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Review

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.

Contents

1. 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 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 (Fig. 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

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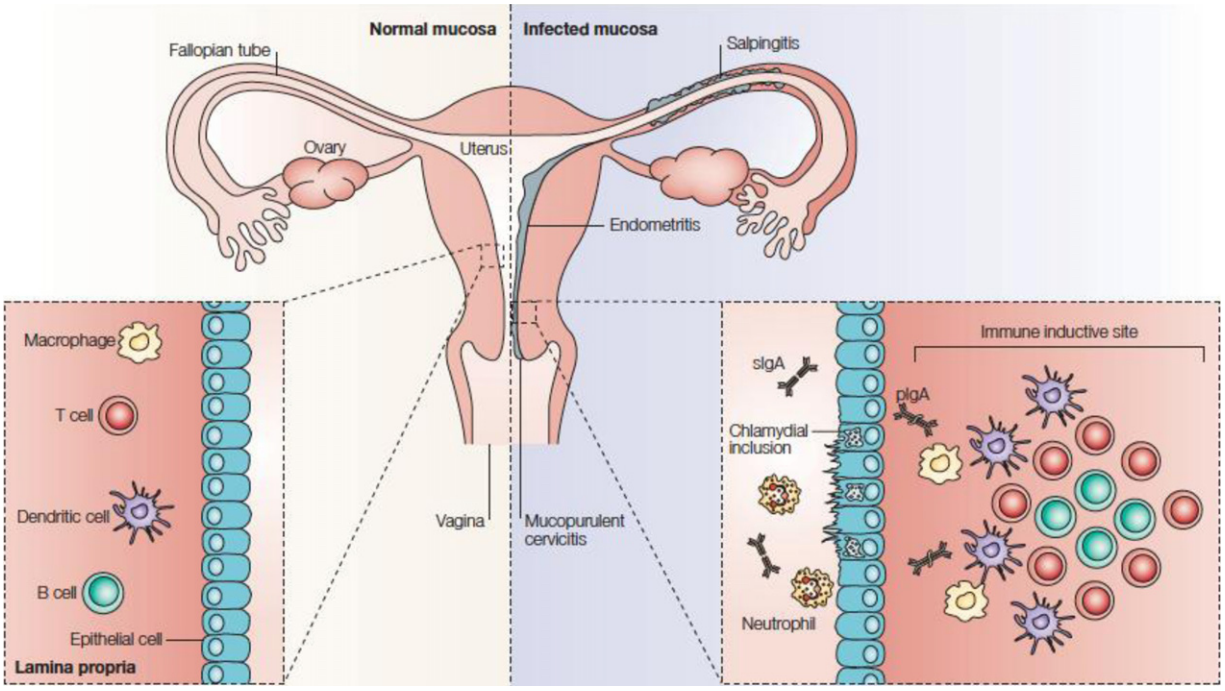

Fig. 1. Infection of the female genital tract with *Chlamydia trachomatis*. *C. trachomatis* infect the columnar epithelial cells of the cervix, and can ascend to infect the endometrium and the fallopian tubes, causing pelvic inflammatory disease which can lead to infertility or ectopic pregnancy. The 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].

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 (Fig. 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 demonstrated that early treatment interrupted 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 (Fig. 2) [13]. Since *Chlamydia* disease pathogenesis is immune mediated [14] the control program also appears to be arresting the development of immunopathology following infection which is the cause of PID and its sequelae.

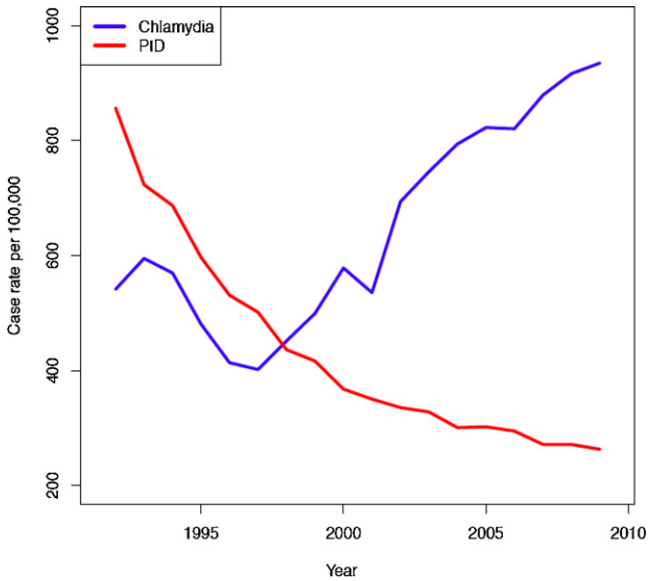

Fig. 2. Shown are case rates for *C. trachomatis* infection (blue) among women between the ages of 15 and 39 years and clinical PID (red) among women between the ages of 14 and 44 in the province of British Columbia, Canada between the years 1994 and 2009. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)