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Chlamydia trachomatis Control Requires a Vaccine

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Abstract

As the most common reported communicable disease in North America and Europe, *Chlamydia trachomatis* is the focus of concerted public health control efforts based on screening and treatment. Unexpectedly control efforts are accompanied by rising reinfection rates attributed in part to arresting the development of herd immunity. Shortening the duration of infection through the testing and treatment program is the root cause behind the arrested immunity hypothesis and because of this a vaccine will be essential to control efforts. Advances in *Chlamydia* vaccinomics have revealed the *C. trachomatis* antigens that can be used to constitute a subunit vaccine and a vaccine solution appears to be scientifically achievable. We propose that an accelerated *C. trachomatis* vaccine effort requires coordinated partnership among academic, public health and private sector players together with a commitment to *C. trachomatis* vaccine control as a global public health priority.

The Public Health Problem

Today *Chlamydia trachomatis* is the commonest reported bacterial infection in the United States as it is in many other developed countries [1]. *Chlamydia* is even more important in developing countries and globally WHO estimates that 92 million sexually transmitted infections occur annually with most infections occurring in the most impoverished parts of the world where control programs are virtually absent [2]. Because untreated infection in women causes long term problems with reproduction such as infertility and ectopic pregnancy *Chlamydia* has been the focus of public health control programs for nearly two decades [3]. In 2002 the estimated tangible costs of *C. trachomatis* illness in the United States exceeded $2.6 billion [3]. Globally the costs are uncalculated.

C. trachomatis normally infects the single cell columnar layer of epithelium of the endocervix of women and urethra of men. At the mucosal site intense inflammation characterized by erythema, edema and mucous discharge causes mucopurulent cervicitis in

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women and non-gonococcal urethritis in men. Despite initiating local inflammation, *C. trachomatis* infection remains subclinical in 70-90% of women and 30-50% of men [4]. Asymptomatically infected women on vaginal speculum examination can show signs of mucopurulent endocervical discharge, hypertrophic cervical ectopy and friability (that is, easily induced bleeding of the cervical epithelium)[5]. When women are symptomatic they may complain of dysuria, abnormal vaginal discharge, abnormal menstrual bleeding, postcoital bleeding and lower abdominal pain. In some untreated women infections spread along the epithelial surface through the endometrium to the fallopian tubes to cause pelvic inflammatory disease (PID), infertility, ectopic pregnancy and chronic pelvic pain (Figure 1). Spread along epithelial surfaces results in clinical PID (approximately 30% of clinical PID cases are due to *C. trachomatis*)[6] or occurs silently to cause infertility or ectopic pregnancy. Over 50% of women with infertility or ectopic pregnancy due to *Chlamydia* do not recall a history of PID [7, 8]. Because *C. trachomatis* infections are commonly subclinical screening at risk persons is at the core of *Chlamydia* control efforts.

National screening recommendations for *C. trachomatis* infection have been in place for nearly two decades in many countries [3]. Despite wide scale roll out of *Chlamydia* control programs in the United States, Canada and Scandinavia reported case counts of *Chlamydia* have not exhibited sustained declines [9]. In 2000 in the United States nearly 710,000 cases of *Chlamydia* were reported while in 2009 over 1.2 million infections were reported and 2.8 million infections were estimated to have annually occurred that year [1]. The question as to whether public health control programs have failed to interrupt *Chlamydia* transmission has been studied in detail in British Columbia (BC) Canada which has had a population wide control program in place since 1994 [10]. Over the course of the BC control program *Chlamydia* case rates initially declined but since 1998 have risen to levels approximately 50% above what was seen prior to the introduction of the program (Figure 2). Over the course of the control program reinfection rates significantly increased at approximately 5% per year with reinfection significantly more common among young women [10].

Reasons for rising case rates are likely multifactorial and include expansion of the screening program into higher risk populations and improved sensitivity of diagnostic tests. In BC expansion of screening and improved sensitivity of diagnostic tests accounted for less than half of the annual increase in rates. Instead it has been hypothesized that the control program is treating individuals at earlier and earlier stages of infection before the development of protective immune responses thereby perturbing the development of herd immunity. This has been called the arrested immunity hypothesis [11]. Even before these epidemiological observations were made experimental studies in the murine model of *Chlamydia* genital infection had already demonstrated that early treatment prevented the acquisition of protective immunity [12].

