoa,^{71,72} possibly promoting rapid ascension into the upper genital tract.⁷³ Second, the characteristics and production of the mucus plug, which is important for the protection against microorganisms, can be changed by hormonal fluctuations during the menstrual cycle, possibly influencing ascension.⁷⁴ Hormone levels at menarche also increase cervical ectopy in young women,⁷⁴ which provides a larger area for bacterial attachment. Lastly, subendometrial contractions, which are amplified prior to ovulation, may also promote ascension.⁷⁵

C. trachomatis is a frequent pathogen of PID,^{76–78} and is isolated in the upper genital tract of about a quarter of PID patients.^{77,79,80} *C. trachomatis* has been found

to be associated with both endometritis^{81,82} as well as laparoscopically confirmed salpingitis.^{77,83–85} However, rates of progression vary widely between patients. Among untreated *C. trachomatis*-positive women, studies have reported that 2.0%–4.5% developed clinical PID within approximately 14 days.^{86–88} However, studies with longer follow-up have reported lower rates of PID following untreated chlamydial infection, ranging from 0%–9.5%.^{89–92} In the largest study, conducted in Norway between 1990 and 2005, 1.09% (48/4413) of women who tested positive for *C. trachomatis* were hospitalized for PID.⁹¹ However, several methods for chlamydia testing were used throughout the study period. Furthermore, severe PID resulting in hospitalization represents a small proportion of PID cases.⁷⁴ Because most cases of PID are mild to moderate and treated as outpatients, this study likely represents an underestimation of chlamydia-associated PID. In the randomized controlled Prevention Of Pelvic Infection (POPI) trial, 9.5% (7/74) of untreated chlamydia-positive women (determined by nucleic acid amplification test) developed clinical PID within 12 months of follow-up.⁹² However, only 17% of self-reported PID cases were verified by medical records. In a prospective study of 1170 women from five US sites, 19% (23/122) of those with treated chlamydial infection at baseline (nucleic acid amplification test) developed clinical PID within three years of follow-up.⁹³

Actual rates of progression of chlamydial infection to reproductive sequelae are unknown. Studies have found associations with prior chlamydial infections and tubal factor infertility,^{94–97} as well as ectopic pregnancy.^{5,98,99} However, very few prospective studies have examined infertility following chlamydial PID. Haggerty et al reported that, among a cohort of women with clinically suspected PID, sequelae following chlamydial upper genital tract infection was high (19.0% infertility, 15.0% recurrent PID, 20.7% chronic pelvic pain), although no significant associations were found.⁸⁰ It is possible that women in this cohort could have had prior chlamydial infections that resulted in tubal damage preceding the PID episode, resulting in bias towards the null. Brunham et al found that seven of 13 women with nongonococcal infection had an adverse reproductive outcome, compared with none of 10 women with gonococcal infection ($P = 0.007$).⁴ Of the seven infertile women, three had evidence of chlamydial infection. A retrospective study of 51 women with PID found that those who were culture-positive for *C. trachomatis* were more likely to experience involuntary infertility compared with those who tested negative for chlamydia (relative risk [RR] 2.5, 95% CI 1.0–6.2).¹⁰⁰ Because rates of progression

vary widely between individuals, it is imperative that studies strive to understand further the natural history and pathogenesis of *C. trachomatis*. This will improve treatment and control measures, and aid in vaccine development.

Repeated chlamydial infections are common^{101,102} and may increase the risk of sequelae.^{102–104} In a study of 11,000 women aged 10–44 years, those who had \geq three chlamydial infections, determined by nucleic acid amplification test, were six times more likely to be diagnosed with PID (odds ratio [OR] 6.4, 95% CI 2.2–18.4).¹⁰² Furthermore, those with two infections and \geq three infections were two times (OR 2.1, 95% CI 1.3–3.4) and four times (OR 4.5, 95% CI 1.8–5.3) more likely to have an ectopic pregnancy.¹⁰² Similarly, a prospective study among 302 female sex workers in Nairobi, Kenya, reported that repeated *C. trachomatis* infection was associated with a cumulative risk of PID over 18 months (OR 1.8, 95% CI 1.3–2.4).¹⁰³ Lastly, Ness et al reported that in 443 women with clinically suspected PID, recurrence was higher (HR 2.48, 95% CI 1.00–6.27) and pregnancy rates were significantly lower (HR 0.47, 95% CI 0.28–0.79) among women whose antibody titers to chlamydia elementary bodies were in the highest tertile.¹⁰⁴

Determining the risk of sequelae following repeated chlamydial infections is difficult because the duration of infection is generally unknown. Furthermore, ascertainment bias may be present, because physicians who are aware of previous infections may be more inclined to diagnose pelvic pain as clinically suspected PID. Still, studies generally suggest that repeated chlamydial infections may increase the risk of sequelae. It is important to determine the epidemiology of repeated infections, particularly if they are caused by treatment failures, increased susceptibility to infection due to host immunity, or reinfection from an untreated partner.

