Chapter 20
Sexual Transmission: *Chlamydia trachomatis*

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20.1 Introduction

20.1.1 Basic Biology

Chlamydia trachomatis is an obligate intracellular Gram negative bacterium, which infects mucosal epithelial cells (Schachter and Stephens 2008). *Chlamydia* display a unique two-stage life cycle consisting of an infectious stage and a replicative stage. During the infectious stage the organism assumes a metabolically inactive form, the elementary body, which can survive in the host extracellular environment. Upon entry into a host cell the elementary body transforms within a host cell vacuole into a metabolically active, replicating form, the reticulate body. Over a period of approximately 36–72 hours of growth and replication, the reticulate bodies transform into infectious elementary bodies, which are extruded from the cell and repeat the cycle by infecting additional cells of the same or a second host.

A serotyping scheme, based on antibodies to the *C. trachomatis'* major outer membrane protein, permits the division of *C. trachomatis* strains into serovars (Schachter and Stephens 2008). Strains belonging to serovars A–C, the trachoma biovar, infect conjunctival epithelium, which can progress to the disease trachoma. The subject of this chapter is the group of *Chlamydia trachomatis* strains that causes sexually transmitted genital mucosal infections, the most common bacterial sexually transmitted disease. Characteristic of such strains is a predilection for asymptomatic infection. A principal focus for concern, and a focus of this chapter, is preventing ascending reproductive tract infection in women resulting in clinical pelvic inflammatory disease (PID) and, with or without symptomatic PID, sequelae that include tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. An increasing number of countries are implementing national chlamydia screening programs that are motivated by apparent prior success with such

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programs for gonorrhea and randomized controlled trials that demonstrate reduction of PID among screened women. Recent observational studies of chlamydial natural history and the introduction of population chlamydial prevalence and sexual behavior surveys and dynamic models of transmission within virtual populations have helped to quantify and explain varying chlamydial prevalence. These studies have also raised questions about chlamydial pathogenesis and immunity and the impact of screening programs. Addressing these questions will require continued studies of pathogenesis and immunity and better evaluation of public health programs by improved measurement of the intensity of interventions and better and less invasive methods to detect onset of tubal disease. The remainder of this chapter is devoted to heterosexually transmitted infections with genital biovar strains, which are widely distributed in developed as well as developing countries. We focus on *C. trachomatis* infection in North American and northern European countries that are developing early diagnosis and treatment interventions.

20.1.2 Overview of Natural History of C. trachomatis Infection

Heterosexual vaginal or penile exposure to genital biovar *C. trachomatis* strains results most commonly in endocervical and male urethral infections, respectively. Symptoms, including vaginal and penile discharge and dysuria, can develop due to an inflammatory response at the site of infection, but many *C. trachomatis* infections are asymptomatic. Ascending reproductive tract infection resulting in epididymitis occurs in a small minority of men and responds to treatment so that sequelae such as infertility are rare. Ascending reproductive tract infection occurs in a larger minority of women resulting in salpingitis or, more generally, pelvic inflammatory disease (PID). PID may be associated with acute lower abdominal symptoms, but commonly occurs with minimal or no symptoms. In either case, sequelae of PID include infertility, ectopic pregnancy, and chronic pelvic pain. The natural history and epidemiology of uncomplicated male and female *C. trachomatis* infections and of PID will be discussed below. Additional manifestations of *C. trachomatis* infection, which will not be further discussed, include an uncommon reactive arthritis and transmission from mother to baby at delivery followed by neonatal conjunctivitis and infant pneumonia, which are not sight or life threatening, but are associated with substantial morbidity.

20.2 Descriptive Epidemiology of *C. trachomatis* Infection

20.2.1 Prevalence of C. trachomatis Infection

National or community population probability surveys that include testing for *C. trachomatis* infection provide prevalence estimates not susceptible to the

selection bias inherent in case reporting and health care provider-based testing. In the United States (the USA) (Datta et al. 2007) and the United Kingdom (the UK) (Fenton et al. 2001) surveys, C. *trachomatis* prevalence was highest among sexually active adolescent girls and the youngest adult women. Prevalence was not markedly lower among men, but peak prevalence among men occurs a few years later than among women. In the USA, prevalence was highest among females aged 14–19 (4.6%, 95% CI 3.7–5.8%) and among males aged 20–29 (3.2%, 95% CI 2.4–4.3%) (Datta et al. 2007).

In such surveys, *C. trachomatis* prevalence has been weakly to moderately associated with socioeconomic status, although socioeconomic status is difficult to assess in adolescents and young adults (Datta et al. 2007; Fenton et al. 2001; van Bergen et al. 2005). In the USA, *C. trachomatis* prevalence has been more strongly associated with race ethnicity than socioeconomic status. In a US survey of young adults, ages 18–26, prevalence of *C. trachomatis* infection among black women (14.0%, 95% CI 11.3–17.2%) and men (11.1%, 95% CI 8.5–14.4%) was substantially higher than among white women (2.5%, 95% CI 1.9–3.3%) and men (1.4%, 95% CI 0.9–2.0%) (Miller et al. 2004). Where assessed, *C. trachomatis* prevalence was lower among married individuals (Datta et al. 2007; Fenton et al. 2001).

20.2.2 Disease Burden Attributable to C. trachomatis Infection

It has been difficult to determine what proportion of PID and its sequelae are attributable to *C. trachomatis* infection. Detecting tubal inflammation and scarring and determining whether infertility, ectopic pregnancy, or chronic pelvic pain is attributable to such disease requires invasive diagnostic procedures. Serologic tests to detect untreated prior *C. trachomatis* infection are subject to errors of sensitivity and specificity. Other sexually transmitted organisms, in particular *Neisseria gonorrhoeae*, but also, possibly, *Mycoplasma genitalium*, as well as enteric and anaerobic gram negative organisms commonly found in the vagina contribute to the occurrence of PID. Parsing out the contribution of *C. trachomatis* from these other contributors to clinical and subclinical PID and subsequent sequelae has been difficult and only partly successful.

