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Impact of a potential Chlamydia vaccine in the USA: mathematical modelling analyses

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ABSTRACT

Introduction *Chlamydia trachomatis* (CT) infection is a global health challenge. New approaches are needed to control CT disease burden.

Methods An age-structured deterministic mathematical model calibrated to nationally representative population-based data was developed to investigate the impact of CT vaccination on the population of the USA if a vaccine becomes available. The model's parameters were chosen based on current knowledge from the literature on CT's natural history and epidemiology. The model's calibration used age-specific CT prevalence data sourced from the biannual rounds of the National Health and Nutrition Examination Surveys. The reported data are based on the outcomes generated by the model's simulations.

Results Over a 10-year period, vaccinating 80% of individuals aged 15–49 with a vaccine that reduces by 50% susceptibility to infection ($VE_S = 50\%$), infectiousness ($VE_I = 50\%$) or duration of infection ($VE_P = 50\%$) resulted, respectively, in 36.3%, 26.5% and 42.1% reduction in CT prevalence, and 38.8%, 28.6% and 24.1% reduction in CT incidence rate. Number of averted infections was 11 346 000, 7 583 000 and 6 012 000, respectively. When efficacies acted together ($VE_S = VE_I = VE_P = 50\%$), CT prevalence and incidence rate were reduced by 66.3% and 61.0%, respectively. Number of vaccinations needed to avert one infection was 17.7 for $VE_S = 50\%$, 26.5 for $VE_I = 50\%$, 33.4 for $VE_P = 50\%$ and 12.0 for $VE_S = VE_I = VE_P = 50\%$. Vaccinating individuals aged 15–19 and at highest risk of infection was most effective, requiring only 7.7 and 1.8 vaccinations to prevent one infection, respectively. Vaccination benefits were larger beyond 10 years.

Conclusion A moderately efficacious CT vaccine can significantly reduce CT disease burden. Targeting specific populations can maximise cost-effectiveness. Additional potential 'breakthrough' effects of the vaccine on infectiousness and duration of infection could greatly increase its impact. CT vaccine development and implementation should be a public health priority.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *Chlamydia trachomatis* (CT) infection is highly prevalent and causes diseases such as pelvic inflammatory disease, infertility and ectopic pregnancy in women, and urethritis and epididymitis in men. Large-scale 'test and treat' programmes appear to yield varied outcomes and may not have achieved their objective of substantially reducing CT prevalence. These programmes may have also resulted in adverse consequences, including relationship break-ups, overdiagnosis and overtreatment.

⇒ A fundamental control strategy is needed to address the burden of CT infection, such as vaccination. Based on the understanding of CT immunity, the development of a partially effective vaccine within the next few years holds promising potential.

⇒ A search conducted on PubMed did not identify any studies examining the population-level impact of a CT vaccine in the USA, encompassing various potential efficacies, target populations and epidemiological outcomes.

INTRODUCTION

Chlamydia trachomatis (CT) is a sexually transmitted bacterial infection (STI) that is highly prevalent globally.[1] The majority of CT infections are asymptomatic, regardless of the site of infection.[2] However, if left untreated, the infection can cause serious health problems, including pelvic inflammatory disease (PID), chronic pelvic pain, infertility and ectopic pregnancy in women, and urethritis and epididymitis in men.[3–7] According to the WHO, there were an estimated 127.2 million new CT cases worldwide among women and men aged 15–49 years in 2016.[1] In 2021, the Centers for Disease Control and Prevention (CDC) in the USA reported 1.6 million documented cases, making it the most common notifiable STI in that year.[8]

Despite efforts to control CT infection, the prevalence of this STI remains high. Large-scale 'test and treat' programmes implemented in different countries over the past 2–3 decades seem to yield varied outcomes,[2 9 10] and may not have achieved their objective of substantially reducing CT prevalence.[2] These

WHAT THIS STUDY ADDS

⇒ Mathematical modelling was used to assess the impact of a hypothetical CT vaccine in the USA on infection rates, considering different efficacy levels, durations of protection and population targeting, aiming to inform vaccine development, implementation and cost-effectiveness.

