Time to rethink the expectations for a chlamydial vaccine

Genital *Chlamydia trachomatis* infections are the most common bacterial sexually transmitted diseases worldwide, with more than 90 million new cases, mostly asymptomatic, occurring each year. The rate of infection continues to rise despite the ready availability of antibiotic therapy. Infection is most common in the young (15–29 years old), with the disease sequelae disproportionately affecting women. Indeed, the capacity to diagnose and treat at the early stage of infection, through sensitive nucleic acid amplification tests and effective single doses of azithromycin, could potentially interfere with the development of natural immunity and thus actually contribute to the increased incidence of infection (the arrested-immunity hypothesis[1]). Given the failure of antibiotics to halt this "epidemic," most investigators have concluded that a vaccine is the only way to control the spread of infection. But what characteristics must a vaccine possess to be acceptable? Do we need to achieve sterilizing immunity in order to make a difference?

Chlamydia vaccine research has relied heavily on the mouse model of infection, using *C. muridarum*, or in some cases, human serovars of *C. trachomatis*. Like all animal models, it has limitations, but it has been used extensively to identify new chlamydial antigens, to test adjuvants and delivery systems, to compare routes of immunization, and to define the immune mechanisms required for resolution of infection.[2–9] Several important lessons can be learned from these studies. First, the only vaccine approach that comes close to eliciting sterilizing immunity, as defined by vaginal shedding of *Chlamydia*, is a prior infection with the same chlamydial strain. However, this subsequently results in severe upper-tract pathology and is therefore unacceptable. Second, most studies, despite using different adjuvants, antigens, and delivery routes, have resulted in only a modest reduction in shedding or shortening of the normal 21- to 25-day duration of infection by 3–6 days. Third, the majority of the studies did not investigate protection against upper-tract pathology as the end point. We believe that such protection is in fact the most important goal. Recent studies in our laboratory using the mouse model have shown that immunization with combinations of novel antigens, although resulting in only a modest reduction in infectious burden in the lower genital tract (similar to the findings in most other reports), did confer significant protection against upper-reproductive-tract inflammation.

The data from animal trials may require us to re-evaluate what we need from a human chlamydial vaccine if it is to have a major effect on the chlamydia epidemic, at least in the near future. If the induction of sterilizing immunity is not possible, because of the nature of the pathogen, would a vaccine that reduces the magnitude and duration of acute infection be beneficial and acceptable at a population level? A recent modeling study[10] suggests that the answer is yes. A vaccine that even moderately reduces the likelihood of transmission can be highly beneficial. Similarly, vaccines that reduce the peak load and/or duration of infection in infected individuals can also have a major impact on transmission at the population level. If either of these criteria can be achieved, and if vaccination could also prevent ascending infection and subsequent inflammation, then such a vaccine could have a major impact on the chlamydia epidemic. For a pathogen such as *Chlamydia*, with which the consequences of acute infection are relatively minor but the long-term consequences impose a major and increasing health burden, is the goal of a vaccine that elicits sterilizing immunity too high? Perhaps we should we aim for a more realistic goal of a vaccine that limits the magnitude and duration of infection and reduces or eliminates upper-tract pathology and thus still has the potential to substantially mitigate chlamydia epidemics.

Kenneth W Beagley, Associate Editor
Peter Timms
Joseph Debattista
David P Wilson

1. Brunham, R.C. & Rekart, M.L. The arrested immunity hypothesis and the epidemiology of chlamydia control. *Sex. Transm. Dis.* **35**, 53–54 (2008).
2. Berry, L.J. *et al*. Transcutaneous immunization with combined cholera toxin and CpG adjuvant protects against *Chlamydia muridarum* genital tract infection. *Infect. Immun.* **72**, 1019–1028 (2004).
3. Eko, F.O. *et al*. A novel recombinant multisubunit vaccine against Chlamydia. *J. Immunol.* **173**, 3375–3382 (2004).
4. Pal, S. *et al*. Immunization with the *Chlamydia trachomatis* major outer membrane protein, using adjuvants developed for human vaccines, can induce partial protection in a mouse model against a genital challenge. *Vaccine* **24**, 766–775 (2006).
5. Crane, D.D. *et al*. *Chlamydia trachomatis* polymorphic membrane protein D is a species-common pan-neutralizing antigen. *Proc. Natl. Acad. Sci. USA* **103**, 1894–1899 (2006).
6. Murphey, C. *et al*. The protective efficacy of chlamydial protease-like activity factor vaccination is dependent upon CD4+ T cells. *Cell. Immunol.* **242**, 110–117 (2006).
7. McNeilly, C.L. *et al*. Expression library immunization confers partial protection against *Chlamydia muridarum* genital infection. *Vaccine* **25**, 2643–2655 (2007).
8. He, Q. *et al*. Live-attenuated influenza viruses as delivery vectors for Chlamydia vaccines. *Immunology* **122**, 28–37 (2007).
9. Barker, C.J. *et al*. In silico identification and in vivo analysis of a novel T-cell antigen from Chlamydia, NrdB. *Vaccine* **26**, 1285–1296 (2008).
10. Gray, R.T. *et al*. Modeling the impact of potential vaccines on sexually transmitted Chlamydia epidemics. *J. Infect. Dis.*, in press.