Modeling the Impact of Potential Vaccines on Sexually Transmitted *Chlamydia* Epidemics

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Abstract

Background: We investigate the likely impact of vaccines on the prevalence and morbidity of *Chlamydia trachomatis* infections in heterosexual populations.

Methods: An individual-based mathematical model of *C. trachomatis* transmission is developed and linked to the infection course in *Chlamydia*-infected individuals. The model describes the impact of a vaccine through its affect on the chlamydial load required to infect susceptible individuals (the 'critical load') and the chlamydial load in, and subsequent infectiousness of, infected individuals. The model is calibrated using behavioral, biological and clinical data.

Results: A fully protective chlamydial vaccine administered prior to sexual debut can theoretically eliminate *C. trachomatis* epidemics within 20 years. Partially effective vaccines can still greatly reduce *Chlamydia* incidence. Vaccines should primarily aim to increase the critical load in susceptible individuals and secondarily decrease the peak load and/or the duration of infection in vaccinated individuals who become infected. Vaccinating both genders has a beneficial impact on *Chlamydia*-related morbidity but targeting women is more effective than targeting men.

Conclusions: Our findings can be used in laboratory settings to evaluate vaccine candidates in animal models, by regulatory bodies in the promotion of candidates for clinical trials, and by public health authorities in deciding upon optimal intervention strategies.

Keywords: *Chlamydia trachomatis*, vaccines, mathematical modeling.

Introduction

The incidence of sexually transmitted *Chlamydia trachomatis* is increasing in many countries [1-3]. This is of important public health and economic concern as *C. trachomatis* infections are a leading cause of pelvic inflammatory disease (PID), ectopic pregnancy, and infertility in women [4] and male infertility [5]. Public health interventions have been ineffective thus far [6] and may even have increased *Chlamydia* incidence [7]. Over the long term an effective vaccine will be the most successful intervention against *Chlamydia* epidemics [8, 9].

Although chlamydial vaccine research has been conducted for more than 35 years, progress has been modest [8]. Apart from some early, unsuccessful attempts in humans [8, 10], all vaccine work has been in animal models. Recently, efforts have been made to identify chlamydial antigens that elicit protective immunity against the multiple serovars (D-K) of *C. trachomatis* responsible for genital tract infections [11]. In the mouse model, immunization with many of these antigens, as well as with the commonly used major outer membrane protein (MOMP) reduces infection duration and the amount of *Chlamydia* shed. However, sterilizing immunity has not been achieved. Defining immunization routes that target immunity to the reproductive tract and adjuvants that elicit both a strong Th1 response and a mucosal antibody response required to control infections is essential for a successful vaccine. The protection provided by experimental vaccines against live challenge is usually modest although the level required in animal models to be useful in human studies is never discussed.

Currently, the population-level impact of vaccines on *Chlamydia* epidemiology is unknown. Understanding the ability of a vaccine to control the incidence, prevalence, and morbidity of *Chlamydia* infections in the general population is important in the development, evaluation, regulation, and implementation of candidate vaccines. To predict the impact of potential *Chlamydia* vaccines we develop a mathematical model that simulates transmission in a heterosexual population by linking the within-host biology of susceptible and *Chlamydia*-infected individuals to their sexual behavior and partnership dynamics. Our model tracks the infection time course, disease

progression, and dynamic infectiousness of infected individuals and the transmission to others. We investigate the population-level impact of vaccines that: (i) protect uninfected people by raising the infectiousness threshold required to transmit an infection; (ii) alter the natural course of infection in *Chlamydia*-infected people by changing the growth rate, peak chlamydial load, or duration of infection; (iii) increase the duration of immunity post-infection due to treatment or natural clearance; and (iv) provide sterilizing immunity but only for a finite duration. We also explore the likely effect of public health interventions based on various gender-specific vaccine coverage levels.

Methods

We develop an individual-based transmission model that tracks 20,000 sexually-active heterosexual people, with a 1:1 ratio of men to women. Our model is calibrated to biological, behavioral, and epidemiological data from general heterosexual populations such that the median pre-vaccine prevalence of *Chlamydia* is 4-5%. Model parameters are listed in Table 1 and a detailed description of the model is presented in the Supplementary Material.

In our model, individuals enter the population upon sexual debut as others age out, keeping the population constant. Homogenous sexual mixing is assumed with the formation and break-up of short-term (casual) and long-term (regular) partnerships dynamically modeled. Concurrent partnerships are restricted to a core group of people (5% of the population). Sexual behavior dynamics (including intercourse frequency and condom use) are simulated according to probabilistically-inferred rates defined in Table 1.

For each infected person, the chlamydial load (the number of IFUs per ml of mucosal cervicovaginal secretion) is tracked over time. Between individuals the IFU growth and decay rates vary while the peak IFU load and inoculum size are fixed (unless the infected person was previously vaccinated) (Table 1). Infections are naturally cleared when the load falls below 10 IFU, leading to mean infection duration of ~14 months. We assume that 75% of infected individuals are asymptomatic with a low

background rate of testing and treatment [6, 12] and that most symptomatic individuals seek treatment within a short time (see Table 1). We assume that 20% of infections in women ascend to the upper genital tract [13] and that PID can uniformly occur at any time during a woman's infection. This results in a PID prevalence of ~0.4-0.5% (agreeing with empirical estimates [14]) and a realistic distribution for the lifetime number of PID episodes with ~15% of women having an episode of PID in their lifetime and a small proportion of women having three or more episodes. We assume short-term immunity following a naturally cleared infection with successfully treated individuals having shorter immunity [7].