⇒ Introducing a CT vaccine with 50% efficacy against acquisition of infection in 2025 and achieving 80% coverage by 2035 among individuals aged 15–49 years could reduce prevalence, incidence rate, and annual new CT infections by 36.3%, 38.8% and 35.8%, respectively by 2035, preventing around 11 346 000 CT infections by 2035 and 31 427 000 by 2050.

⇒ The number of vaccinations needed to prevent one infection decreased over time from 17.7 by 2035 to 12.0 by 2050, and targeting specific population groups, such as the 15–19 age group and high-risk populations, reduced the number of vaccinations needed to prevent one infection.

⇒ Vaccination may have additional benefits, such as reducing infectiousness and duration of infection in vaccinated individuals who become infected, with comparable population-level impact to the vaccine's effect against CT acquisition.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Introducing a CT vaccine with moderate efficacy can substantially reduce rates of CT infection and related economic and disease burdens. The benefits of the vaccine become evident shortly after its launch and continue to increase over time.

⇒ The vaccine has the potential to be cost-effective, and its costeffectiveness can be further enhanced by targeting specific population groups.

⇒ Prioritising vaccine development and vaccination against CT should be regarded as a public health priority.

programmes may have also resulted in adverse consequences, including relationship break-ups, overdiagnosis and overtreatment, and could potentially contribute to antimicrobial resistance.[2 11 12] Furthermore, early detection and treatment of CT infection may hinder the development of an adequate immune response,[13 14] increasing susceptibility to reinfection at the individual level and reducing herd immunity at the population level, which counters reductions in prevalence.[13 15 16] A fundamental control strategy is needed to address this persistent infection and its disease and economic burdens.[17 18]

CT infection appears to confer partial protection against reinfection.[19 20] Studies conducted on laboratory animals suggest that CT infection induces both short-term complete immunity and long-term partial immunity.[21] The evidence for immune protection is further supported by several other observations, including the rapidly declining CT prevalence with age, similarity in prevalence among populations despite high variability in sexual risk behaviour, lower organism load with age and repeat infection, reduction in concordance rate in couples with age, and an apparent treatment attenuation of protective immunity.[19 22 23] Mathematical modelling studies estimated the effectiveness of primary CT infection against reinfection to be greater than 65%.[16 24] This partial protection may manifest as reduced susceptibility to reinfection, shorter duration of infection on reinfection and/or reduced infectiousness on reinfection (lower organism load).[16] Given this evidence, it is reasonable to believe that it might be possible to develop at least a partially effective vaccine against CT infection. Although the development of a CT vaccine is ongoing, it remains in the early stages.[25–27]

This study used mathematical modelling to investigate the impact of a prophylactic vaccine against CT infection. The main objective was to assess the effect on the prevalence and incidence of CT infection across various forms and levels of vaccine efficacy, as well as different durations of vaccine protection. Additionally, the study explored the optimal impact of the vaccine by targeting specific populations based on age, sex and sexual risk behaviour. These analyses are meant to inform vaccine's potential impact, preferred product characteristics, pathways and costs for vaccine development and implementation, licensure, and expected cost-effectiveness and return on investment, just as done for other infectious diseases.[28–33]

METHODS

Mathematical model

An age-structured, population-based, deterministic compartmental mathematical model was developed to describe the transmission of CT, building on previously published models,[16 23 34–40] and the canonical approach of Garnett and Anderson for modelling the force of infection.[41 42] The model was further extended to incorporate the potential impact of a prophylactic CT vaccine, informed by vaccine models developed for STIs and other infections.[30–32 43–46] The population was stratified by age, sex, sexual behaviour, CT infection status, and stage of infection, as well as vaccination status. The dynamics of infection were modelled using sets of nonlinear differential equations, with each set corresponding to a specific risk and age group. To reduce complexity, the model did not explicitly differentiate between different modes of sexual transmission. However, since input data were specific for urogenital infections, the model does not capture effects on infections at extragenital sites.

