Chapter 7


Chlamydia Vaccine Development

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Abstract

The search for a safe and efficacious human chlamydial vaccine has been ongoing for more than 5 decades. Unfortunately, the dream has yet to be realized. However, much progress has been made in defining the immunologic requirements of a potentially efficacious vaccine, which involve the induction of a strong CD4 T cell-driven Th1 response, as well as an accessory antibody response that is vital for a rapid and robust memory response to reinfections. While a subunit vaccine is currently preferred to the whole organism, the vaccine antigen(s) may be a single or a multisubunit, provided it furnishes ample T and B cell epitopes to induce adequate protective immune responses without immunopathogenic responses. In addition, any subunit vaccine prospect would require a delivery vehicle and method that can together produce an effective immunomodulation to both boost the protective immunity and target immune effectors to the mucosal site of infection. Furthermore, a vaccine that confers broadly specific and long-term protective immunity against both chlamydial infection and disease is the ultimate goal; however, a vaccine that prevents only the development of serious complications (e.g. blinding trachoma, pelvic inflammatory disease, ectopic pregnancy, infertility and pneumonia) could be an acceptable short-term goal.

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Need for a Chlamydia Vaccine

Members of the major clinically relevant bacterial species of the genus Chlamydia cause ocular, genital and respiratory infections as pathogens that infect only humans (e.g. Chlamydia trachomatis and C. pneumoniae), as zoonotic pathogens (e.g. C. psittaci) or as veterinary pathogens (e.g. C. pecorum and C. abortus). However, all Chlamydia species have a similar developmental cycle, comprising two prominent morphologically distinct forms, the infectious elementary body (EB) form and an obligate intracellular, noninfectious and vegetative form called the reticulate body (RB; see Introduction to this book for details on the developmental cycle). The public health significance of chlamydial infections is underscored by the huge socioeconomic bur-
den of the ocular, genital and respiratory diseases, as well as the economic losses in the veterinary industry. Human ocular infections by serovars A, B, Ba and C of *C. trachomatis* cause trachoma, the world’s most common preventable blinding disease, essentially an epidemic in several developing nations in Africa, South East Asia and the Middle East. An estimated 150 million people are infected worldwide, of which 6 million are visually impaired or irreversibly blinded [1]. Human genital chlamydial infections and the clinical outcomes account for more than 90 of the 500 million annual new sexually transmitted diseases (STDs) worldwide, thus ranking as the most common bacterial cause of STD [2, 3]; the USA alone spends over USD 3 billion annually on an estimated 4 million reported clinical cases of genital chlamydial infections [4, 5]. In addition to self-limiting urethritis in both males and females, cervicitis in women, and epididymitis and proctitis in men, pelvic inflammatory disease and tubal factor infertility are major complications of female genital chlamydial infection, occurring in approximately 40 and 10% of untreated infections, respectively, and constituting an enormous morbidity and socioeconomic burden [6–9]. Infants who are infected during birth by genitally infected mothers may develop conjunctivitis and respiratory disease that progress to pneumonia. A joint disease called Reiter’s syndrome is also a complication of genital chlamydial infection. Finally, reports suggesting that genital chlamydial infection may be rising in some populations [5, 10, 11] and could predispose to HIV-related AIDS [11–18] and human papilloma virus-associated cervical dysplasia have heightened these concerns [3] and the urgency to develop preventive measures. Infections caused by *C. pneumoniae* are rampart in the human population, with approximately over 60% of most American, European and Asian societies being exposed. *C. pneumoniae* infections cause mild to sublethal acute respiratory diseases, such as pharyngitis and bronchitis, and are considered to be responsible for over 10% of community-acquired pneumonia [19]. Initial claims of a possible link between *C. pneumoniae* infection, atherosclerosis and some age-related chronic and autoimmune diseases on the basis of correlative data [20–22] have yet to be substantiated clinically and experimentally. Infections by the zoonotic *C. psittaci* produce an assortment of clinical manifestations which, in animals and birds, are psittacosis, hepatitis, mastitis, conjunctivitis, pneumonia, abortions and diarrhea; in humans, it is a psittacosis-like disease that may, in rare cases, become systemic or fatal pneumonia [23]. *C. psittaci* is thus an occupational hazard for workers in the poultry and farming industry and in persons exposed to infected avian species [24]. Finally, *C. pecorum* causes infectious pneumonitis in domestic animals [25, 26] as a veterinary pathogen.

