on the regulation of gene expression, protein localization, the type III secretion system, the roles of CD4+ and CD8+ T lymphocytes in the host response, and T lymphocyte trafficking.

The chlamydial heat-shock protein, which shares antigenic epitopes with similar proteins of other bacteria and with human heat-shock protein, may sensitize the host, and repeated infections may cause host cell damage. Persistent or recurrent chlamydial infections are associated with fibrosis, scarring, and complications following simple epithelial infections. A common endpoint of these late consequences is scarring of mucous membranes. Genital complications can lead to pelvic inflammatory disease (PID) and its late consequences of infertility, ectopic pregnancy, and chronic pelvic pain, while ocular infections may lead to blinding trachoma. High levels of antibody to human heat-shock protein have been associated with tubal factor infertility and ectopic pregnancy. Without adequate therapy, chlamydial infections may persist for several years, although symptoms—if present—usually abate.

The pathogenic mechanisms of *C. pneumoniae* have yet to be completely elucidated. The same is true for *C. psittaci,* except that this agent infects cells very efficiently and causes disease that may reflect direct cytopathic effects.

CHLAMYDIA TRACHOMATIS INFECTIONS

GENITAL INFECTIONS

Spectrum Although chlamydiae cause a number of human diseases, localized lower genital tract infections caused by *C. trachomatis* and the sequelae of such infections are the most important in terms of medical and economic impact. Oculogenital infections due to *C. trachomatis* serovars D–K are transmitted during sexual contact or from mother to baby during childbirth and are associated with many syndromes, including cervicitis, salpingitis, acute urethral syndrome, endometritis, ectopic pregnancy, infertility, and PID in female patients; urethritis, proctitis, and epididymitis in male patients; and conjunctivitis and pneumonia in infants. Women bear the greatest burden of morbidity because of the serious sequelae of these infections. Untreated infections lead to PID, and multiple episodes of PID can lead to tubal factor infertility and chronic pelvic pain. Studies estimate that up to 80–90% of women and >50% of men with *C. trachomatis* genital infections lack symptoms; other patients have very mild symptoms. Thus a large reservoir of infected persons continues to transmit infection to sexual partners.

As their designations reflect, the LGV serovars (L_1, L_2, and L_3) cause LGV, an invasive sexually transmitted disease (STD) characterized by acute lymphadenitis with bubo formation and/or acute hemorrhagic proctitis (see "Lymphogranuloma Venereum," below).

Epidemiology *C. trachomatis* genital infections are global in distribution. The World Health Organization (WHO) estimated in 2008 that >106.4 million cases occur annually worldwide. This figure makes chlamydial infection the most prevalent sexually transmitted bacterial infection in the world. The associated morbidity is substantial, and economic costs are high.

In the United States, chlamydial infections are the most commonly reported of all infectious diseases. In 2012, 1.3 million cases were reported to the U.S. Centers for Disease Control and Prevention (CDC); however, the CDC estimates that 2–3 million new cases occur per year, with substantial underreporting due to lack of screening in some populations. Rates of infection have increased every year; higher rates among women than among men reflect the focus on expansion of screening programs for women during the past 20 years, the use of increasingly sensitive diagnostic tests, an increased emphasis on case reporting, and improvements in the information systems used for reporting. The CDC and other professional organizations recommend annual screening of all sexually active women ≤25 years of age as well as rescreening of previously infected individuals at 3 months. Young women have the highest infection rates; in 2012, the figures were 3416.5 and 3722.5 cases per 100,000 population at 15–19 and 20–24 years of age, respectively. Age-specific rates among men, while much lower than those among women, were highest in the 20- to 24-year-old age group, at 1343.3 cases per 100,000. In 2012, rates increased for all racial and ethnic groups, with the highest rates among African Americans. For example, the rate of chlamydial infection among African-American girls 15–19 years of age was 7507.1 cases per 100,000—almost six times the rate among Caucasian girls in the same age group (1301.5/100,000). The rate among African-American women 20–24 years old was 4.8 times the rate among Caucasian women in the same age group. Similar racial disparities in reported rates of chlamydial infection exist among men. For boys 15–19 years of age, the rate among African Americans was 11.1 times the rate among Caucasians. The rate among Native Americans/Alaska Natives was more than four times the rate among Caucasians (648.3), and the rate among Latinos (383.6) was two times higher than that among Caucasians. These disparities are important reflections of health inequities in the United States.

The above statistics are based on case reporting. Studies based on screening surveys estimate that the U.S. prevalence of *C. trachomatis* cervical infection is 5% among asymptomatic female college students and prenatal patients, >10% among women seen in family planning clinics, and >20% among women seen in STD clinics. The prevalence of genital *C. trachomatis* infections varies substantially by geographic locale, with the highest rates in the southeastern United States. However, asymptomatic infections have been detected in >8–10% of young female military recruits from all parts of the country. The prevalence of *C. trachomatis* in the cervix of pregnant women is 5–10 times higher than that of *Neisseria gonorrhoeae*. The prevalence of genital infection with either agent is highest among women who are between the ages of 18 and 24, single, and non-Caucasian (e.g., African-American, Latina, Asian, Pacific Islander). Infections recur frequently in these same risk groups and are often acquired from untreated sexual partners. The use of oral contraception and the presence of cervical ectopy also confer an increased risk. The proportion of infections that are asymptomatic appears to be higher for *C. trachomatis* than for *N. gonorrhoeae*, and symptomatic *C. trachomatis* infections are clinically less severe. Mild or asymptomatic *C. trachomatis* infections of the fallopian tubes nonetheless cause ongoing tubal damage and infertility. The costs of *C. trachomatis* infections and their complications to the U.S. health care system have recently been estimated to exceed $516.7 million annually.

Clinical Manifestations • ***NONGONOCOCCAL AND POSTGONOCOCCAL URETHRITIS***

C. trachomatis is the most common cause of nongonococcal urethritis (NGU) and postgonococcal urethritis (PGU). The designation *PGU* refers to NGU developing in men 2–3 weeks after treatment of gonococcal urethritis with single doses of agents such as penicillin or cephalosporins, which lack antimicrobial activity against chlamydiae. Since current treatment regimens for gonorrhea have evolved and now include combination therapy with tetracycline, doxycycline, or azithromycin—all of which are effective against concomitant chlamydial infection—both the incidence of PGU and the causative role of *C. trachomatis* in this syndrome have declined.

In the United States, most of the estimated 2 million cases of acute urethritis are NGU, and *C. trachomatis* is implicated in 30–50% of these cases. The cause of most of the remaining cases of NGU is uncertain, but recent evidence suggests that *Ureaplasma urealyticum, Mycoplasma genitalium, Trichomonas vaginalis*, and herpes simplex virus (HSV) cause some cases. The rate of involvement of *C. trachomatis* in urethral infection ranges from 3–7% among asymptomatic men to 15–20% among symptomatic men attending STD clinics. A multisite study of men in Baltimore, Seattle, Denver, and San Francisco reported an overall chlamydial prevalence of 7% in urine samples assessed by nucleic acid amplification tests (NAATs). As in women, infection in men is age related, with young age as the greatest risk factor for chlamydial urethritis. The prevalence among men is highest at 20–24 years of age. In STD clinics, urethritis is usually less prevalent among men who have sex with men (MSM) than among heterosexual men and is almost always much more common among African-American men than among Caucasian men. One study reported prevalences of 19% and 9% among nonwhite and white heterosexual men, respectively.