The goal of public health efforts in control of *Chlamydia* has been to improve the reproductive heath of women and reassuringly clinical PID rates have substantially declined during the control era. For instance in BC PID rates have declined over 80% during the 18 years of the control program (Figure2)[13]. Since *Chlamydia* disease pathogenesis is immune mediated [14] the control program also is arresting the development of immunopathology following infection which is the cause of PID and its sequelae.

The unexpected response of *Chlamydia* to control efforts suggests that its immunology determines its epidemiology. Clearly the response of *C. trachomatis* to seek and treat public health and medical control efforts suggests that vaccine development is the next essential step for control. The goal of a successful *C. trachomatis* vaccine would be to prevent the acquisition and transmission of infection and to prevent the development of inflammatory disease sequelae. Similar to the HPV vaccine a *C. trachomatis* vaccine would likely be first offered to school-aged girls.

Immunology

C. trachomatis is both an immunizing and immunologically sensitizing infectious disease [14]. Immunity to *C. trachomatis* natural infection is incomplete and long to acquire likely due to a number of immune evasion mechanisms [15]. Such mechanisms include antigen variation of the principal protective antigens (allelic variation of the major outer membrane protein [MOMP] and phase variation of the polymorphic membrane proteins [Pmps]), and a developmental cycle responsive to the cytokine environment of the host cell enabling the establishment of a persistent form associated with reduced expression of the major protective antigens. *Chlamydia* replication within epithelial cells puts the organism in a protected sanctuary shielded from immune effectors and likely represents its most elite strategy for immune evasion. This ‘bag of dirty little tricks’ of organismal pathobiology means that vaccine immunity will need to outdo natural immunity for a vaccine solution to successfully control *C. trachomatis*.

In humans mounting evidence supports the acquisition of natural immunity despite the major immune evasion mechanisms exploited by *Chlamydia*. Infection is less common among older than younger individuals including sex workers and among sex workers resistance to infection is related to duration of prostitution independent of age suggesting the development of acquired immunity [16]. The time to clear infection takes many months suggesting that the development of immune effector mechanisms takes months to acquire perhaps as a consequence to immune evasion [17]. HIV infection among sex workers prevents the development of immunity [16] and risk for PID is increased by repeated *Chlamydia* infection and by the loss of CD4 T cells among HIV infected women [18]. The prevalence of cervical antibody to *Chlamydia* is inversely correlated with shedding of the organism from the cervix [19]. Production of interferon gamma to *Chlamydia* antigen by peripheral blood mononuclear cells correlates with reduced risk of infection [20].

C. trachomatis infection of non human primates replicates key attributes of human *C. trachomatis* infection such as long duration to acquisition of immunity, partial resistance to reinfection and tissue pathology preferentially occurring in hosts that have been immunologically sensitized. In primates primary cervical infection generates significant resistance to reinfection[21]. Resistance is partial rather than complete in the sense that the duration and magnitude of infection is substantially attenuated. Repeated infection directly into the primate fallopian tube incites immunopathology characterized by inflammation and adhesion formation, the hallmarks of PID and its sequelae [22].

The immunological mechanism for resistance has been best studied in rodent models of *Chlamydia* infection which in general support human data[23]. Rodent models are based on *C. muridarum* infection in the mouse and *C. caviae* infection in the guinea pig. However, since immunity arises very quickly in the rodent model which does not appear to be the case in humans there needs to be caution in generalizing mechanistic results from rodent models to human infection.

The murine *C. muridarum* model has demonstrated that CD4 T cells are necessary and sufficient to resolve primary infection while either CD4 T cells or antibody is necessary and sufficient to resolve reinfection [23](see Figure 3). The reason(s) behind the differences for immunity to primary infection and reinfection is unclear and its implications for vaccine design is yet to be elucidated. The mechanism for antibody mediated immunity appears to be dependent on Fc receptors [24]. These findings suggest that both CD4 T cell and antibody will be needed for a vaccine and that native conformation and surface localization will be important antigen properties.