Screening

Routine screening for *C. trachomatis* has been implemented worldwide, with the goal of interrupting progression or reducing transmission to prevent long-term morbidity. However, there is no single accepted screening strategy that has been consistently implemented. Many screening programs target young women under the age of 26 years, focusing on identification and treatment, screening for asymptomatic infection, and partner notification.^{20–23} Recommendations for screening men varies, but should be evaluated because screening both men and women may more adequately reduce transmission.²² Frequency of screening also varies between programs. The US and the UK often use opportunistic screening approaches whereby physicians offer chlamydia

screening to young women when they attend health care or similar settings for unrelated reasons.¹⁰⁵ Retesting is generally the responsibility of the physician. Register-based (proactive) screening, used in some parts of The Netherlands, utilizes a register of the target population and sends invitations for screening (invitations are resent to nonresponders) to ensure that a high proportion of the target population is reached at adequate intervals.¹⁰⁵ It is important that countries evaluate their screening rates in the population. A high proportion of the target population should be reached to ensure that regular screening and partner notification are achieved to reduce morbidity significantly.

In selected populations, such as sexually active adolescents and young women, chlamydia screening is suggested to be cost-effective.^{106–109} However, there is little evidence that chlamydia screening is cost-effective in other populations or in males. Furthermore, cost-effectiveness is suggested to be influenced by the rate of complications,^{110–112} which may be lower than previously estimated.^{111,112} In fact, two studies using a dynamic simulation model reported that when complication rates are low, chlamydia screening may not be cost-effective.^{113,114} These findings suggests that better estimates of morbidity risk are needed to evaluate screening programs fully.¹¹² However, because the natural history of *C. trachomatis* has not been completely delineated, estimating these risks may be difficult.

Despite screening programs, many countries, such as the US, Sweden, and Canada, have recently seen rising rates of chlamydia cases.^{20,22–30} For example, in 2008, 1.2 million cases of chlamydia were reported to the US CDC, ie, a 9.2% increase from 2007 and the largest number of cases ever reported to the US CDC for any disease.²⁰ Estimates based on case reports need to be interpreted with caution because they do not truly reflect prevalence or incidence of chlamydial infections. However, *C. trachomatis* is still very much underreported due to its asymptomatic nature, and the increased rates may not be artificial.^{28,30} For example, there may be a true increase in incidence, which could ultimately lead to an increase in chronic untreated asymptomatic infection, thus leading to a higher prevalence.

There are several possible explanations for the rising rates. For example, the switch to more sensitive tests, such as nucleic acid amplification testing, introduced in the 1990s, which can be performed on both urine and female self-collection swabs, may contribute to the increase in chlamydial rates. However, Gotz et al report that, in Sweden between 1991 and 1999, increases in chlamydia were reported in both laboratories that changed to more sensitive methods

and those that did not,²⁸ suggesting that changes in diagnostics did not completely account for the increasing rates in Sweden.²⁸ Collection by urine or female self-collection swabs is an advantage over other testing methods which rely on urethral and endocervical swabs. Self-collection swabs may be mailed directly from home to a laboratory. Because these methods may be more acceptable to people, testing rates may have increased as a result. For example, a study out of Denmark reported that home-sampling increased the number of women tested by 11-fold compared with sampling at a doctor's office.¹¹⁵

There are several other hypotheses that may explain the increasing chlamydia rates including changes in sexual behavior, increases in chlamydia reporting, changes in treatment failure, failure to achieve adequate partner notification, and changes in natural immunity. In the early 1990s in countries without screening programs, reduced chlamydia rates coincided with human immunodeficiency virus prevention campaigns.^{105,116} This may suggest that an increase in condom use and abstinence could have accounted for the decreasing rates, and increases in risky sexual behavior could influence rates today. Other hypotheses also exist. The "arrested development" hypothesis suggests that aggressive early treatment blunts the natural immune response to chlamydial infection, essentially increasing the rate of chlamydial reinfection.^{26,30} Studies have shown that there is an increase in repeated chlamydial infections following treatment.^{117–119} In addition, Brunham et al reported that despite changes in diagnostics at different times, *C. trachomatis* reinfection has increased 4.6% per year in British Columbia since 1989.²⁶ It is possible that women who are screened are in general at higher risk for sexually transmitted infections, and thus are more likely to have reinfection independent of screening and treatment. Still, studies should continue to evaluate the role of host immunity in both the course and outcome of chlamydial infections, as well as compare immunity, duration, and risks of complications in initial and repeated infections. If repeated infections truly cause more sequelae than initial infections, then more frequent screening or screening focused on repeated infections should be evaluated. There is also a need for better estimates of chlamydia incidence. Indeed, if the observed increases in chlamydia cases do reflect a true increase in chlamydia incidence, then current screening strategies may not be efficient in reducing transmission.