The model stratified the population into 20 age groups, with each group representing a 5-year age band (0–4, 5–9, 10–14, …, 95–99 years). However, most analyses focused on individuals aged 15–49 years. Sexual debut was assumed to occur at age 15 or older. Each age group was further divided into five sexual risk groups, based on a hierarchy of low to high sexual risk behaviour, as informed by data on the number of sexual partners over the last 12 months per the National Health and Nutrition Examination Surveys (NHANES).[47] The level of sexual risk behaviour was modelled using a power-law function that was informed by sexual partnership data[48] and network simulations and analyses.[49–52] The mixing of individuals across age and risk groups was described

using matrices that bridged two extremes of sexual mixing[42]: fully assortative (partnerships formed only within age or risk groups) and fully proportionate (partnerships formed with no preferential bias by age or risk). Description of the partnership change rates by risk and age and the prescription for balancing sexual partnerships between females and males can be found in online supplemental material, pp13–15.

The natural history of CT infection was modelled as a progression from a susceptible state to either symptomatic or asymptomatic infection, followed by natural temporary immunity, as supported by empirical evidence.[1 16 34 53] Both symptomatic and asymptomatic individuals were eligible for treatment in the model, but at different rates.

The model and its equations are described in online supplemental text and table 1. A schematic diagram is shown in online supplemental figure 1. The basic reproduction number of CT infection in a fully unvaccinated population and in a fully vaccinated population were derived using the next generation matrix method[54] (online supplemental text). The model was implemented, fitted and analysed using Matlab R2019a.[55] Simulations were conducted in part using the Red Cloud infrastructure of Cornell University.

Data sources

The model's parameters were determined based on current understanding of CT natural history and epidemiology, as well as on reported sexual behaviour patterns, as outlined in online supplemental text. Online supplemental table 2 lists the values of the model parameters. It is worth noting that the model's parameterisation was informed by a thorough review of existing STI models and their parameterisation (see Johnson and Geffen[34]), as well as by the parameterisation approach adopted by the WHO STI model (see Rowley *et al* and Newman *et al*[1 53]).

We estimated CT prevalence in the USA using age-specific data from the publicly available (1999–2016) NHANES biannual rounds.[47] CT treatment rates were informed by the WHO's STI model, for both symptomatic and asymptomatic infections.[1 53] Coital act frequency was based on empirical age-specific data.[16 56] We used the United Nations' World Population Prospects database for sex-specific demographics (see online supplemental figure 2).[57]

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Model fitting

The model was fitted to NHANES time series data for CT prevalence, as well as to age-specific CT prevalence.[47] The age-specific CT prevalence was pooled over the nine NHANES rounds using DerSimonian-Laird random-effects meta-analysis.[58] To fit the model to CT data, we varied the fitting parameters describing the overall level of partnership change rate by sex in the population as well as the age-specific partner change rates (note parametrisation in online supplemental material, pp14–15). We obtained birth and mortality rates by fitting the sex-specific population sizes of the US population,[57] using Gaussian-logistic functions.[59 60] Non-linear least-square fitting was used to minimise the sum of squares between all data points and model predictions, with the Nelder-Mead simplex algorithm[61] being employed for the fitting.

Vaccine efficacies

The conventional measure of a vaccine's effect is its efficacy VE_S, which quantifies the proportionate reduction in susceptibility to infection on vaccination[32] (figure 1 and online supplemental table 3). However, CT vaccines are expected to provide only partial protection against acquisition of the infection.[26 45] As a result, it is critical to assess how the vaccine influences the natural history and transmission of the infection in vaccinated individuals who still contract the infection.[45 62] Understanding these effects is essential to determine the vaccine's population-level impact.