In the murine model systemic and subepithelial CD4 T cells that secrete interferon gamma and tumor necrosis factor alpha correlate with protection [23] and the loss of CD4 T cells from the subepithelial site correlates with susceptibility to reinfection [25]. CD4 T cells directly inhibit epithelial cell growth of *Chlamydia* by contact dependent up regulation of epithelial cell indoleamine 2,3 dioxygenase and inducible nitric oxide synthase and T cell secretion of Plac8 explaining the essential nature of local mucosal immunity to *Chlamydia* [26]. *Chlamydia* antibody amplifies T cells responses by augmenting dendritic cell antigen presentation especially at low antigen levels found during early reinfection [27]. The immunological mechanism for tissue damage is less understood but may involve weak CD4 Th1 cell responses and over exuberant CD8 T cell responses consistent with the observation that loss of CD4 cells due to HIV infection increases the risk of *C. trachomatis* PID [18, 28].

Chlamydia Vaccines

Although vaccines have a long history in *Chlamydia* research the last human vaccine trial occurred nearly 50 years ago [29]. Initial approaches were entirely based on empiric Pasteurian principles of isolate, inactivate and inject. Shortly after *C. trachomatis* was first isolated in egg yolk sac in China in 1959 the organism was chemically inactivated and parenterally delivered in a variety of oil in water adjuvants. Trials were conducted in children at risk for trachoma because a sibling with the disease was living in the same household. The best of these trials showed that up to 70% of the children were protected against disease but that immunity waned with time and was no longer detectable three years after vaccination [30]. The vaccine formulations were studied in greater detail in non human primates. These studies demonstrated that the best protection required the highest concentration of organism suggesting that the preparations were of limited immunogenicity. Furthermore protection was most marked when the same strain was used for vaccine and challenge. Finally when breakthrough infections occurred in non human primates vaccinated with heterologous strains the inflammatory pathology was exacerbated. The investigators suggested that protective immunity was induced by type specific antigens and immunopathology was induced by antigens shared among the strains [30]. A more rational,

designed based approach based on modern principle of vaccinomics is currently yielding a new path toward a subunit based *Chlamydia* vaccine [31].

More than a decade after these initial studies were completed the *Chlamydia* type specific antigen was identified as the major outer membrane protein (MOMP) and this protein became the near exclusive focus of vaccine development for nearly 20 years [32]. However MOMP is an integral membrane protein notoriously difficult to prepare in its native conformation. Denatured recombinant MOMP failed as a vaccine in multiple animal model systems including primates, mice, guinea pigs and sheep [29]. However MOMP can be enriched in its native conformation when the organism has its cytosolic proteins extracted with detergent leaving a protein rich insoluble shell termed the *Chlamydia* Outer Membrane Complex (COMC). Immunization of mice, guinea pigs, sheep and primates with COMC produced immunity characterized by reduced duration and intensity of shedding suggesting that native conformation was essential to MOMP efficacy as a vaccine antigen[33-36]. Purifying MOMP with selective detergents and columns yielded a native trimeric structure which produced excellent protection in mice [37] but only partial protection in primates [38]. These results suggested that conformationally intact proteins in addition to MOMP found in the COMC may be necessary for a successful vaccine.