Low et al argue that the evidence examining the effectiveness of chlamydia screening is limited, because very few randomized clinical trials exist.¹⁰⁵ Furthermore, there are no randomized trials that have examined complications, such

as infertility or ectopic pregnancies. One randomized trial of 2607 high-risk women recruited from a Seattle health maintenance organization found that one-time screening significantly reduced the risk of clinical PID (RR 0.44, 95% CI 0.20–0.90) within one year of follow-up (see Table).¹²⁰ Nonresponders in the intervention group were aggressively contacted, which may have resulted in selection bias.¹²⁰ In addition, only 64% of the screening group actually attended a study clinic for chlamydia testing, and 24% were lost to follow-up. In a cluster randomized trial among male and female high school students, Østergaard et al reported that one-time screening significantly reduced PID (based on self-reported treatment and hospitalization for PID) within one year when home sampling was compared with usual care (4.2% versus 2.1%, $P = 0.045$).¹²¹ The usual care group was offered free screening at a local clinic or doctor's office, although only 63 of 833 females in the control group were reported to be tested for chlamydia. However, this trial was not blinded and approximately 45% were lost to follow-up. Furthermore, because chlamydia is not the only cause of PID, the estimated effect of screening on PID incidence has been suggested to be overestimated in both studies.^{92,105} In another randomized trial (POPI), there was a limited impact of annual *C. trachomatis* screening on self-reported clinically suspected PID incidence (RR 0.65, 95% CI 0.34–1.22) between women who were screened (1.3%, 15/1191) and controls (1.9%, 23/1186).⁹² However, the incidence of PID was only 1.9%, which was lower than the estimated 3% used to power the study.

When evaluating the effectiveness of screening programs to reduce reproductive morbidity, there are several possible limitations in using PID as an outcome. First, several other microorganisms have been implicated in the etiology of PID, making it difficult to determine the proportion of PID cases specifically attributed to *C. trachomatis*. Second, signs and symptoms of PID vary widely, thus diagnosis of clinically suspected PID is nonspecific. Lastly, *C. trachomatis* has been found to increase the odds of subclinical PID six-fold (OR 6.1, 95% CI 1.8–2.1),¹²² suggesting that increases in *C. trachomatis* upper genital tract infection may increase subclinical PID in the population. Women with subclinical PID have very mild or no symptoms,⁷⁴ and PID may go undiagnosed in many women with chlamydial infection. Thus, the effectiveness of screening programs to reduce other reproductive sequelae should be explored. However, infertility can also be difficult to diagnose, because it can take years to develop and has several different causes. In addition, infertility can only be measured in women actively

trying to conceive or those who rarely or never use reliable contraceptive methods. This same issue applies to ectopic pregnancy. Therefore, improved diagnostic methods for postchlamydial complications with high sensitivity and specificity are needed.

Treatment and prevention

Treatment of *C. trachomatis* infection is considered to be effective in preventing transmission to sexual partners.¹²³ Several drugs are active against *C. trachomatis* in tissue cultures, including rifampin, tetracyclines, macrolides, sulfonamides, some fluoroquinolones, and clindamycin.¹ Rifampin is highly active in vitro, but resistance to this drug can be readily developed.¹²⁴ Thus, rifampin is not used to treat human chlamydial infections.¹ *C. trachomatis* is also susceptible to sulfonamides, but they are not used for genital chlamydial infections.¹²⁵ Currently, the US CDC recommends treatment with azithromycin (1 g, single dose taken orally) or doxycycline (100 mg, twice per day for seven days).¹²³ A recent meta-analysis revealed similar microbiological cure rates for azithromycin (97%) and doxycycline (98%).¹²⁶ Azithromycin is recommended when compliance may be an issue, such as in adolescents or those with low socioeconomic status due to its ability to be given in a single dose. Alternative regimens can include erythromycin base (500 mg four times per day for seven days), erythromycin ethylsuccinate (800 mg four times per day for seven days), ofloxacin (300 mg twice a day for seven days), or levofloxacin (500 mg daily for seven days).¹²³ Erythromycin is effective in treating chlamydia, but has side effects, which may reduce compliance.¹²³ Levofloxacin and ofloxacin are also effective, but are expensive.¹²³ There is currently no solid evidence of any in vivo antibiotic resistance for *C. trachomatis* genital tract infection.^{1,30,125} However, very few laboratories actually monitor chlamydial antibiotic resistance.³⁰ Although recurrent infections are common in both men and women, it is unclear if they are due to treatment failures. In the US, it is likely that many treatment failures go unnoticed in asymptomatic infection, because test-of-cure (repeat testing three to four weeks after completing therapy) is not recommended, except in pregnant women.¹²³