In figure 1, a conceptual diagram illustrates two additionally possible vaccine efficacies, VE_I and VE_P.[32] If vaccinated individuals contract the infection, their immune response may inhibit bacterial growth and reduce the organism load, resulting in a reduction of their infectiousness relative to unvaccinated individuals.[26 45 62] This defines VE_I as the proportional reduction in the infectiousness of vaccinated individuals compared with unvaccinated individuals.[32] Additionally, the vaccine-primed immune response may shorten the duration of infection (faster clearance rate), resulting in a reduction in the time an infected individual remains infectious.[45] This defines VE_P as the proportional reduction in the duration of infection for vaccinated individuals compared with unvaccinated individuals.[32]

As the protection offered by a CT vaccine is likely to be finite in duration and not lifelong,[26 45] the duration of protection is a critical factor in determining the vaccine's impact. Our main analysis assumed that the vaccine would offer protection for an average of 20 years, to cover individuals aged 15–34 years who are at highest risk of infection (figure 2C,D).[47] Achieving this duration of protection may require a primary vaccination series supplemented by booster shots.

The model of this study operated under the assumption that individuals lose their vaccine protection at a constant rate, implying an exponentially distributed duration of protection. Consequently, although the average duration of protection is 20 years, a considerable number of individuals would lose their vaccine immunity within a few years after vaccination, while others would maintain their immunity for over 20 years.