Transmission of *C. trachomatis* within a sexual partnership depends on the infectiousness of the infected person and their partner's susceptibility. These characteristics are modeled in terms of the chlamydial load within infected individuals. Infectiousness is directly related to the within-host chlamydial load while susceptibility is measured by the minimum chlamydial load required to infect, which we define as the *critical load*. Potential vaccines may provide protection to uninfected individuals directly by increasing their critical load and/or indirectly by changing the chlamydial load within vaccinated individuals who become infected. Full protection occurs if the critical load increases to a value greater than the peak load of an infected individual; otherwise a vaccine is only partially protective.

In our model males and females are only vaccinated before sexual debut. Vaccinated individuals are given different parameter values for their critical load, mean IFU doubling time, peak IFU load, mean IFU half-life, and duration of immunity. These parameters specify the properties of a vaccine and for a vaccinated person their value is fixed until the vaccine wanes. The impact of vaccines is investigated by independently changing one parameter at a time for vaccinated individuals.

The model is implemented using Matlab® R2008a with each simulation tracking the dynamic sexual network and chlamydial transmission over 70 years. We simulate various vaccine interventions. Vaccination is introduced at 50 years and continued until the end of each simulation. Each parameter set and vaccine regime is run 10 times; to compare different vaccine properties and intervention strategies we took the median trajectory of the 10 simulations.

Results

How long would it take to eradicate sexually transmitted *Chlamydia* with an effective vaccine?

When there is no vaccination, all simulations show a stochastically oscillating prevalence ranging from 3-6% with median ~4.5% [IQR 4.1-4.9%] (Fig. 1a). The median prevalence of these simulations was chosen as the baseline for comparison with other scenarios. Our simulations reveal that an ongoing vaccination campaign using a completely protective vaccine with 100% coverage of individuals before sexual debut results in a declining epidemic and theoretical elimination within 15-20 years (Fig. 1a). There would be a noticeable decrease in prevalence a few years post vaccine introduction and, despite stochastic oscillations, all simulations reach zero prevalence at a similar time (median 16.9 years; IQR 16.3-17.6 years) (Fig. 1a).

Vaccines that wane after a finite duration

Vaccines that wane in their protective immunity over time can still have a large impact with a noticeable reduction in prevalence even if the vaccine is effective for just one year (Fig. 1b). In order for a vaccine to eliminate a *Chlamydia* epidemic it would need to confer immunity for around 10 years, in which case eradication would take more than 20 years (Fig. 1b). A vaccine that is effective for at least ten years should be a goal for vaccine developers; if administered prior to sexual debut then adolescents are covered for the period in which they are at greatest risk of acquiring infection [15].

The impact of vaccine coverage rates

If sub-optimal coverage is achieved then fully protective vaccines obviously have less impact (Fig. 2a). In such cases, targeting coverage can be beneficial. For example, vaccinating 50% of males and females before sexual debut (Fig. 2a, red line) appears to have less effect than vaccinating 100% of females (Fig. 2a, blue line) even though the same number of people are vaccinated. Figure 2b shows the incidence of PID in unvaccinated females according to the same coverage scenarios shown in Fig. 2a.

These results show a direct relationship between the prevalence of *Chlamydia* infections and the incidence of PID. Vaccinating 100% of females before sexual debut (Fig. 2b, blue line) has a greater affect on PID incidence than vaccinating 50% of males and females (Fig. 2a, red line) suggesting that vaccination strategies should concentrate on females whilst also vaccinating males if feasible.

The impact of partially protective vaccines

Partially protective vaccines may be unable to eradicate *Chlamydia* epidemics even with 100% coverage (Fig. 3). The attainable critical IFU load, below which infection cannot occur, is highly important. Even a small increase in the critical load can greatly reduce the prevalence and incidence of *Chlamydia* infections (Fig. 3). While increasing the critical load from 500 IFUs to 10^3 IFUs in vaccinated individuals has no observable effect, increasing it to 10^4 IFUs ($3\log_{10}$ from the peak load of 10^7 IFUs) leads to a small decline in the *Chlamydia* prevalence to under 4% twenty years post vaccine introduction. This decline shows a slow continual rate of decrease that could result in the elimination of the epidemic over a large timescale but is more likely to converge to a lower endemic level. Each order of magnitude increase in the critical load produces a faster decrease in prevalence. When the critical load is 1/10th of the peak load (Fig. 3, purple line) the epidemic appears to be converging to zero prevalence with elimination greater than 20 years post vaccine introduction, showing that it is still possible to eliminate a *Chlamydia* epidemic with a partially effective vaccine. Clearly, the critical load induced by a vaccine is the key determinant of the epidemiological impact and whether eradication is possible. Around the peak of infection a *Chlamydia*-infected person remains highly infectious to someone vaccinated with an imperfect vaccine. While increasing the critical load has no effect on the duration of infection, it reduces the time that an infected person is infectious to a vaccinated uninfected partner. This highlights the large gain that is possible by decreasing the duration of infectiousness.

Vaccines that alter infection course in infected people

We investigated the effect of imperfect vaccines that have no preventative effect but alter the duration of infectiousness, the duration of infection, or the peak IFU within vaccinated individuals who become infected. We found that increasing the doubling time had no significant effect on the prevalence (Fig. 4a). This is not unexpected as

the time to reach the peak load is only a small proportion of the overall infection time. It is likely that changing the doubling time affects other characteristics of the chlamydial load, such as the peak IFU level. Decreasing the peak load within vaccinated individuals who have become infected greatly decreases the prevalence and can potentially eliminate an epidemic (Fig. 4b). A reduction in the peak load to a value less than 10^4 IFUs (a reduction of $3\log_{10}$ (99.9%) from the unvaccinated peak load) could eradicate an epidemic in ~20 years (Fig. 4b). A similar result is achieved by reducing the peak load by $2\log_{10}$ IFUs (99%), with a slightly longer time to eradication (Fig. 4b, red line). Reducing the peak load by 90% (to $1\log_{10}$ from the unvaccinated peak IFU level) results in a slower decline in the epidemic, with a prevalence of ~2.5% after 20 years of vaccination. In contrast, protective vaccines that increase the critical load to a level $1\log_{10}$ from the peak load theoretically eliminate an epidemic in less than 20 years (Fig. 2). Decreasing the infection peak load to 1/10th of its original value has a much smaller effect than increasing the critical load in a susceptible person to 1/10th of the peak value. This is due to the respective decreases in the duration of infectiousness (76% for increasing the critical load as opposed to 23% for the reduction in the peak load).