Vaccinomics

Genomics has transformed *Chlamydia* vaccinology with the introduction of three new unbiased approaches to discovery of antigens relevant to vaccine design. Mining of the whole genome by reverse vaccinology through bioinformatic analysis allowed prediction of novel genes coding for membrane or secreted proteins, or proteins with homology to known virulence factors. *Chlamydia* secrete several proteins into the host cells cytoplasm which are expected to be preferentially loaded onto major histocompatibility complex (MHC) class I molecules for recognition by CD8 T cells. However, because murine studies demonstrate that CD8 T cells play little or no role in protective immunity, secreted *Chlamydia* proteins are not currently seen as priority vaccine candidates. Rather identification of proteins that load onto MHC class II molecules for CD4 T cell recognition or *Chlamydia* outer membrane molecules recognized by antibody are lead candidates for a subunit vaccine. In one study 120 *Chlamydia* proteins were identified, expressed in *E. coli* and analyzed for their ability to be recognized by sera of infected people or by CD4 T cells of experimentally infected mice [39]. The analysis led to the discovery of 21 novel antigens inducing antibodies and 16 proteins recognized by CD4 T cells of infected animals. Surprisingly the majority of T cell proteins were not recognized by antibody. A subgroup of the T cell proteins was shown to be protective in the animal models and when four of them were combined they made a partially efficacious vaccine. A second approach used genome wide screening of human antibodies to over 80% of the expressed *C. trachomatis* proteome [40]. Most of the 719 tested proteins were recognized by sera from at least one subject among the 99 naturally infected women studied. However, only 27 proteins were recognized by 50% or more of the subject sera and were suggested as potential vaccine candidates although the observation that proteins with T cell sites do not substantially overlap with B cell proteins raises concern that this approach may not identify T cell antigens. The third approach identified T cell antigens via determining *Chlamydia* proteins which generated peptides binding to MHC

class II molecules during natural infection of dendritic cells [41]. Twenty seven proteins generated over 70 peptides which bound to class II MHC molecules. Several of these proteins were shared between *C. muridarum* and *C. trachomatis* immunoproteome. Seven proteins containing MHC class II binding peptides produced protective immune responses in the murine model of infection and when five of them were combined they generated a partially protective vaccine [42].

Vaccinomics emphasized the role for a new family of outer membrane protein antigens which had undergone only limited characterization during the pre-genomic era. This new family of outer membrane proteins is called the polymorphic membrane protein family (Pmps)[43, 44] and like MOMP they are selectively enriched in the COMC[45, 46]. Pmps are thought to be involved in *Chlamydia* host cell interaction such as attachment [47] and are commonly immunogenic in infected humans [48]. There are nine members of the Pmp family that are phase variable in expression[49]. Three members are also allelically variable [50] including one member whose sequence variability accurately maps to the biological variation of serovar correlated disease expression [51]. Four Pmp members are selectively enriched in T cell antigen sites and are partially protective in murine models of infection [52]. Antibody to one member of the Pmp family is neutralizing in cell culture [47].

Successful bacterial vaccines that are based on subunit components such as capsule, toxin or outer membrane vesicles often require adjuvants and can be limited by the conformational state of the vaccine antigen. Live attenuated bacterial vaccines overcome these problems which are inherent in molecular vaccines. Thus the discovery that a *C. trachomatis* strain that has lost the 7.5kb plasmid is attenuated in virulence allowed for exploration of such a strain as a potential vaccine. Studies in a primate trial of trachoma demonstrated for the first time in the modern vaccine era an approach that produced protection against both infection and disease [53]. Unfortunately efficacy was limited to primates that shared a common MHC class II allele suggesting that specific antigens presenting via MHC class II to CD4 T cells are vitally important to immunity and prevention of inflammatory pathology.

To complete the rational development of a *Chlamydia* subunit vaccine will require further knowledge about the reasons why subunit vaccines produce only partial immunity, the role for and mechanisms of antibody mediated immunity and elucidation of adjuvant technologies that engender polarized CD4 T cell together with antibody responses. Fortunately these gaps in knowledge are being rapidly bridged with advances in human immunology that allow for tackling questions of the difference between protective immunity and pathology caused by the immune response [31, 54]. Novel adjuvants and vaccine delivery technologies enable selective induction of the protective response while avoiding immunopathology [55]. Particularly promising approaches to a *Chlamydia* vaccine include immunization with conformationally intact outer membrane proteins in the form of COMC or the use of outer membrane vesicles containing recombinantly expressed *C. trachomatis* outer membrane proteins [56]. The recent development of a genetic transformation system for *C. trachomatis* [57] may allow the design of a *C. trachomatis* strain that constitutively over expresses protective CD4 T cell antigens such as the phase variable Pmps. Such genetically engineered *C. trachomatis* strains may be useful in preparing antigenically enhanced COMC as vaccine antigen.