20.2.2.1 Pelvic Inflammatory Disease

Most cases of PID are managed in ambulatory settings and few countries or communities can determine frequencies of ambulatory cases of PID. The US Centers for Disease Control and Prevention has tracked physician diagnoses of PID utilizing national surveys of hospital discharges, visits to hospital emergency rooms and outpatient clinics, and visits to office-based practitioners (Sutton et al. 2005).

During 1995–2001, the average estimated annual rate of hospital discharges and ambulatory visits for acute and unspecified PID in the USA was highest for age group 25–29 with a discharge rate of 1.1 (95%, CI 0.9–1.3%) per 1,000 women and an ambulatory visit rate of 19.0 (95%, CI 12.0–26.0%) per 1,000 women. In a retrospective cohort study, Low et al. (2006) selected female residents of Uppsala, Sweden, that were between 15 and 24 years of age between 1985 and 1989 and conducted a record search through 1999 for in-hospital, and for the last 6 years of that interval, for hospital outpatient diagnoses of PID. Although non-hospital ambulatory cases of PID were missed, the study provided a unique cumulative incidence minimum estimate, 3.9% (95%, CI 3.7–4.0%) of females by age 35.

The proportion of PID that is caused by *C. trachomatis* is not well defined. The overall cervical isolation rate was 29% with a range of 5–51% in a compilation of studies published between 1975 and 1995 (Paavonen et al. 2008). More recently, an English study conducted during 2000–2002, using nucleic acid amplification testing of endocervical or urine specimens, detected *C. trachomatis* in 12% of 140 outpatient PID cases (Simms et al. 2006). A large US study detected *C. trachomatis* by PCR or *N. gonorrhoeae* by culture testing of endocervical specimens in 40% of patients who were eligible for out-of-hospital care (Ness et al. 2002). The relatively low specificity of outpatient clinical diagnosis of PID (Jacobson and Westrom 1969; Simms et al. 2003) contributes a substantial negative bias to estimates of *C. trachomatis* prevalence among patients with outpatient-diagnosed PID.

Subclinical PID caused by *C. trachomatis* appears to be a significant problem. Although these cases impose no burden with respect to acute disease, they may be very important, since the majority of women presenting with tubal infertility or ectopic pregnancy occur among women with no prior history of PID (reviewed in Wiesenfeld and Cates 2008).

20.2.2.2 Sequelae of PID

In 2002, a US household probability survey estimated that 7.4% of married or cohabiting US women were infertile (Stephen and Chandra 2006). No population survey has included the invasive diagnostic procedures required to identify tubal disease as the cause of infertility. However, in 2006, 18% of US couples who utilized assisted reproductive technology were affected by tubal infertility (Macaluso et al. 2008). Using health services data published for an English health district (Hull et al. 1985), Wiesenfeld and Cates estimated that one in six couples would seek infertility treatment from a specialist during their lives with tubal damage accounting for the infertility in 14% of infertile couples (Wiesendfeld and Cates 2008). In a Danish study, approximately 20% of infertility was attributed to tubal damage (Schmidt et al. 1995).

Determining what proportion of tubal infertility is attributable to *C. trachomatis* infection is difficult. A recent review of 15 cross-sectional and case–control studies

provides the percent of tubal-factor infertility cases and nontubal-factor infertility controls, respectively, that had chlamydial antibody (Wiesenfeld and Cates 2008). These percents yield odds ratios of 5–93 (authors calculations). A recent Netherlands study utilized a serologic test that was species specific (den Hartog et al. 2004). The percent test positive for the cases and controls were 54% and 8%, respectively (odds ratio 14). These estimates might overstate the role of *C. trachomatis* if the serologic tests for *C. trachomatis* are less sensitive among controls than cases and if *C. trachomatis* infection is a marker for other causal infections, such as *N. gonorrhoeae* or *Mycoplasma genitalium*.

Determining the frequency of ectopic pregnancy has become difficult due to the increasing proportion of cases that are treated as outpatients. Recently, 1–3% of pregnancies were reported to be ectopic (Bakken 2008; Farquhar 2005). Wiesenfeld and Cates reviewed 12 case–control studies of ectopic pregnancy and *C. trachomatis* infection (Wiesenfeld and Cates 2008). The odds ratios for ectopic pregnancy following *C. trachomatis* infection, based on *C. trachomatis* serologic tests, are slightly lower than for infertility with point estimates ranging from 2 to 24. The caveats described above for infertility regarding these associations also apply to ectopic pregnancy.

Chronic pelvic pain is also an important sequela of *C. trachomatis* tubal infection because of the impact on the quality of life and the costs associated with diagnostic procedures and treatment (Haggerty et al. 2003). Although chronic pelvic pain is common, affecting 15% of women in the USA (Mathias et al. 1996), studies have not been conducted to assess the role of prior *C. trachomatis* infection.

20.3 Determinants of the Epidemiology of *C. trachomatis* Infection

Transmission of communicable infections through populations depends on a set of key variables: risk of transmission during contact between infected and susceptible individuals; time course of infections, including onset of symptoms; and rates and patterns of contacts, in this case, sexual contacts (Garnett 2002). Dynamic transmission models that are being used to evaluate chlamydial interventions (described subsequently) depend upon having estimates for these key model parameters.