The impact of vaccines that decrease the half-life of the chlamydial load in infected individuals is shown in Figure 4c. While minor reductions (10%) in the half-life have little effect on an epidemic, reducing the half-life to less than 1/10th the value of the unvaccinated case a vaccine can theoretically eliminate an epidemic ~20 years post vaccine introduction. For vaccines that reduce the half-life by 90%, both the infection duration and duration of infectiousness are substantially reduced (by almost 90%, to 47 days and 35 days respectively).

The relative impact of each simulated vaccine on *Chlamydia* incidence and PID cases is shown in Figure 5. Maximum reduction in *Chlamydia* incidence and PID cases will obviously be achieved with 100% protective vaccines with 100% coverage. However, partially effective vaccines can still have a substantial effect on *Chlamydia* epidemics with vaccines that increase the critical load to ~1/10th of the peak level, decrease the peak load by ~3log10 (99.9%), or decrease the duration of infection by ~90% having similar effects. Similar relative impacts could be expected between *Chlamydia*

incidence and the number of PID cases for each type of vaccine, except for vaccines that reduce the duration of infection (Fig. 5).

We also simulated the potential epidemiological effect of *Chlamydia* vaccines that neither protect against acquiring infection nor change the infectiousness of infected people but increase the duration of immunity after clearance. We found that such vaccines would likely have only modest impacts on *Chlamydia* prevalence (Fig. 4d).

Discussion

What constitutes a fully protective immune response against genital *Chlamydia* infection remains unknown. However, evidence from animal models and limited human studies suggests a strong IFNγ-mediated Th1 response and a strong antibody response eliciting neutralizing antibodies in mucosal secretions are required for protective immunity [8]. Interferon-mediated mechanisms of protection are believed to be essential for limiting infection, whilst adoptive transfer of monoclonal antibodies against surface antigens (such as MOMP) can also limit infection in animal models [16]. A strong humoral response is also essential for effective recall immunity against secondary infections in animal models [17]. Therefore, most studies in animal models measure a variety of biomarkers including cytokines associated with Th1 (IL-12, IFNγ) and Th2 (IL-4 and IL-10) responses, inflammatory cytokines such as TNFα as well as neutralizing antibody in mucosal secretions. These biomarkers should be used to evaluate human vaccine trial outcomes, where it will be essential to monitor local mucosal responses at the site of infection, using cells obtained by cervical cytobrush techniques [18] and evaluating antibody responses in cervicovaginal secretions. The choice of antigen is also an important factor in determining the success of a potential vaccine. Most studies to date have used MOMP, however, protection induced by MOMP is serovar-specific and short-lived making it unlikely that a vaccine based on MOMP alone will be effective. Recently, numerous novel chlamydial antigens have been identified that elicit partial immunity against multiple serovars of *C. trachomatis* in animal models [19-21]. Combinations of these antigens, administered as a multi-subunit vaccine may provide the best means of eliciting

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protective immunity. Currently, combinations that are effective in animal models are being identified prior to testing in human subjects.

We have shown that if a fully protective vaccine was available, *Chlamydia* epidemics could be eradicated within 20 years. Unsurprisingly, greater vaccine coverage results in greater epidemiological outcomes. However, targeting 100% of one gender (females) is likely to have a greater epidemiological impact than administering vaccines to 50% of both genders. If lifelong sterilizing immunity cannot be attained then a *Chlamydia* vaccine would need to be effective for at least ten years for population-level eradication to become possible. Partially protective vaccines that increase the infectious threshold required for transmission can still be highly beneficial, although they would need to increase the critical load to ~1-2$\log_{10}$ from the peak load. Similarly, albeit not as effective, vaccines that reduce the peak load or the duration of infection in infected individuals can also have substantial population-level impacts. Our model suggests that *Chlamydia* vaccines can successfully control epidemics if they substantially reduce the time that infected people are infectious to susceptible people. Thus, microbiologists developing candidate vaccines should focus on vaccines that protect individuals by raising the infectiousness threshold and secondarily reduces the peak load and duration of infection of vaccinated individuals that become infected.

There is concern that partial immunity could result in vaccine immunopathology. Early attempts at developing chlamydial vaccines were sometimes plagued by worsened immunopathology in individuals who had either been reinfected with *Chlamydia* or with a crude, whole organism vaccine after clearing a previous infection. However, it has now been demonstrated that the major contributor to the development of the observed immunopathology in chlamydial infections is likely to be the high homology that exists between human and chlamydial heat shock 60 proteins [22-24]. Therefore, current vaccines aim to overcome this by only using purified recombinant proteins and screening the vaccine proteins against the human proteome and eliminating any targets that have even low levels of homology. Consequently, current chlamydial vaccines should generally be safe and should not cause an enhanced immunopathological reaction. Of course, safety studies are

necessary in early phases of clinical trials. But there is reason to believe that a chlamydial vaccine that was partially protective could be used safely.