Conclusions

This review aims to be a call to action to mobilize all the actors of the global vaccine community around a problem that is defeating modern medicine. The development of a *Chlamydia* vaccine today is scientifically tractable: genomics made available virtually all potential antigens; several animal and in vitro models are available to prioritize them; the advances in immunology provided novel adjuvants and antigen delivery systems; clinical trials to test vaccine efficacy are feasible. Therefore now that science is not the bottleneck any longer, we must focus on the non scientific obstacles. The main obstacle is the low priority on the public health agenda for *Chlamydia* vaccine development.

We need a vision able to mobilize the passion of scientists in different disciplines to work together and form an enterprise that can tackle a project that no one can do alone. The enterprise must involve experts in microbiology, biotechnology, immunology, animal models and systems biology to tackle vaccine discovery; experts in epidemiology and health economics to define the medical need and provide the rationale for vaccine recommendation to the public sector; experts in clinical trials, Good Clinical Practices and regulatory sciences to define the feasibility of clinical trials, the endpoints for clinical proof of concepts and efficacy studies; experts in technical development, adjuvants, formulation and Good Manufacturing Practices to develop the vaccine(s) to be tested in clinical studies. Finally, once proof of concept in humans is achieved, a private industrial partner needs to take leadership to industrialize the process, get regulatory approval and commercialize the vaccine (Figure 4). In conclusion, an increase in the priority of a *C. trachomatis* vaccine is the first important step in mobilizing the global vaccine community and the private sector around a problem that has become scientifically tractable. With a coordinated vaccinology approach we predict that the science is in place for a *C. trachomatis* vaccine to reach human trials within five years.

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Highlights

We review the epidemiological evidence supporting the need for a *Chlamydia* vaccine

We review the immunological basis for *Chlamydia* immunity

We review the vaccinomic approaches taken to develop a *Chlamydia* vaccine

We propose that the development of a *Chlamydia* vaccine requires global commitment

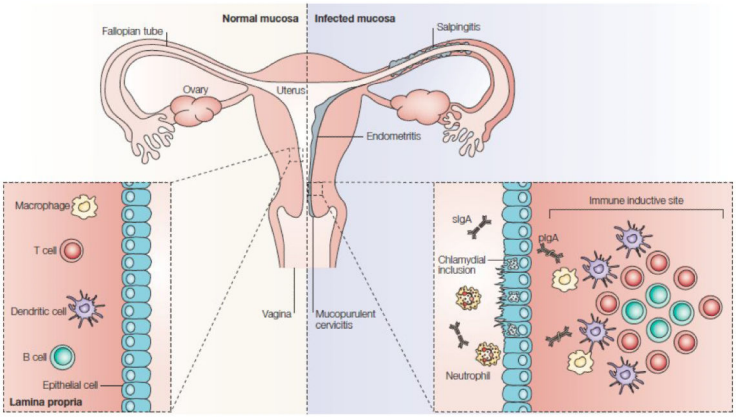

Figure 1.

Infection of the female genital tract with *Chlamydia trachomatis*.

C. trachomatis elementary bodies infect the columnar epithelial cells of the cervix, and can ascend to infect the endometrium and the fallopian tubes, causing pelvic inflammatory disease which can lead to infertility or ectopic pregnancy. The inflammatory reaction is characterized by an influx of macrophages and neutrophils and the formation of immune inductive sites in the submucosa containing B cells, T cells, dendritic cells and macrophages [15].