20.3.1 Risk of an Initial C. trachomatis Infection

The risk of chlamydial infection following a single sexual exposure has not been estimated directly. Instead, Kretzschmar et al. (2001) utilized results of a study of the concordance of chlamydial infection between heterosexual partners attending an STD clinic (Quinn et al. 1996). The percents that were *C. trachomatis* test positive among female and male partners of test-positive index patients were approximately 70%. Treating transmission during individual exposures as independent binomial

probability events, Kretzschmar et al. (2001) derived a per-contact probability of infection of 0.108 by assuming a mean of 10 exposures per casual partnership. Regan et al. (2008) similarly derived a transmission risk per exposure range of 0.0165–0.17 by assuming a range of exposures per partnership. However, such an approach may not provide an accurate estimate if, among concordantly positive partners, presumed source partners are actually "spread" partners. Turner et al. (2006a) arrived at a transmission probability per sex act of 0.0375 by fitting a simulation model to sexual behavior and prevalence information obtained from surveys and the literature.

20.3.2 Symptoms and Time Course of C. trachomatis Genital Infection

Given the 36–72 hour replication cycle of *Chlamydia*, a few days to 2–3 weeks is required for *C. trachomatis* infection to become established at which time an individual is presumed to be infectious. In the absence of a screening program, the infection would be expected to persist until (1) symptoms develop and the infected individual obtains curative treatment; (2) the individual is referred for curative treatment because an infected sex partner develops symptoms; or (3) the infection is resolved by an immune response. Determining the proportional distribution of incident *C. trachomatis* infections among these categories and the duration of infection within each is critical to modeling *C. trachomatis* infection in populations and to designing community interventions. However, such determinations are very problematic, since it is difficult to determine the time of onset of most infections and it is not ethically feasible to follow untreated individuals.

An early dynamic transmission model of *C. trachomatis* infection assumed that 75% of infected males and 30% of infected females develop symptoms (Kretzschmar et al. 1996). Subsequent studies have resulted in markedly reduced values for males. Korenromp et al. (2002) modeled the probability of developing symptoms, the probability of treatment, the point prevalence of symptoms, and the duration of infection. They fit their model to values for these variables obtained from the literature, survey data from Rakai District, Uganda, and expert opinion. They estimated that 6 and 11% of infected females and males, respectively, develop symptoms. Farley et al. (2003) conducted a retrospective cohort study in the United States by enrolling men and women who presented to potential chlamydia screening sites for reasons unrelated to chlamydial infection. Using a combination of history of symptoms during the prior year, medical chart review, and current prevalence of infection, they estimated that only 11% of males and 29% of females that became infected during the year developed symptoms and 85 and 80%, respectively, of these sought care and were treated.

In addition to the proportion asymptomatic, the duration of infection among those without symptoms importantly affects the effectiveness of screening. A number of

studies have investigated the proportion of individuals with chlamydial infection who were still infected at a return visit for treatment. For a set of such studies, Korenromp et al. (2002) assumed that the rate of resolution of infection is constant and independent of the past duration of infection and, by applying an exponential distribution, calculated the total mean duration of infection for each study from the proportion still infected at the follow-up and the mean days of follow-up. The authors pooled the results for each gender, reporting an estimated mean duration of infection of 132 days for males and 499 days for females.

Clearly, considerable uncertainty exists regarding the proportion of incident chlamydial infections that result in symptoms and the duration of untreated infections. Nevertheless, these estimates suggest that only a small minority of infected individuals seek curative health care and, in the absence of treatment, infection persists for a few months in males and for over a year in females. The frequency with which infections are ended due to treatment secondary to onset of symptoms in an infected sex partner is unknown.

20.3.3 Time Course of Complicated C. trachomatis Genital Infection

A few studies provide some insight regarding risk of clinically evident PID following acquisition of chlamydia. Two early studies involved clinical trials in which 20 women with *N. gonorrhoeae* infection (Stamm et al. 1984) and 15 female partners of men with nongonococcal urethritis (Paavonen et al. 1980) were determined to have *C. trachomatis* infection but did not receive effective treatment for that organism. At follow-up, 30 and 20%, respectively, of the women had clinically evident PID compared with 2% and none of controls that received antibiotics active against *C. trachomatis*.

Subsequent studies, which involved follow-up of untreated women who tested positive for *C. trachomatis* infection, have reported lower rates of clinically evident PID. In these studies, 2%, 3.6%, and none of infected women developed evidence of PID during intervals without treatment of up to 60 days (Geisler et al. 2008), for 90 days (Rahm et al. 1986), and for 1 year (Morre et al. 2002), respectively. The reasons for the disparity in these rates of clinically evident PID during follow-up of women with chlamydial infection are unclear.

The classical cohort study of 1,309 Swedish women followed after treatment for laparoscopically confirmed PID is the principal source of estimates of the risk of sequelae following treated PID (Westrom et al. 1992). The authors reported a confirmed tubal infertility rate of 10.8% among treated PID cases compared with none among controls. Ectopic pregnancy occurred in 9.1% of the women treated for PID compared with 1.4% of controls. Chronic abdominal pain developed in 18.1% of a subsample of PID cases and 5% of controls (Westrom 1975).

The case–control studies described earlier in this chapter suggest that a substantial proportion of PID that progresses to sequelae is subclinical. The risk of sequelae

following untreated chlamydial infection in the absence of clinically evident PID is unknown.