Although we decoupled vaccine properties in our analysis, they are unlikely to be completely independent. For example, vaccines could have both a protective effect and change the chlamydial load profile within infected individuals; such vaccines would be even more beneficial in controlling *Chlamydia* epidemics and reducing PID incidence. In our study we assumed that the probability of developing PID is constant over the course of an infection. If developing PID depends on the chlamydial load then a vaccine which reduces the peak load is likely to be the most beneficial. Similarly, if PID depends on the duration of infection then vaccines that reduce this time will have an even greater effect (Fig. 5). While immunity is possibly very important to *Chlamydia* epidemiology [7] and is included in our model, we did not investigate sensitivity to the duration of immunity. Although the average rate of sexual partner acquisition changes with age, we assumed homogeneous mixing with an average number of partners (Table 1). Another limitation of our analysis is that the relationship between chlamydial load and the probability of transmission is unknown. Various studies have reported transmission estimates: Quinn et al. [25] used a cross-sectional study of sexual partnerships to estimate transmission probabilities from males-to-females and females-to-males over a partnership and found no significant differences (at 68% transmission frequencies); Viscidi et al. [26] used cell culture and PCR to analyze the level of *Chlamydia* infection in sexual partners of *Chlamydia*-infected men and women and found transmission rates over the partnerships of 45-75%. Other transmission studies [27-29] have estimated similar transmission rates, in the range of 25-40% of male sexual partners of *Chlamydia*-infected women and 40-60% of female sexual partners of *Chlamydia*-infected men. No study has investigated the relationship between chlamydial load and transmission risk and no estimates of transmission risk have been based on longitudinal studies. Such a relationship has been investigated for HIV [30, 31]. In the absence of other data, we assumed a similar relationship exists for *Chlamydia* but we calibrated the association to reflect the different overall transmission probability of *Chlamydia*.

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Vaccination could be substantially more effective than other biomedical interventions in controlling *Chlamydia* epidemics. The best public health intervention that is

currently available is increasing the rate of screening and treating infected cases. Previously we estimated the relative reduction in population prevalence that could be attained with different screening coverage levels, targeted at different populations groups [32]. We showed that an 80% reduction in prevalence could be achieved after 10 years of a screening intervention if 30% of all individuals younger than 30 years of age are tested and treated for *Chlamydia* each year [32]. This relative reduction in prevalence could not be achieved if *teenagers* are targeted for screening, even with 100% coverage [32]. However, 80% reduction in prevalence could be obtained if a protective vaccine was administered to adolescents prior to sexual debut (Fig. 1a).

Our current study sheds light on vaccine development. It has been suggested that an effective chlamydial vaccine will need to produce sterilizing immunity. Our study shows that a vaccine does not need to achieve sterilizing immunity to have an effect on the prevalence and incidence of infection. Even moderate vaccine-induced reductions in peak load and duration of infection can have major effects on *Chlamydia* epidemiology. This suggests that parameters commonly measured in animal models of infection (e.g., the ID50, duration of bacterial shedding, and amount of *Chlamydia* shed during an infection) are valid for the design of human vaccines and can be evaluated using our current model in terms of the potential population level impact on human infections. Our modeling approach can therefore be used to evaluate the results and impact of vaccination studies using new adjuvants and antigens and to guide future animal studies to achieve significant levels of protection in human populations.

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Table: Model parameters and values for the baseline case of no vaccination.

Symbol	Description		Value/Range	Reference
Sexual behavior parameters				
$a_{\min}$	Minimum age of sexually debut		13 years	¶[33]
$a_{\min} + \lambda_b$	Average age of sexual debut		17 years	¶[33]
$a_{\max}$	Average age of departure from sexually active population (in terms of choosing new sexual partners)		50 years	¶[33]
f_s^r	Average number of sex acts per regular (long-term) partnership per week		1.75	[34]
f_s^c	Average number of sex acts per short-term partnership per week		3	[34, 35]
p_c^c	Proportion of sex acts in a short-term partnership in which a condom is used		30%	[35, 36]
p_c^r	Proportion of sex acts in a regular partnership where a condom is used		$p_c^r = (1-\alpha)p_c^c$	[37]
α	Relative reduction in condom use for regular partnerships compared with short term partnerships		0.9	
ε	Per-act effectiveness of condoms in preventing transmission		90%	[37, 38]
p_{core}	Percentage of people who may have concurrent sexual partnerships (we define as core group)		5%	¶ [39]
p_r	The probability that a newly formed sexual partnership becomes a regular partnership		0.4	¶ [34, 39]
t_r	The average time duration of a regular (long-term) partnership		8 years	¶ [34, 40]
t_c	The average time duration of a short term partnership		14 days	¶ [34, 40]
t_a	The average time duration between partnerships for non-core group people		315 days	¶ [34, 40]
t_a^c	The average time duration between partnerships for core group people		$21 < t_a^c < t_a$	¶
p_p^i	Probability that a core group person is available to form another partnership if they currently have:	no partners	$p_p^0 = 1$	¶
		1 partner	$p_p^1 = 0.5$	
		2 partners	$p_p^2 = 0.25$	
		3 partners	$p_p^3 = 0$	
Chlamydial load parameters				
l_p	The peak chlamydial load in an infected individual (number of bacterial copies)		10^7	‡
l_0	The initial chlamydial load in a newly infected individual		100	‡

t_e	The average doubling time of chlamydial load during the early expansion phase at the onset of infection	6 hours	‡
	Person-to-person variability in the doubling time	± 2.4 hours	
t_h	Chlamydial load half-life following the peak load	21 days	‡
	Person-to-person variability in the half-life	± 10 days	
l_c	The minimum chlamydial load required to be infectious (number of bacterial copies)	500	‡
$l_{\min}$	The chlamydial load at which infection has 'cleared'	10	¶
β_p	Transmission probability per act at the peak chlamydial load	0.45	†
	Transmission probability per act for any given chlamydial load level	§	
Clinical parameters			
p_i^s	Probability that a chlamydial infection becomes symptomatic	0.25	[6, 12]
p_a	Probability that an infection in a female ascends to the upper genital tract	0.2	[13]
t_n	The duration of immunity after natural recovery from infection before which an individual is susceptible to re-infection.	45days	[41, 42]
	Person-to-person variability in the duration of immunity following natural recovery of infection	± 15 days	
t_t	The duration of immunity for a person that has recovered from infection through treatment	$5 < t_t < t_n$ days	[7, 43]
	Person-to-person variability in the duration of immunity following recovery due to treatment	± 53 days	
p_t^s	Percentage of people with symptoms that seek treatment	0.8	[44, 45]
θ	Test sensitivity (proportion of infected that test positively)	85%	[46, 47]
t_s	The time after symptoms arise that a person is likely to seek treatment. Uniformly distributed between 1 and t_s^m	$1 - t_s^m$ days	[46, 48]
t_s^m	The maximum time that it takes for a symptomatic person to seek treatment	10 days	[46, 48]

f_t^a	The probability per year that a female with an asymptomatic infection is tested for *Chlamydia*	0.04	[44, 45]
m_t^a	The probability per year that a male with an asymptomatic infection is tested for *Chlamydia*	0.025	[44, 45]