Considering the magnitude and near epidemic state of ocular, genital and respiratory chlamydial infections in some populations, the continued spread in communities worldwide, and the economic stress on the healthcare system, several prevention and control strategies have been proposed and/or executed. These control and prevention measures include mass screening and treatment, mass antibiotic treatment of at-risk populations, health education programs on prevention methods, and the use of an efficacious vaccine as an immunoprophylaxis and preventive. Interestingly, a number of
the proposed or executed control and prevention measures are now known to be either very challenging to develop, impractical to execute or ineffectual to control the endemcity and spread of chlamydial ocular, genital or respiratory infections in the human population [27–29]. Table 1 summarizes these control and prevention measures, their advantages and limitations. It is important to point out that results from the measures executed so far have led to the current medical opinion that the vaccine option will likely represent the most reliable and cost effective means to achieve the greatest impact [21, 30] for a number of reasons: first, the mass screening and treatment, or mass and targeted population treatment with antibiotics such as azithromycin have not produced the desired long-term result to eliminate chlamydial ocular or genital infections [27, 29]; second, although chlamydial infections are treatable with antibacterial agents if detected early (e.g. use of tetracycline derivatives, especially doxycycline, and the macrolides or azalides including erythromycin and azithromycin [21]), the high proportion of asymptomatic infections often lead to severe and sometimes irreversible complications, usually presenting as the first symptoms of an infection [30, 31]. In addition, it has been reported that a significant proportion of treated infections may lead to persistence [32, 33], casting doubt on the long-term value of certain chemotherapies. Moreover, most other prevention strategies have economic, convenience and acceptance issues. Furthermore, computer modeling has predicted that a partially protective chlamydial vaccine that prevents certain severe sequelae in a vaccination pro-

<table>
<thead>
<tr>
<th>Chlamydial control and prevention measure</th>
<th>Advantages</th>
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<tbody>
<tr>
<td>Targeted and/or mass screening and treatment</td>
<td>Treatment of diagnosed cases to: Prevent transmission and spread of infections Prevent evolution of infections to complications/sequelae (pelvic inflammatory disease, infertility, trachoma, etc.)</td>
</tr>
<tr>
<td>Mass treatment of populations or communities</td>
<td>Indiscriminate mass treatment could: Prevent the transmission and spread of infections Prevent evolution of infections to complications/sequelae (pelvic inflammatory disease, infertility, trachoma, etc.)</td>
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<tr>
<td>Educational prevention and control programs</td>
<td>Stimulate public awareness of risk factors and behaviors that lead to infection Public awareness of mode of transmission and general practices to prevent or avoid infection</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Prevents infection and disease, cost effective and can make worldwide impact</td>
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Disadvantages

- Population coverage may be infeasible
- Indiscriminate use of antibiotics may create selection pressure for producing resistant strains
- Misdiagnosed (false negative) cases that are not treated (due to assay or technical or other errors) may lead to continued spread of infections and diseases
- Will early treatment cause arrested immunity?
- Population coverage may be infeasible
- Indiscriminate use of antibiotics may create selection pressure for emergence of resistant strains
- Cost in most societies may be unattainable!
- Will early treatment cause arrested immunity?
- Low compliance with guidelines
- Historically has been unsuccessful due to socioeconomic and behavioral issues
- Not available. A human vaccine remains an elusive goal in design and efficacy
gram would constitute an acceptable short-term goal [34]. Thus, with epidemiologic data indicating persisting and sometimes increasing incidence of ocular and genital *C. trachomatis* infections in the human population worldwide, the urgency for an efficacious vaccine cannot be over emphasized. Unfortunately there is no acceptable human chlamydial vaccine to date due to a number of challenges, ranging from safety considerations through insufficient immunogenicity of vaccine candidates and lack of effective delivery systems, to how to induce long-term immunity (discussed below).

**Chlamydia Vaccine Design Requirements and Challenges**

**Historical Considerations**

From the time of early attempts at diagnosis, associations with ocular, genital and respiratory diseases in humans and animals [35–38], and etiologic proof by reinoculation of normal human hosts in the eye with culture isolated chlamydiae [39], the use of an effective vaccine prophylaxis against chlamydial infection and disease has been an important consideration for prevention. Some of the early questions bordered on whether vaccines could be designed separately for ocular, genital and respiratory infections, or for the entire *Chlamydia* genus, members of a species, or subspecies and serotypes (also called serovars or genovars). The valid case for separate approaches to designing human versus veterinary chlamydial vaccines was settled when animal vaccines that prevented specific chlamydial diseases were easily achieved by conventional vaccination methods [40]. Veterinary *Chlamydia* vaccines consisting of live attenuated or inactivated *C. psittaci* strains have been developed and used successfully to protect ewes from chlamydia-induced abortion [25, 41]. The successful animal *Chlamydia* vaccines in current veterinary use consist of live-attenuated or fixed elementary bodies of *C. psittaci* feline strains, which protect against *Chlamydia*-induced abortion in ewes or feline pneumonic chlamydial disease, respectively [25, 40, 41]. Although the successful veterinary vaccines do not prevent infectivity and lack the rigorous immunization schedules, efficacy, safety and toxicity standards of a human vaccine, their efficacy would suggest that a safe and efficacious human vaccine is a possibility. Also, the veterinary chlamydial vaccine success story provides the impetus and hope for future live attenuated human vaccines if the suspected immunopathogenic concerns are alleviated. Unfortunately, despite the successful animal vaccines, early efforts in human vaccines met with considerable challenges that have persisted to date [42–45]. The challenges facing human chlamydial vaccine design first came to light in the early attempts to use basic vaccinology methods to develop a vaccine against trachoma. Thus, whole organism-based vaccines derived by formalin inactivation of culture- or chick embryo-grown EBs, when delivered intramuscularly in alum or mineral oil adjuvant into children in trachoma-endemic areas of Taiwan, East Africa (Ethiopia), northern India and The Gambia in Africa produced mixed and some alarming results [46–52]. Depending on the trial, the results included a transient or temporary