20.3.4 Formation and Dissolution of Sexual Partnerships

STI are transmitted through sexual partner networks embedded in and connecting communities. Network theory together with infectious disease modeling has been used extensively in recent years to better understand how these complicated and dynamic networks affect the frequency and distribution of STI, including chlamydial infection (Doherty et al. 2005; Garnett 2008; Morris et al. 2008). Important aspects of sexual partnering include the rate of formation and dissolution of sexual partnerships, the extent to which individuals form sexual partnerships with individuals of similar chlamydial risk status (assortative mixing), and the extent to which sexual partnerships overlap (concurrency).

Age is a strong risk factor for STI in general and especially for chlamydial infection. This is particularly true in developed countries where first sexual partnerships occur during the mid-to-late teens or early twenties, but marriage is delayed (Berman and Ellen 2008; Wellings et al. 2006). Median age at marriage/cohabitation is later for men than women (Wellings et al. 2006). Compared with older persons, a higher proportion of the sexually active in younger age groups report multiple or new partners (Johnson et al. 2001; Kretzschmar et al. 1996; Kretzschmar et al. 2001; Low et al. 2006; Mosher et al. 2005; Regan et al. 2008), have primary monogamous partnerships of shorter duration (Laumann 1994; Low et al. 2007; Turner et al. 2006a; Turner et al. 2006b), and are more likely to enter a new partnership, i.e., a concurrent partnership, while continuing a current relationship (Johnson et al. 2001; Kelley et al. 2003). Sexual partnering by age is strongly assortative, further contributing to the relative concentration of chlamydial infections among teens and young adults; males, however, tend to be slightly older than their female partners (Laumann 1994; Low et al. 2007; Morris et al. 2008; Regan et al. 2008; Turner et al. 2006a; Turner et al. 2006b). Increased susceptibility to chlamydial infection due to cervical ectopy in adolescent girls and relative lack of any immunity may add to their increased risk. The fact that *C. trachomatis* infections, unlike HIV or herpes simplex virus type 2, do not persist and accumulate with increasing age also serves to concentrate transmission within the teen and young adult age groups (Morris et al. 2008).

Sexual network differences also contribute to race-ethnicity disparities in prevalence of STIs, including chlamydial infections. National population surveys in Britain and the USA indicate differences by race ethnicity in numbers of partners, especially for males (Fenton et al. 2005; Mosher et al. 2005). Analyses of results from an earlier US survey, conducted in 1992, demonstrated strong

assortative mixing by black and white races (Laumann and Yoosik 1999). Assortative mixing by race was greater for blacks than whites and, in part, explains the racial disparities in STDs; in addition, mixing between risk groups was more random among blacks than whites, which facilitates STD transmission through a population and also contributes to the observed racial disparities. These differences in mixing patterns reinforce the effects of differences in number of sex partners and other STI risk differences, e.g., health-care utilization, on race-ethnicity disparities.

20.4 Public Health Interventions

The four essential interventions related to STD prevention are clinical, screening, partner management, and individual and community behavioral services. Clinical services for individuals with symptomatic chlamydial infections are important, but most infections are asymptomatic. Consequently, identification and treatment of asymptomatic infections have been the focus of chlamydia prevention efforts. Screening appropriate populations for chlamydia and providing effective treatment reduce transmission – accomplishing primary prevention – by shortening duration of infection. Partner notification serves the same objective. In addition, both approaches can also serve secondary prevention objectives, by treating infected individuals, especially women, and preventing the development of complications, such as PID. The chlamydia-specific aspects of these activities are discussed below in some detail. Few aspects of individual or community level behavioral interventions are specific to chlamydia and are not addressed in this chapter.

20.4.1 Dynamic Models of Early Diagnosis and Treatment

Dynamic models that simulate heterosexual transmission of chlamydial infection through virtual communities have been used to evaluate early diagnosis and treatment interventions (Andersen et al. 2006; Brunham et al. 2006; de Vries et al. 2008; Fisman et al. 2008; Gift et al. 2008; Kretzschmar et al. 1996; Kretzschmar et al. 2001; Low et al. 2007; Regan et al. 2008; Turner et al. 2006a; Turner et al. 2006b). These models are based on the proximate determinants of transmission: rates of sexual contact; risk of transmission given contact between infected and susceptible sex partners; and the duration of infection (Garnett 2002). More realistic models involve greater complexity, subdividing groups of infected and susceptible males and females into subgroups, based on combinations of age and risky sexual behavior. Mixing matrices are applied to generate assortative sexual mixing between combinations of age and sexual behavior subgroups. The dynamic models are generally run under baseline conditions until chlamydial prevalence stabilizes at equilibrium. An intervention is then introduced and the model continued for sufficient time to capture the effect of the intervention on chlamydia prevalence.

The simplest of the dynamic models are deterministic compartmental models, which do not consider events at the individual level (Brunham et al. 2005; de Vries et al. 2006; de Vries et al. 2008; Fisman et al. 2008; Gift et al. 2008; Regan et al. 2008). These models consider only average rates of events (e.g., sexual contact and resolution of infection) that determine the flow of individuals between subgroups (Garnett 2002). Most *C. trachomatis* transmission models have been of the susceptible-infected-susceptible type, i.e., *C. trachomatis* infected individuals have been assumed to return immediately to a susceptible state upon resolution of their infection. Certain recent models have considered the impact of immunity by adding compartments for immune individuals (Brunmhan et al. 2005; Fisman et al. 2008; Regan et al. 2008).

A concern with deterministic compartmental *C. trachomatis* models has been their inability to take into account events within a given dyad – for example, that one member of a dually infected partnership may continue with that partnership following screening and treatment rather than selecting a new partner at random (Morris et al. 2008). The effect of screening may be nullified by reinfection if the partner is not referred and treated. Furthermore, the deterministic models do not adequately reflect the impact of concurrent relationships. To address these concerns, dynamic models have been developed that track individuals and sexual partnerships (Andersen et al. 2006; Kretzschmar et al. 1996; Kretzschmar et al. 2001; Low et al. 2007; Turner et al. 2006a; Turner et al. 2006b).