¶: Experimental variable based on our assumption. The sexual behavior parameters are calibrated so that the cumulative distribution of the lifetime number of partners matches those obtained from sexual behavior surveys (see Fig. S3 in the Supplementary Material).

‡: The chlamydial load parameters are based on well-documented studies in animal models [41, 49], with the exception of the half-life of the chlamydial load. Since it is thought that humans are infected for 9-18 months on average in the absence of treatment [50], we assume a half-life that provides duration of infection of ~14 months. The chlamydial load function is described in the Appendix.

†: This is the per act transmission probability for someone with a chlamydial load of l_p. This is set to calibrate the model such that the median prevalence of *Chlamydia* in the population is in the specified range of 4-5%.

§: The probability of transmission per act, β, is dependent on the chlamydial load within an infected person at the time of sexual intercourse. This relationship is described in detail in the Supplementary material.

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Figure Legends:

Figure 1: (a) The prevalence of *Chlamydia* in a heterosexual population versus time, indicating the impact of a 100% protective vaccine. All model simulations are shown for 100% vaccine coverage before sexual debut (green with median in black) in comparison to the baseline scenario of no vaccine (red with median in blue). **(b)** Prevalence of *Chlamydia* as a function of time for vaccines that wane after a finite duration of 1 year, 5 years, and 10 years.

Figure 2: The impact of different male and female coverage rates before sexual debut on **(a)** *Chlamydia* prevalence and **(b)** PID incidence for a 100% protective vaccine. Results are median values for ten model simulations. The results for 100% coverage of males and females are the same as in Fig. 1.

Figure 3: The prevalence of *Chlamydia* after the introduction of partially protective vaccines with 100% coverage of incoming sexually active individuals. Each curve shows the median prevalence for 10 simulations of the same parameter set. The vaccine critical load is measured relative to the peak load in an infected person. In the no vaccine case the critical load is $4.3\log_{10}$ from the peak load. Here, the duration of infectiousness is 306 days (no vaccine), 284 days ($l_c=10^3$), 213 days ($l_c=10^4$), 143 days ($l_c=10^5$), 72 days ($l_c=10^6$), and 0 days ($l_c=l_p=10^7$). The blue and black lines are the same as in Fig. 1.

Figure 4: Prevalence of *Chlamydia* versus time, indicating the impact of vaccines that change the chlamydial load profile in a vaccinated person who becomes infected by **(a)** increasing the doubling time, **(b)** decreasing the peak load, and **(c)** decreasing the half-life. In each figure the blue curve is the median curve for the no vaccine case in Fig. 1a. **(d)** Prevalence of *Chlamydia* as a function of time, indicating the impact of vaccines that increase the duration of natural immunity post infection by a factor of 2, 5, and 10.

Figure 5: Percentage decrease in the total number of *Chlamydia* (red) and PID (blue) cases 20 years post vaccine introduction for each vaccine strategy shown in Figs. 1-4. Results were obtained by calculating the median total number of infections and PID cases for the 10 simulations of each vaccine. The decreases were then calculated by comparing the median values for the vaccine to the median incidence and PID cases when no vaccine is introduced.

Figure 1a

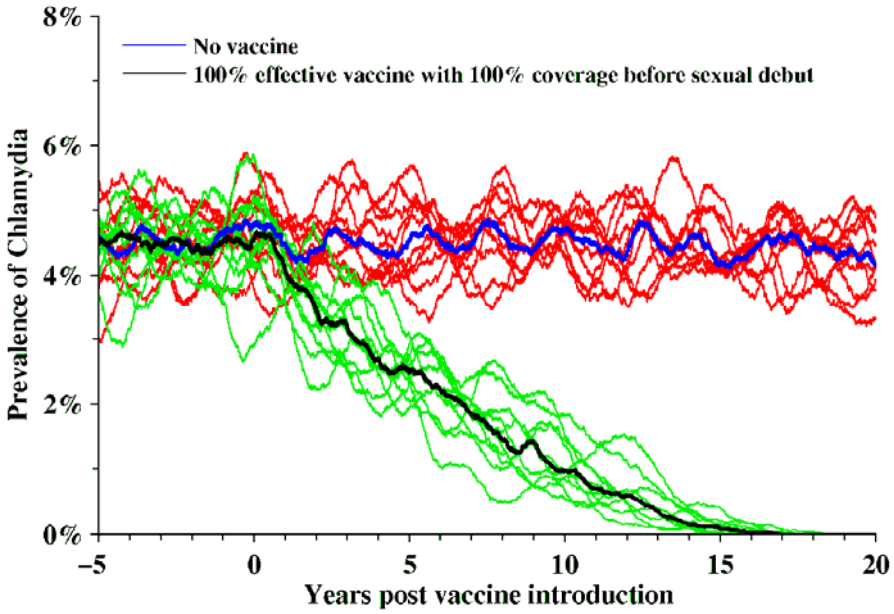

8%
6%
4%
2%
0%
Prevalence of Chlamydia
No vaccine
100% effective vaccine with 100% coverage before sexual debut
−5
0
5
10
15
20
Years post vaccine introduction