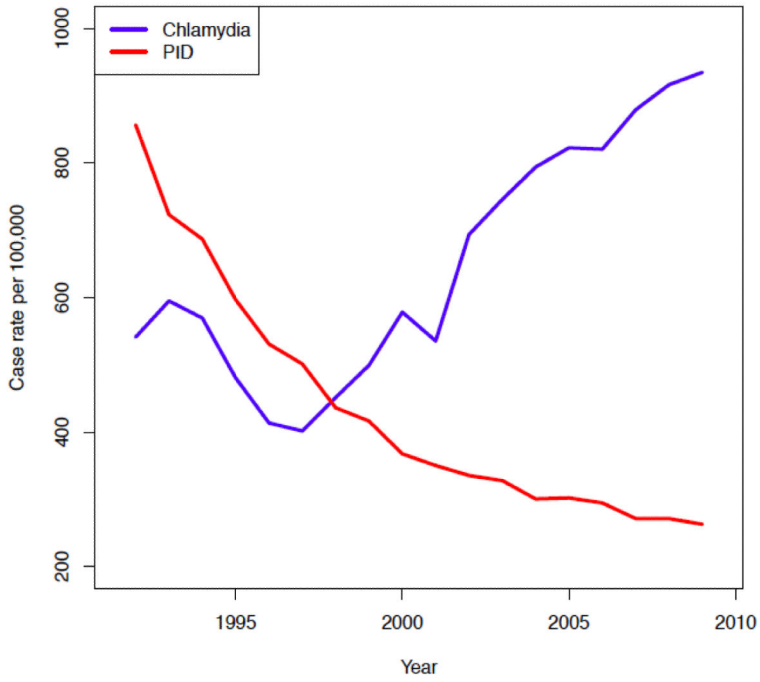

Figure 2.

Shown are case rates for *C. trachomatis* infection (blue) among women between the ages of 15 to 39 years and clinical PID (red) among women between the ages of 14 to 44 in the province of British Columbia, Canada between the years 1994 and 2009.

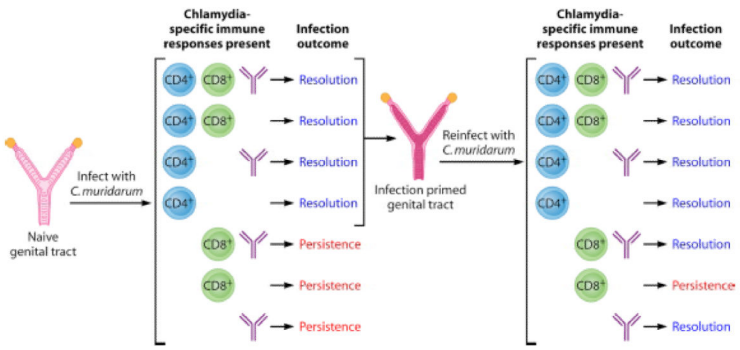

Figure 3.

Shown are the relationship between Chlamydia specific immune responses and infection outcomes among primarily and reinfected animals [23].

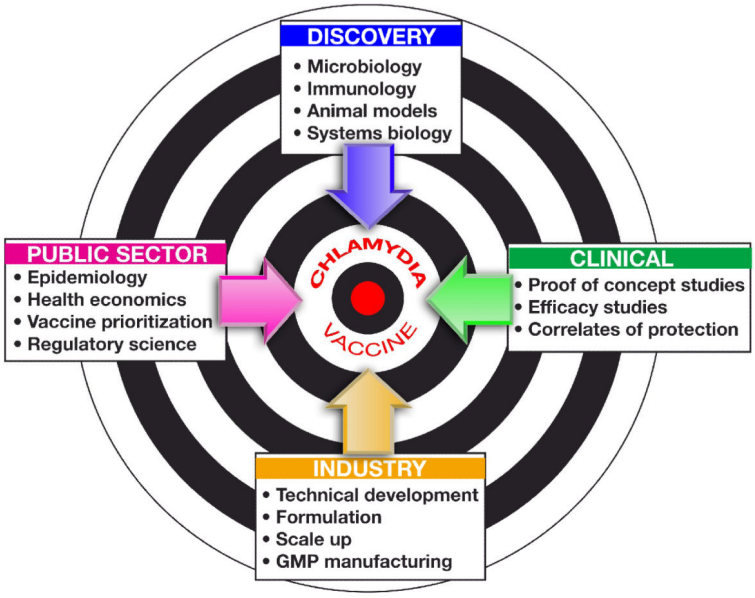

Figure 4.

Successful development of a *C. trachomatis* vaccine requires organizing activities across four key sectors. We propose the creation of a global public health enterprise dedicated to this purpose.