Immunity to *Chlamydia trachomatis*

Robert C. Brunham
BC Centre for Disease Control, University of British Columbia, Vancouver, Canada

*(See the major article by Geisler et al on pages 1850–6.)*

**Keywords.** chlamydia; immunity; epidemiology.

In this issue of the Journal, Geisler and colleagues [1] report convincing epidemiological evidence that cervical infection with *Chlamydia trachomatis* produces immunity in at least a subset of naturally infected women. Over a 2.5-year period, they enrolled 243 *C. trachomatis*-infected women in a treatment study. A standardized nucleic acid amplification test with high predictive value was used to document all infections. Two hundred women were seen in follow-up and constituted all infections. Two hundred women were enrolled, compared with only 2 (5%) of persistently positive women were reinfeated when seen in follow-up on average 183 days post-treatment. Strikingly, 31 (20%) of the 156 (17%) women were reinfected when seen in follow-up for treatment, 44 (22%) had spontaneously cleared infection. All women were treated with azithromycin 1 gm orally and scheduled for a subsequent visit approximately 6 months later. Thirty-three (17%) women were reinfected when seen in follow-up on average 183 days post-treatment. Strikingly, 31 (20%) of the 156 persistently positive women were reinfected, compared with only 2 (5%) of 44 women who spontaneously cleared infection (*P* = .02). This difference remained significant after controlling for age and treatment status of the reported sexual partner.

This study provides the most convincing evidence yet that natural infection in humans engenders protective immunity. That said, immunity to *C. trachomatis* is clearly complex, and the mechanisms underlying immunity were not studied by Geisler et al. *C. trachomatis* is well suited for producing incomplete immunity. Its intracellular replication within epithelial cells shields it from antibody and T-cell attack. The replication cycle senses extracellular cytokines, and low concentrations of interferon gamma induce an aberrant, poorly replicating form of the organism that downregulates several of the protective antigens. Its major surface proteins demonstrate antigenic variation, either through allelic variation of the major outer membrane protein or phase variation of the polymorphic membrane proteins. In aggregate, these mechanisms probably delay the acquisition of immunity.

Immunity in humans appears to take a long time to acquire. Molano et al [2] demonstrated that 50% of women continue to shed the organism 1 year after infection is first documented, and 5%–10% continue shedding even 3 years later. In terms of immune effector mechanisms, CD4 T cells secreting interferon gamma correlate with immunity, and human immunodeficiency virus infection interferes with the acquisition of immunity [3, 4]. Local immunoglobulin A antibodies correlate with reduced shedding of the organism [5].

Although immunity in rodent models of *Chlamydia muridarum* infection is rapidly acquired, this model has yielded some of the most useful insights into human *C. trachomatis* immune biology. In the murine model, CD4 T cells secreting interferon gamma correlate with clearance of primary infection, and CD4 T cells or antibody correlates with resistance to reinfection [6]. Why these differences in immune defenses occur between primary infection and reinfection is not yet elucidated, and how antibody mediates resistance is not yet clear. Antibody-mediated immunity depends on receptors to the constant region fragment (Fc portion) and is directed to surface molecules on the organism, suggesting a role for antibody in amplifying antigen-presenting cell functions and T-cell immunity [7, 8].

What are the implications of the Geisler et al study? First, the epidemiological model that Geisler et al studied is ideally suited to lead to an investigation of the basis for human *C. trachomatis* immunity. Finding correlates of immunity is essential to vaccine development and evaluation. There exists an opportunity for the Chlamydia research community to organize their efforts to elucidate correlates of protection using standardized immune assays that are...
built on the immune mechanisms already defined in mice. The challenges will be to develop standardized human cellular and humoral immune assays and to coordinate their application at multiple study sites.

Second, it should be possible to test the arrested immunity hypothesis [9, 10] using this epidemiological study design. As noted by Geisler et al, their findings of immunity among women who spontaneously clear infection but not among persistently infected women is consistent with the arrested immunity hypothesis. The arrested immunity hypothesis is based on the notion that the current seek and treat Chlamydia control program is shortening the average duration of infection and that Chlamydia immunity is dependent on the duration of infection. It should be possible to infer epidemiologically the duration of infection by determining the time of first exposure to the source sexual partner in these studies. The arrested immunity hypothesis predicts that those who spontaneously cease shedding will have been infected longer. It may even be possible to immunophenotype the immune response and develop time-dependent immune correlates of infection. The arrested immunity hypothesis also posits that antibiotic treatment interrupts the expansion and memory effector phases of the protective immune response. This interruption has already been demonstrated in the murine models of C. muridarum infection [11] and has been well characterized immunologically in murine listeriosis [12]. Thus, it should be possible to demonstrate that treatment is more likely quantitatively or qualitatively to alter the immune response in persistently infected women, as compared with women who spontaneously clear infection. These and other questions can be answered through high quality clinical investigations using the epidemiological approaches pioneered by Geisler et al.

The Geisler et al. findings also have broader implications. As is becoming apparent to most public health experts, a vaccine will be essential to achieving control of sexually transmitted C. trachomatis infection. Vaccine research has identified key Chlamydia B-cell and T-cell antigens that could form the basis of a subunit vaccine [13–15]. Critical challenges remain, including vaccine delivery systems and adjuvant systems that boost protective immune responses while avoiding pathological immune responses. It is also apparent that vaccine immunity will need to outperform natural immunity, but that should be possible because infection immunity is attenuated by the sophisticated immune evasion mechanisms exploited by Chlamydia that a vaccine will not need to contend with. Thanks to Geisler et al, we may soon have biomarkers for correlates of protection, accelerating the opportunities for vaccine evaluation. With collaborative global efforts, it seems possible to imagine a Chlamydia vaccine soon coming to human trial, the first time in nearly 50 years.

Note

Potential conflict of interest. R. C. B. reports receiving research and development funding from the National Institutes of Health and Prevent Inc for the development of a C. trachomatis vaccine.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References