Figure 1b

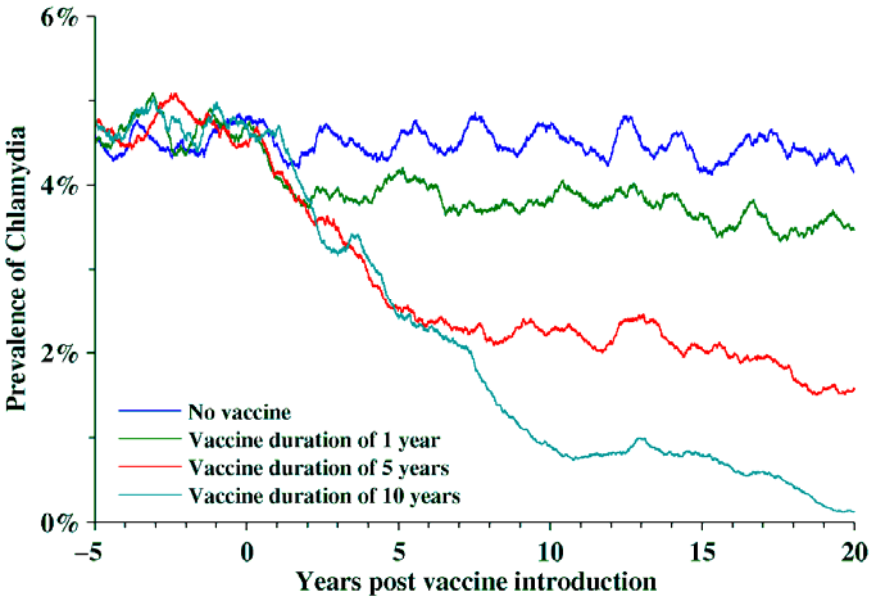

6%
4%
2%
0%
Prevalence of Chlamydia
No vaccine
Vaccine duration of 1 year
Vaccine duration of 5 years
Vaccine duration of 10 years
−5
0
5
10
15
20
Years post vaccine introduction

Figure 2a

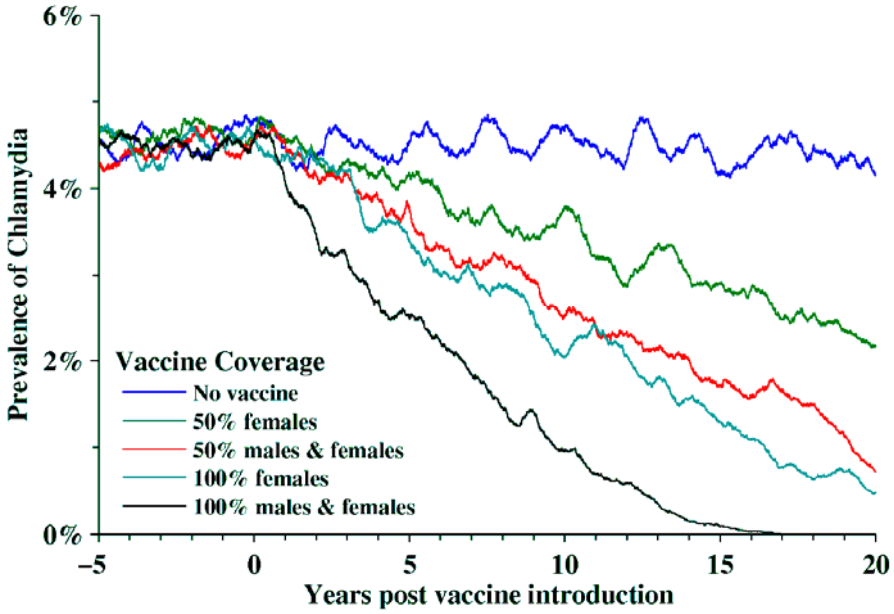

6%
4%
2%
0%
Prevalence of Chlamydia
Vaccine Coverage
No vaccine
50% females
50% males & females
100% females
100% males & females
−5
0
5
10
15
20
Years post vaccine introduction

Figure 2b

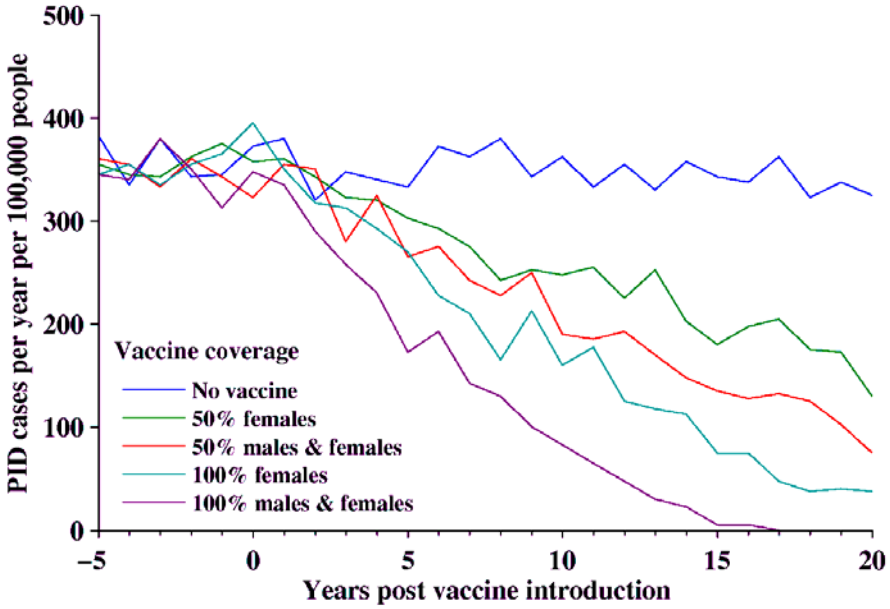

PID cases per year per 100,000 people
500
400
300
200
100
0
−5
0
5
10
15
20
Years post vaccine introduction
Vaccine coverage
No vaccine
50% females
50% males & females
100% females
100% males & females