Parameter values for these models have been chosen by reviewing the literature and conducting local sexual behavior and chlamydial prevalence surveys. If initial model results deviate from the results of the surveys, the modelers have used their judgment to adjust, i.e., calibrate initial parameter values until the model generates results that reasonably fit survey results. As a consequence, some of the parameter values used in the published *C. trachomatis* dynamic modeling studies, e.g., probability of an infection becoming symptomatic and rate of resolution of infections differ substantially among studies even though the structure of the models and local survey results are similar.

Taken together, the modeling studies support a prediction that screening of females aged 15–24 would be an effective core component of a screening program intended to reduce prevalence in the population (Brunham et al. 2005; Fisman et al. 2008; Kretzschmar et al. 1996, 2001; Regan et al. 2008). Roughly a quarter to a third of that group must be screened annually to begin to have a substantial impact; the impact appears to accelerate with expanded screening and then the incremental gains decline as coverage exceeds a majority of the target population (Kretzschmar et al. 1996; 2001; Turner et al. 2006a; Turner et al. 2006b). The individual person models demonstrate the importance of partner notification (Andersen et al. 2006; Kretzschmar et al. 1996; Kretzschmar et al. 2001; Turner et al. 2006a; Turner et al. 2006b). The effect of partner notification interacts with screening, since partner notification cannot be initiated until the index individual′s infection is detected. If screening coverage of women was high, increasing notification and treatment of male partners had a greater impact on prevalence among women than screening males (Kretzschmar et al. 2001). Some combination of partner notification and

screening to detect and treat infected males contributed importantly to reducing prevalence when coverage of females aged 15–24, in particular, but also aged 15–29, was not high (Fisman et al. 2008; Turner et al. 2006a; Turner et al. 2006b).

An important exception to the findings of the dynamic transmission modeling studies described immediately above is the results of a study conducted to evaluate potential home-based screening in the UK (Low et al. 2007; Roberts et al. 2007). Although the structure and parameterization of the model used in this study appear to be similar to the individual-based models used in the foregoing studies, the reported impact of screening and partner notification on chlamydial prevalence was much lower.

20.4.2 Cost-Effectiveness of Early Diagnosis and Treatment

Appended to several of the chlamydia dynamic transmission models are economic models, which take chlamydial incidence, the probabilities of chlamydial complications and sequelae, and the costs of intervention activities and disease as inputs and provide estimates of the costs, the effectiveness, and the cost-effectiveness as outputs (Adams et al. 2007; Andersen et al. 2006; de Vries et al. 2008; de Vries et al. 2006; Gift et al. 2008; Roberts et al. 2007; Welte et al. 2000). Welte et al. (2000), in an early dynamic modeling cost-effectiveness study of chlamydia screening, found annual provider-based screening of females aged 15–24 to be cost saving, given a very high screening compliance rate, a moderately high partner treatment rate, and relatively high PID risk (0.25), PID hospitalization rate, and hospitalized PID treatment cost. In that study, the program was cost saving under a variety of univariate sensitivity analyses.

Recent *C. trachomatis* cost-effectiveness screening studies have utilized lower screening and partner notification rates based on the results of field studies, reduced the risk of PID associated with untreated infection in response to cohort studies of chlamydial infection, and reduced estimated costs associated with PID, to reflect that the vast majority of cases are managed without hospitalization. Certain studies have also added quality adjusted life years (QALYs) to major outcomes averted (MOAs) to provide an outcome measure that permits comparison of chlamydial interventions with interventions that target other diseases. Studies vary in whether they consider direct costs only (health systems perspective) or include indirect patient costs as well (societal perspective).

A study that simulated population-based *C. trachomatis* screening in Denmark by mailing of test specimens utilized a PID risk of 0.20. Program direct costs decreased steadily over the 10-year simulation, becoming negative in the 10th year (Andersen et al. 2006). The simulation study of provider-based opportunistic screening in the UK, described above (Turner et al. 2006a; Turner et al. 2006b) included a separately published cost-effectiveness component (Adams et al. 2007). The modelers considered only symptomatic PID and decided that a PID risk of 0.10 and hospitalization rate of 6.5% best matched UK PID study results (Simms et al. 2006) and service data. Screening females aged 16–24 or screening both genders aged 16–20 yielded

direct costs per QALY gained compared with no screening of <£20,000. The incremental cost per QALY gained of adding screening of males aged 16–24 to screening of females aged 16–24 was relatively large, yielding direct costs per QALY gained compared with no screening in the £20,000–30,000 range. Overall, applying a UK standard of £20,000–30,000 per QALY gained, the authors considered chlamydia screening to be borderline cost-effective.

Cost-effectiveness dynamic modeling studies that have assessed adding male screening to female screening in schools (Fisman et al. 2008) or adding male screening in high prevalence venues to standard screening of females aged 15–24 years (Gift et al. 2008) yielded very satisfactory cost per QALY gained (Fisman et al. 2008). In general, sensitivity analyses conducted in dynamic modeling cost-effectiveness studies demonstrate low cost-effectiveness as PID rates drop toward 0.01 or as interventions are extended to older age groups (Andersen et al. 2006; Roberts et al. 2007).

20.4.3 Public Health Screening and Partner Treatment Programs

Following is a brief summary of efforts that North American and northern European countries have made to establish national chlamydia screening and partner notification programs.