Vaccines

The asymptomatic nature of chlamydia makes diagnosis, treatment, and prevention of sequelae a challenge. Host immunity induced by chlamydial infections is not long-lasting, and may take several months or years to develop.¹²⁵ Further, a single *C. trachomatis* infection does not adequately

protect against reinfection.¹²⁵ In addition, it is hypothesized that aggressive treatment may blunt natural immunity.^{26,30} Therefore, control and management of chlamydia may depend on a safe and effective vaccine that can induce a better immune response than what occurs naturally.¹²⁵ However, the pathogenesis of *C. trachomatis* has not been completely elucidated, and the role of host immunology is unclear. Coupled with a lack of a suitable animal model and inability to manipulate chlamydia genetically, researchers have yet to develop a successful vaccine.

Chlamydial surface antigens are possible vaccine candidates.¹²⁵ Several chlamydial vaccine trials have used the major outer membrane protein as a vaccine candidate. However, studies using the major outer membrane protein have been inconclusive and immunity is generally short-lived.^{127–131} Furthermore, the major outer membrane protein is not serovar-specific. Thus, other antigens are currently being considered as vaccine candidates. The recently discovered surface-exposed protein, polymorphic membrane protein D, has been shown to act as an adhesion molecule¹³² and can stimulate proinflammatory cytokines through the nuclear factor- κ B pathway.¹³³ Crane et al found that polymorphic membrane protein can recruit host antibodies to the site of infection, making this protein a promising vaccine candidate.¹³⁴ Antibody response was also neutralizing across different serovars. However, chlamydia may undergo a type of antigenic variation.¹³⁵ Thus, it has been suggested that a single antigen may not be optimal as a vaccine candidate. Further increasing our knowledge of chlamydial pathogenesis will bring researchers closer to developing a successful vaccine.

Conclusion

There are several factors which may hinder the implementation of a successful chlamydia screening program. First, the evidence examining the effectiveness of chlamydia screening is limited, because few high quality randomized clinical trials exist. Furthermore, chlamydia screening strategies vary widely, and there is no evidence to suggest which screening strategy would best reduce reproductive morbidity. Second, cost-effective analyses, which are mainly conducted in young women, may be inaccurate because complication risks are lower than previously estimated. In fact, two studies using dynamic simulation models have suggested that chlamydia screening is not cost-effective when based on lower complication rates. Lastly, the high rate of repeated infections in the population and our incomplete understanding of the natural history of *C. trachomatis* have greatly challenged

control efforts. Because the natural history of *C. trachomatis* has not been completely elucidated, it is unclear if screening can successfully interrupt progression before tubal damage and/or reduce transmission in the population.

It is clear that future research is needed to determine the best approach for chlamydia management. While it is difficult to assess screening programs, it would be optimal if the efficacy of more frequent *C. trachomatis* screening on a broader range of sequelae were explored, including infertility and ectopic pregnancy in addition to PID. Due to the previously mentioned limitations of using these outcomes to evaluate screening programs, improved diagnostic methods for chlamydial complications are needed. Alternatively, better estimates of chlamydia incidence can be used to determine if screening can efficiently reduce transmission. Because studies evaluating chlamydia screening have largely been conducted in women, future investigations should also focus on men. This is of particular importance because *C. trachomatis* is asymptomatic in half of men, leaving a high likelihood of transmission to sexual partners. It is imperative that the natural history and epidemiology of *C. trachomatis* continues to be explored in both single and repeated infections. Research should continue to explore host immunology, bacterial antigens, duration, and the role of pathogen load in the course and outcome of chlamydial infections. In addition, it is particularly important that future studies determine if repeated infections are caused by treatment failure. As chlamydia research progresses, current screening programs need to be evaluated carefully and other alternatives to screening, such as vaccine development, should continue to be explored.

Disclosure

The authors report no conflicts of interest in this work.

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