Figure 3

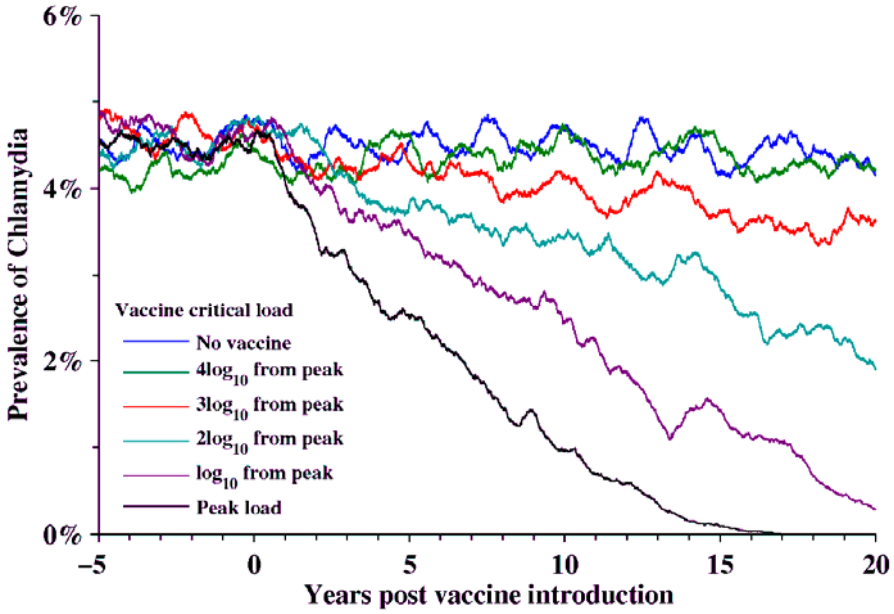

6%
4%
2%
0%
Prevalence of Chlamydia
−5
0
5
10
15
20
Years post vaccine introduction
Vaccine critical load
No vaccine
4log10 from peak
3log10 from peak
2log10 from peak
log10 from peak
Peak load