20.4.3.1 Screening

In 1993, the US Centers for Disease Control and Prevention published "Recommendations for the prevention and management of *Chlamydia trachomatis* infections" (Centers for Disease Control and Prevention 1993). Screening was recommended for all sexually active women less than 20 years of age and for older women who met either (ages 20–24) or both (ages >24) of the additional criteria – inconsistent use of barrier contraception, or new or more than one sex partner during the last 3 months. The Recommendations were justified in part by a pilot project implementing chlamydia screening among attendees in 136 family planning clinics in four states in the northwestern United States. Prevalence decreased from 10.9% in 1988 to 6.8% in the last quarter of 1990 (Britton et al. 1992). Chlamydia screening was also motivated by the apparent success of a gonorrhea prevention program; following a tripling of US gonorrhea rates, rates peaked and then declined impressively subsequent to 1975, just 3 years after nationwide gonorrhea control efforts were implemented (Wasserheit and Aral 1996).

In 2001 the US Preventive Services Task Force recommended chlamydia screening for women <25 years of age (Nelson and Helfand 2001). The Task Force was strongly motivated by a randomized controlled trial that demonstrated a 56% reduction in incidence of PID by screening women selected by a set of risk factors (Scholes et al. 1996). The Task Force did not find convincing evidence that population prevalence rates were decreased as a result of screening. It also pointed out a lack of evidence concerning effectiveness of screening men for chlamydia.

In 1996, the Canadian Task Force on the Periodic Health Examination recommended annual screening of high-risk groups: sexually active women less than 25 years of age; men or women with new or multiple sexual partners during the preceding year; and women who use nonbarrier contraceptive methods (Davies and Wang 1996). Sweden began a program in 1982 to identify asymptomatic infection, and in 1988 passed legislation requiring clinicians to provide free chlamydia testing (Low 2007). However, beyond making free testing available, there is, in fact, no national program in the country; chlamydia control is locally organized, with intensity varying by geographic location (Low 2004).

In England, the National Chlamydia Screening Programme was launched in 2002, with phased implementation (Fenton and Ward 2004). The National Chlamydia Screening Programme targets men and women under 25 years of age and utilizes an opportunistic approach, as does the USA and Canada. An opportunistic screening approach, with screening taking place in health-care settings, rather than a registry-based approach with household screening, was adopted, because the latter was shown to be associated with substantially lower prevalences (Fenton and Ward 2004). The Netherlands, however, is implementing a pilot chlamydia screening project that does in fact utilize a systematic registry-based approach with invitations for testing sent by post (Op de Coul et al. 2007).

One basis for questioning the effectiveness of screening is that countries engaged in chlamydia screening have been experiencing increasing rates of reported chlamydia cases (Fine et al. 2008; Rekart and Brunham 2008; Velicko et al. 2007). However, the modeling studies described previously indicate that achieving decreases in chlamydia prevalence is dependent upon adequate screening coverage. The ability of countries that have implemented screening programs to monitor coverage independently of chlamydia infection rates varies greatly and has contributed to substantial confusion in assessing the effectiveness of these programs.

The UK appears to have the ability to monitor opportunistic screening rates. Unfortunately, the program target to screen 15% of the 15–24 year old population between April 1, 2007 and March 31, 2008 (National Chlamydia Screening Programme 2008) appeared to be aspirational; data suggest that the target was not achieved (White 2008). An analysis of services and outcomes in Uppsala, Sweden, found that, among females who were 15–24 years old between 1984 and 1989, during a follow-up that was up to 10 years, 70.7% were tested for chlamydia at least one time; of those ever tested, almost half (47.8%) were tested only once (Low et al. 2006). An analysis in Sweden evaluating the increases in rates of genital chlamydia that occurred over 10 years nationally reported that approximately 10% of 15–49 year olds were tested for *C trachomatis* in 2006, and that fewer were tested in previous years (Velicko et al. 2007).

Similarly in North America, although there are reports that rates of chlamydia in British Columbia have increased, there is little information about screening coverage; Low has estimated that annual coverage is unlikely to be over 10–20% (Low 2008). In the USA, which may be experiencing a modest decline in chlamydia burden (Datta et al. 2008), opportunistic screening coverage has been monitored in a group of commercial and Medicaid health plans. The chlamydia screening rate

among sexually active female enrollees aged 16–25 years increased from 25.3% in 2000 to 41.6% in 2007, but is now leveling off (Douglas 2008).

20.4.3.2 Partner Notification

Efforts to treat partners of individuals diagnosed with chlamydia are justified for at least two reasons. First, it allows exposed or infected individuals to obtain prompt treatment, hopefully preventing possible sequelae. Second, partner treatment reduces ongoing transmission. The potential effectiveness of such an approach is related to the probability of infection in the exposed partners. Studies have documented a high concordance of infection (68%) in sexual partners (Quinn et al. 1996).

There are several recent excellent reviews of partner notification (Centers for Disease Control and Prevention 2008a; Hogben 2007; Hogben et al. 2007; Trelle et al. 2007). Partner notification has either involved public health professionals notifying partners (provider referral) or required the patient to notify partners (patient- or self-referral) (Hogben et al. 2007). Although the labor-intense provider referral approach is not typically utilized for chlamydia cases in the USA, there is some evidence that the approach is cost-effective (Katz et al. 1988). Evaluations among individuals with chlamydia, gonorrhea, trichomoniasis, or syndromic STDs have found that partner-delivered therapy or another form of expedited partner treatment (EPT, approaches that do not require an intervening clinical encounter with the partner) were associated with a greater number of partners being treated (Golden et al. 2005; Kissinger et al. 2005) and a reduced risk of reinfection with gonorrhea or chlamydia, when compared with simple patient referral methods. Similarly, there is evidence that providing infected patients an informative booklet in addition to relying on the simple patient referral method also increases the number of partners that receive treatment (Kissinger et al. 2006). Recently, the Internet has been utilized for partner notification. However, Internet notification has been evaluated primarily for exposure to syphilis (Hogben 2007).

