Introduction: The Natural History and Immunobiology of *Chlamydia trachomatis* Genital Infection and Implications for Chlamydia Control

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Chlamydia trachomatis genital infection is the most common bacterial sexually transmitted infection worldwide [1], and an estimated 3 million cases occur each year in the United States [2]. In women, *C. trachomatis* genital infection can lead to serious complications, including pelvic inflammatory disease, ectopic pregnancy, tubal infertility, and chronic pelvic pain [3]. Because of this, many countries have implemented chlamydia control efforts that have primarily emphasized enhanced detection and treatment of asymptomatic infection in young women and have achieved varying degrees of screening coverage [4–6]. Early reports from regions that were the first to implement chlamydia control activities (during the late 1980s and early 1990s) revealed that both chlamydia case rates and rates of associated complications were decreasing [7–9]. However, since the mid-1990s, in virtually all countries with substantial investment in chlamydia control, the number of *C. trachomatis* infection case reports has been increasing in the setting of ongoing control efforts [10–12]. In the United States, regions that had initially shown decreases in chlamydia test positivity (prevalence of chlamydia among tested women) have since shown stable or increasing test positivity [11]. Although there are limitations in using these types of surveillance data to assess burden of disease [13], the substantial and continuing decreases in rates of *C. trachomatis* infection that were expected after implementation of control programs have not been observed [14], and many chlamydia control programs are currently at a crossroads.

One possible contributing factor to the observed increase in reported chlamydia case rates is an increase in the rate of repeat infections. Several clinic-based studies have demonstrated high rates of repeat infection during the months after an initial treated infection [15–17]. Successful treatment of *C. trachomatis* infection detected through screening can eliminate risk of subsequent tubal inflammation and damage caused by the detected infection. However, this may also leave the treated woman susceptible to a new, repeat infection, with its own attendant risks. In light of these considerations, questions must be raised about chlamydia control programs based on detection of prevalent asymptomatic *C. trachomatis* infection. For example, at the time that an asymptomatic infection is detected and treated in a typical screening program, what is the remaining risk for subsequent sequelae? In other words, what is the likelihood that new tubal inflammation and damage would have been elicited if the infection were not treated? Is the risk for sequelae associated with a repeat infection inherently greater than the risk associated with a persistent initial infection? In addition, what determines susceptibility to repeat infection? Does protective immunity develop during an initial infection? If so, when? Does treatment abrogate the development of protective immunity in women who receive a diagnosis of and treatment for chlamydia as the result of current screening programs? Answering these questions requires knowledge of the natural history of *C. trachomatis* infection, and the answers have important implications for chlamydia control programs.

On a population level, the way that chlamydia control strategies intersect with the natural history of *C. trachomatis* infection is a critical issue. Brunham et al [18, 19] hypothesized that chlamydia control programs have shortened the mean duration of *C. trachomatis* infection through early detection and treatment and that this has in turn led to population-

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wide reductions in protective immunity and a marked increase in the number of repeat infections. Whether this "arrested immunity" hypothesis is a reasonable explanation for observed epidemiologic trends has been debated [13, 20]. Nonetheless, the hypothesis underscores the importance of gaining a better understanding of the interplay between *C. trachomatis* immunobiology and chlamydia control strategies. Important areas to consider include the nature and timing of immune responses leading to *C. trachomatis* infection clearance, pathogenesis, and protective immunity and how these responses might be affected by chlamydia control strategies.

In April 2008, the Division of STD Prevention of the Centers for Disease Control and Prevention held the Chlamydia Immunology and Control Expert Advisory Meeting to foster a dialogue among *C. trachomatis* basic scientists, clinical researchers, and epidemiologists to explore these issues. The objectives of the meeting were (1) to identify the key questions related to *C. trachomatis* natural history, pathogenesis, and immunobiology that have implications for control of *C. trachomatis* infection and its sequelae; (2) to review and assess how existing data shed light on these key questions, especially with respect to relevance for chlamydia control; and (3) to delineate the most important remaining gaps in knowledge and the research approaches needed to address these gaps. Toward this end, working groups on the following 3 topics were established: clearance of infection, pathogenesis and sequelae, and protective immunity. Experts in these working groups formulated key questions and developed background materials synthesizing the most critical and illustrative evidence to address the key questions. The focus was on understanding human genital tract *C. trachomatis* infection and its reproductive sequelae in women; however, supporting data from in vitro studies, animal models, and human studies including male individuals, as well as studies of ocular *C. trachomatis* infection, were reviewed if they provided insight.

This supplement to *The Journal of Infectious Diseases* contains 9 background articles on *C. trachomatis* immunobiology and implications for chlamydia control programs and a concluding summary and synthesis. The background articles are organized on the basis of the 3 following general topics: clearance and persistence of infection, pathogenesis and sequelae, and protective immunity. The articles are based on the key questions developed by the working groups at the April 2008 meeting and the evidence available for addressing them. Among the articles about clearance and persistence, Wyrick [21] describes the chlamydial developmental cycle and provides an overview of in vitro data related to *C. trachomatis* persistence. Miyairi et al [22] review animal models, and Geisler [23] examines human data on the duration of untreated *C. trachomatis* infection and the immunologic factors associated with resolution of infection. Among the articles about pathogenesis and sequelae, Darville and Hiltke [24] review in vitro, animal, and human data on *C. trachomatis* pathogenesis, including which inflammatory and immune responses occur during initial and repeat chlamydial infections and how pathogenesis may be affected by host factors. Byrne [25] describes potential paradigms for defining *C. trachomatis* strains and virulence attributes that may predict prevalence of infection and disease severity. Haggerty et al [26] describe epidemiologic evidence addressing the risk of sequelae after untreated *C. trachomatis* genital infection and whether the risk of sequelae is greater after repeat infection. Gottlieb et al [27] assess the extent to which detection and treatment of asymptomatic prevalent *C. trachomatis* infection reduces the risk of subsequent sequelae. Among the articles about protective immunity, Rank and Whittum-Hudson [28] review evidence from animal models on the development of protective immunity to chlamydial infection and the underlying immune effector mechanisms. Finally, Batteiger et al [29] review evidence from human studies on protective immunity to *C. trachomatis* genital infection. The supplement concludes with a summary and synthesis of the background articles and implications for chlamydia control programs [30].

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