Figure 4a

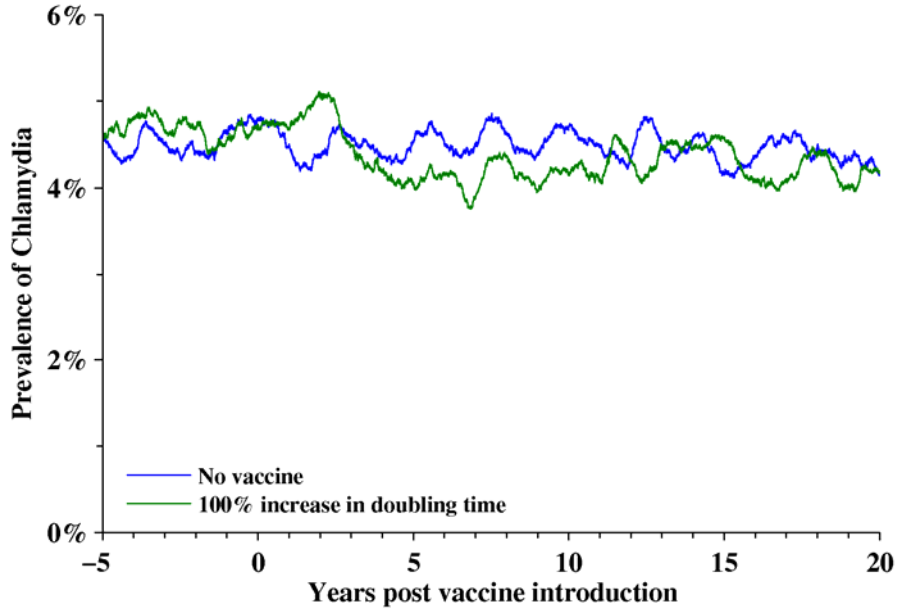


Figure 4b

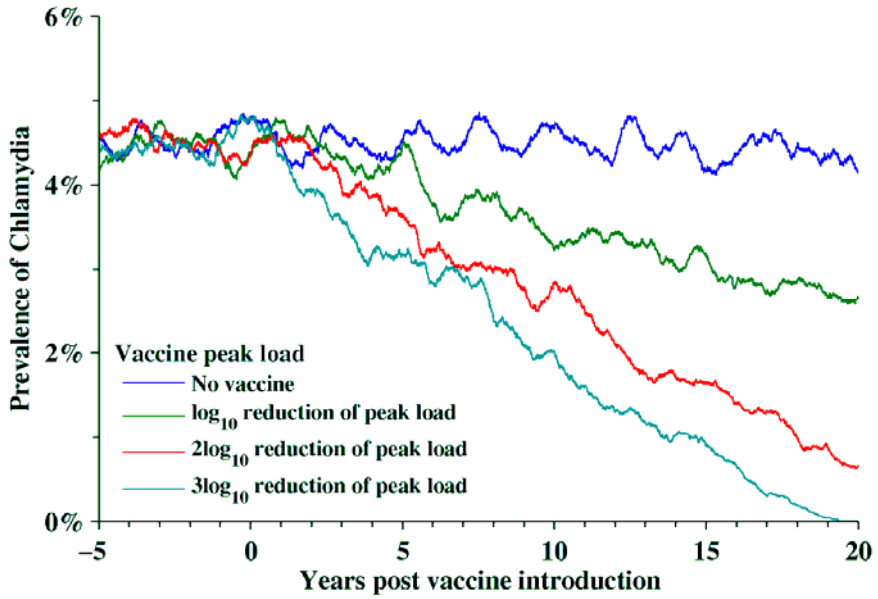


Figure 4c

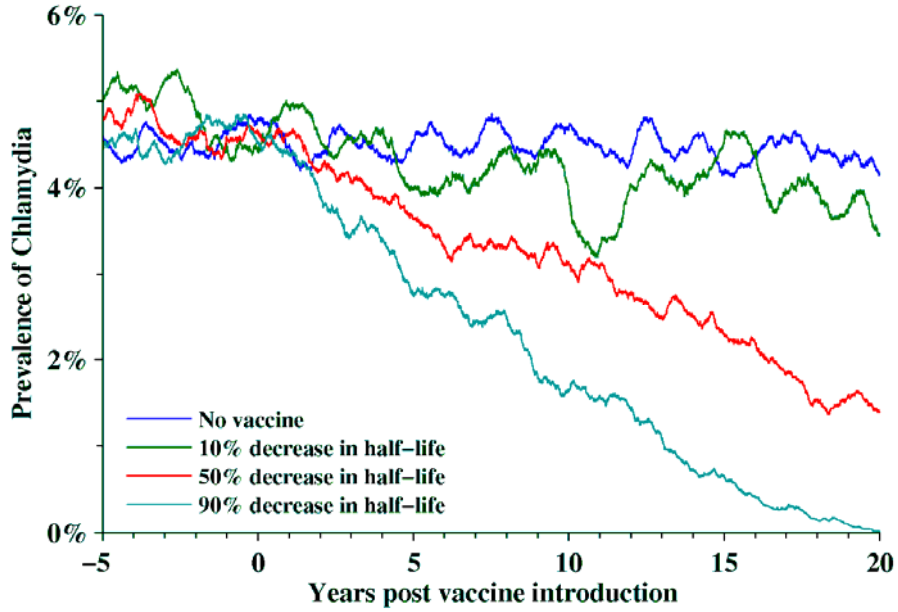


Figure 4d

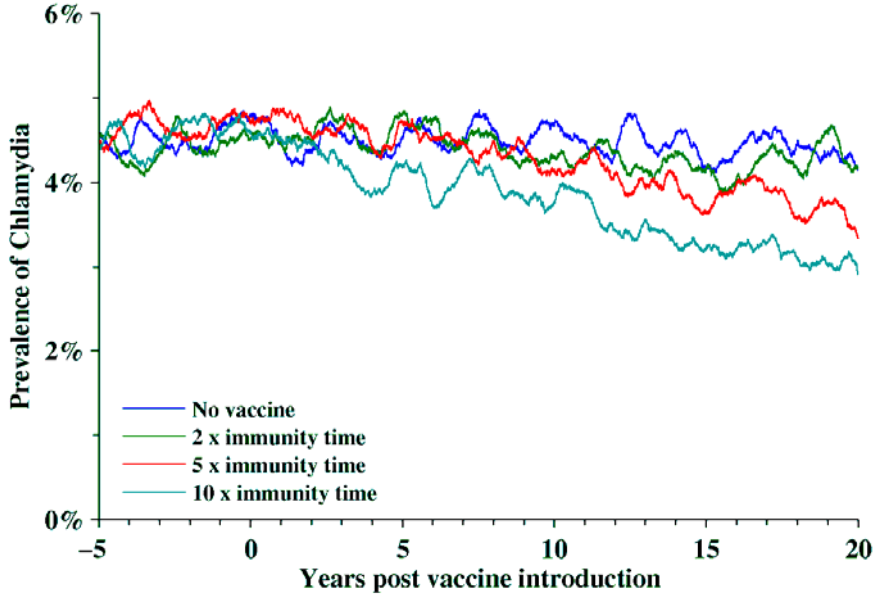
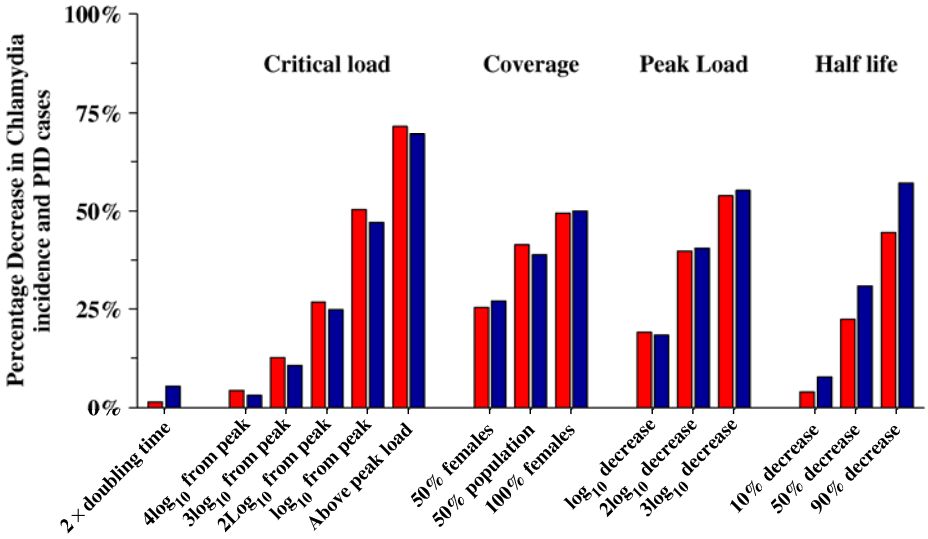


Figure 5


Percentage Decrease in Chlamydia incidence and PID cases
100%
75%
50%
25%
0%
Critical load
Coverage
Peak Load
Half life
2×doubling time
4log10 from peak
3log10 from peak
2Log10 from peak
log10 from peak
Above peak load
50% females
50% population
100% females
log10 decrease
2log10 decrease
3log10 decrease
10% decrease
50% decrease
90% decrease

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