Policies and approaches to partner notification differ by country. In Europe, only in Sweden and Norway is partner notification compulsory (not surprisingly, it is estimated that in Sweden 76–99% of partners exposed to chlamydia are tested and/or treated) (Arthur et al. 2005). In the USA, laws vary by state. Certain states have laws requiring practitioners to warn persons they know to be at risk for infection with a communicable disease, an STD, or HIV because of exposure to their patients. Many other states have laws permitting but not requiring practitioners to warn persons that they are at risk (i.e., privilege to warn) (Centers for Disease Control and Prevention 2008a). Also, in the USA, partner notification efforts undertaken by health department personnel are closely related to the etiologic agent; in one study, partner notification interviews were conducted with 89% of syphilis, 17% of gonorrhea, and 12% of chlamydia cases (Golden et al. 2003).

In the USA, because of differences in laws or pharmacy regulations, EPT is legally permissible in some states, prohibited in others, and potentially allowable

elsewhere (Hodge et al. 2008). In the UK, partner-delivered therapy is clearly not consistent with Good Medical Practice guidance from the General Medical Council. Although there is support for the practice among those in the genitourinary medicine community (Coyne et al. 2007), such support is clearly not universal (Markos 2008).

20.5 Monitoring Impact of Public Health Interventions

Chlamydial interventions described in the previous section began in Sweden in the early 1980s and somewhat later in the USA. Although evaluations were provided that convinced authorities to launch prevention efforts, adequately monitoring the impact of such efforts on chlamydia prevalence and chlamydia-related sequelae has been challenging.

20.5.1 Tracking Prevalence of C. trachomatis Infection

Case report data, expressed as cases per population (typically 100,000), have not proven useful in tracking changes in chlamydia burden, since increased case rates represent expanded efforts at detecting asymptomatic infection rather than disease trends. In the USA, the rate of reported chlamydia has increased every year in all regions (Centers for Disease Control and Prevention 2008b). Furthermore, since screening has been performed primarily among females, the rate of reported infection has appeared substantially greater among females than among males (Centers for Disease Control and Prevention 2008b; Hiltunen-Back et al. 2003; Klovstad and Aavitsland 2009), although prevalence by gender, when measured by a population survey, is actually rather comparable (Datta et al. 2007).

Monitoring chlamydia test positivity is another approach to track chlamydia burden. In the United States, such an approach provides positivity data in all 50 states, stratified by clinic type (i.e., family planning clinics, prenatal care clinics, STD clinics) (Centers for Disease Control and Prevention 2009). Such data have been useful for evaluating screening strategies (La Montagne et al. 2004), and for targeting resources to sites and populations with higher disease burden (Gorgos et al. 2008). Median state-specific positivity among 15–24 year old women tested in family planning clinics has increased steadily from 5.2% in 2000 to 6.9% in 2007 (Centers for Disease Control and Prevention 2008b). However, annual analyses may not include the same individual clinics consistently, and screening criteria employed by the clinics may change over time. Because of such factors, and also because clinic populations themselves may change, some authors have pointed out the marked bias that may be associated with such assessments (Miller 2008). Similarly, in Norway, the proportion of tests for chlamydia that were positive increased from 4.1% in 1993 to 7.7% in 2006. However, the extent to which this represents a true increase in disease burden is not clear, since the case definition had changed, there was increased use of NAATs, and perhaps increased testing among high-risk groups (Klovstad and Aavitsland 2009).

A more methodologically appropriate way to track chlamydia would be to assess prevalence in a defined population, accessed in a consistent fashion. In the United States, the National Health and Nutrition Examination Survey (NHANES) allows tracking of chlamydia in just such a manner. Analysis of data from 1999 to 2006 has provided strong evidence that chlamydia burden has not been increasing, and may actually be decreasing; the overall prevalence of *C. trachomatis* among 14–39 year olds was: 1999–2000, 2.6% (95%, CI 2.0–3.5%); 2001–2002, 1.8%, (1.3–2.6%); 2003–2004, 2.1% (1.5–2.9%); and 2005–2006, 1.4% (0.9–1.9%). Furthermore, statistically significant decreases were seen among females 14–19 years of age, a group targeted for screening (Datta et al. 2008). In addition, in the USA, prevalence has been tracked among National Job Program entrants, economically disadvantaged young people 16–24 years of age, who have met consistent criteria for participation. From 1990 to 1997, chlamydia prevalence among female entrants decreased from 14.9 to 10.0% (Mertz et al. 2001); a more modest decline was seen from 1998 to 2004, 11.7–10.3% (Joesof and Mosure 2006).

The UK is one of the few other countries that have population-based prevalence data on chlamydia. The 2000 National Survey of Sexual Attitudes and Lifestyles (NATSAL 2000) found that *C trachomatis* prevalence was 2.2% (95%, CI 1.5–3.2%) among men and 1.5% (95%, CI 1.11–2.14%) among women; prevalence was greater among young males and females (Fenton et al. 2001). The results of the next evaluation, planned for 2010, will be of great interest, since the National Chlamydia Screening Program was implemented in England in 2002 (Fenton and Ward 2004).

20.5.2 Tracking Complications and Sequelae

20.5.2.1 Pelvic Inflammatory Disease

The diagnosis of PID is clinical and correlation with salpingitis is imperfect; salpingitis was identified in 65 and 46% of PID cases in two studies utilizing specific diagnostic criteria (Chaparro et al. 1978; Jacobson and Westrom 1969). Doxanakis (STI 2008) found in the same clinical setting great clinician variability in the frequency of PID diagnosis (Doxanakis et al. 2008). Furthermore, the criteria recommended in the US Centers for Disease Control and Prevention STD Treatment Guidelines for identifying cases that warrant PID treatment became increasingly sensitive and less specific in the last three versions (Centers for Disease Control and Prevention 1998, 2002, 2006).

These challenges not withstanding, rates of PID in several countries have been decreasing. In Sweden, rates of PID hospitalizations were stable or increased from the 1970s to the early 1980s. Subsequently, from 1987 to 1997, rates fell sharply; during that time endemic *N. gonorrhoeae* was nearly eliminated, and cases of PID were increasingly managed in outpatient settings (Kamwendo et al. 1998). Similarly, during that same time, community rates of PID fell sharply in Lund, Sweden (Westrom et al. 1992). In the United States, where approximately 91% of

PID cases are managed in ambulatory settings (Sutton et al. 2005), rates of hospitalization fell by 68% between 1985 and 2001 and ambulatory visits for PID decreased by 47–68%, depending on the data source utilized (Sutton et al. 2005).

These declines in PID are encouraging. Nevertheless, additional research is clearly needed to identify a reliable surveillance definition that is not so affected by clinician subjectivity and that accurately identifies chlamydia-associated cases.

20.5.2.2 Ectopic Pregnancy

Assessing trends in chlamydia-associated outcomes of ectopic pregnancy or infertility is no easier or more certain. Regardless, incidence of ectopic pregnancy increased substantially in a number of nations, including the USA, during the 1970s and 1980s (Centers for Disease Control and Prevention 1995; Coste et al. 1994; Makinen et al. 1998). More recently, declines in rates of ectopic pregnancy have been noted in some places, but not others (Coste et al. 2004). Sweden experienced a 21% decrease among women $\geq$25 years from 1990–1994 to 1997 (Kamwendo et al. 2000). An ecologic evaluation from 1985 to 1995 in a county in Sweden (Egger et al. 1998) found that falling rates of chlamydia were associated with declines in ectopic pregnancy. However, such an association was not found in Australia, where between 1992 and 2001 hospitalizations for ectopic pregnancy remained constant, while case reports of chlamydia increased fourfold (Chen et al. 2005). Evaluations in the United States have only monitored hospitalizations, which is an increasingly less relevant approach since most ectopic pregnancies are managed as outpatients (Zane et al. 2002).

20.5.2.3 Infertility

Tracking the prevalence of chlamydia-related infertility is also problematic. In fact, some have questioned the estimates of the contribution chlamydial infection makes to overall infertility, highlighting the limitations of the supporting evidence (Wallace et al. 2008). Registry data from some Scandinavian countries have allowed evaluations linking chlamydia case reports or test results with birth and care records, but the results have not been very helpful, since it is not clear how infertility rates following *treated chlamydial infections* relate to chlamydia control activities.

Data available from women in the USA, who have received infertility services, provide some additional information about infertility trends and tubal factor infertility. In 2006, 18% of couples utilizing assisted reproductive technology (ART) to conceive had tubal factor infertility (Macaluso et al. 2008) compared with 33% in 1996 (Macaluso, personal communication). Although such findings suggest that the prevalence of tubal factor infertility is decreasing – consistent with chlamydia control efforts – other factors may well be responsible.

20.6 Challenges

The discipline of epidemiology and the closely related discipline of public health are at an important juncture with respect to understanding and addressing the burden of *C. trachomatis* infection in populations. The distribution of *C. trachomatis* infections is well understood. Accurate, effective, and inexpensive tests and antibiotics are available to detect and treat these infections. The effectiveness of these tools to reduce progression to PID by proactive screening of women, as demonstrated in randomized controlled trials (RCTs) (Scholes et al. 1996), has motivated certain authoritative groups and governments to recommend and institute national screening programs. In parallel, advances in infectious disease epidemiology and simulation modeling have provided powerful tools to better understand the dynamics of *C. trachomatis* transmission through populations and the effects of interventions. With important exceptions, the results of studies that have utilized these tools have encouraged public health workers to expect that the primary prevention benefits of *C. trachomatis* screening programs are a cost-effective extension of the secondary prevention benefits demonstrated by the RCTs.

A number of serious challenges need to be addressed to ensure continuation of the foregoing progress. A particularly pressing challenge is to develop diagnostic methods and population-based surveillance systems to track PID and its sequelae. A second critical challenge is to improve our ability to monitor screening coverage and success rates in notifying sex partners of individuals treated for chlamydial infection. This challenge is especially great in countries such as the USA with highly heterogeneous health-care delivery systems and limited population level information concerning individuals. At least as urgent is the need to develop field evaluations that incorporate the improved measures of burden and intensity of interventions.

The large literature on the immunology of *C. trachomatis* infection, developed largely with a focus on vaccine development, was beyond the scope of this chapter. The transmission modeling studies reviewed in this chapter assumed rapid loss of any immunity following chlamydial infection. However, concerns have been raised about an increase in transmission due to a reduction in herd immunity and an increased reinfection rate following screening (Brunham et al. 2005). This chapter includes a brief mention of dynamic transmission models of chlamydial infection that demonstrate the possibility of such an effect (Brunham et al. 2005). Thus, a final challenge is to integrate the work on vaccine development, the epidemiology of *C. trachomatis* infections, and early diagnosis and treatment interventions.

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