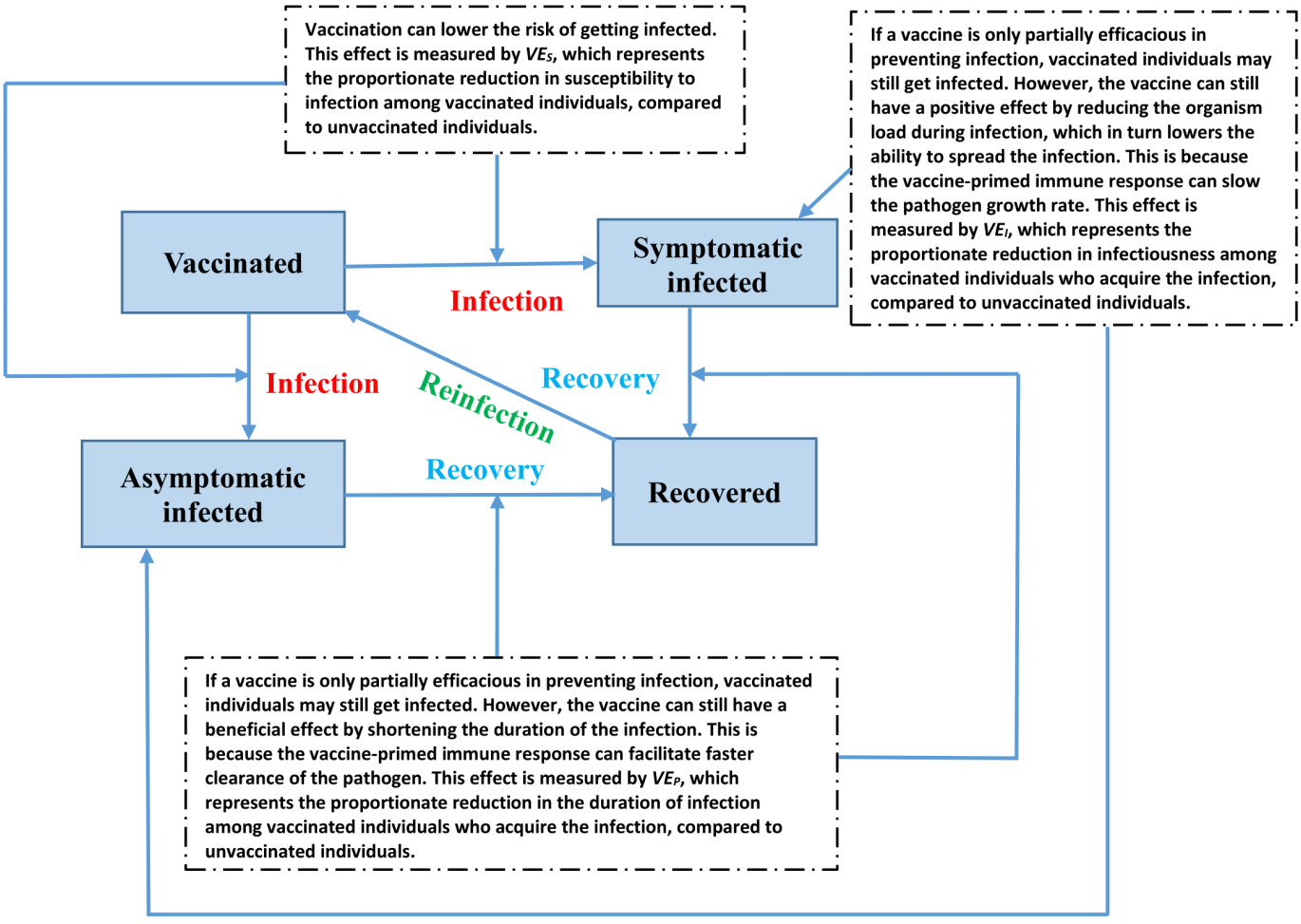

Figure 1 Conceptual diagram of the vaccine's effects on *Chlamydia trachomatis* acquisition, transmission and duration of infection, thereby defining the vaccine efficacies of VE_S, VE_I and VE_P.

Measures of vaccine impact

The impact of a CT vaccine at a population level is determined by both its direct effects (VE_S, VE_I, VE_P and duration of protection) and its indirect effects (reducing the onward transmission of the infection within the population). Vaccine's impact was evaluated by comparing prevalence, incidence rate and annual number of new infections in the presence of vaccination with those in a counterfactual scenario without vaccination. Vaccine impact was also evaluated using the number of vaccinations needed to avert one CT infection over a specific time horizon, calculated by dividing the number of vaccinations over the number of averted infections, both over this specific time horizon.

For instance, the calculation of the number of averted infections by 2050 involves subtracting the number of infections projected from 2025, the year when vaccination begins, to 2050 in a scenario where the vaccine is introduced from the number of infections projected in the same period in a scenario where no vaccination is implemented. Therefore, in estimating these metrics, we have adopted a programme perspective, assessing the number of vaccinations required to prevent one infection from the programme's initiation up to a specific year.

Scenarios for vaccination

The impact of a CT vaccine was evaluated using various scenarios. The primary scenario involved introducing a vaccine with a 20-year average duration of protection in 2025, vaccinating individuals between the ages of 15–49 years, and gradually increasing vaccine coverage (at a constant vaccination rate) to reach 80% by 2035. In this scenario, the impact was assessed for a vaccine with (1) $VE_S = 50\%$ but $VE_I = VE_P = 0\%$, (2) $VE_I = 50\%$ but $VE_S = VE_P = 0\%$, (3) $VE_P = 50\%$ but $VE_S = VE_I = 0\%$ and (4) $VE_S = VE_I = VE_P = 50\%$. To explore the impact through population prioritisation, the primary scenario was adjusted to only vaccinate certain populations based on age, sex and sexual risk behaviour.

Vaccination was implemented in the model as a fixed rate per person-year, representing the rate at which susceptible individuals of a specific age group and risk group are vaccinated (note online supplemental figure 1, tables 1 and 4 and model equations online supplemental material, pp5–6). These rates were determined through model fitting to achieve predefined vaccination coverage levels in each scenario under consideration.

Vaccine coverage, such as 80%, implies that 80% of the targeted population currently has vaccine protection. It

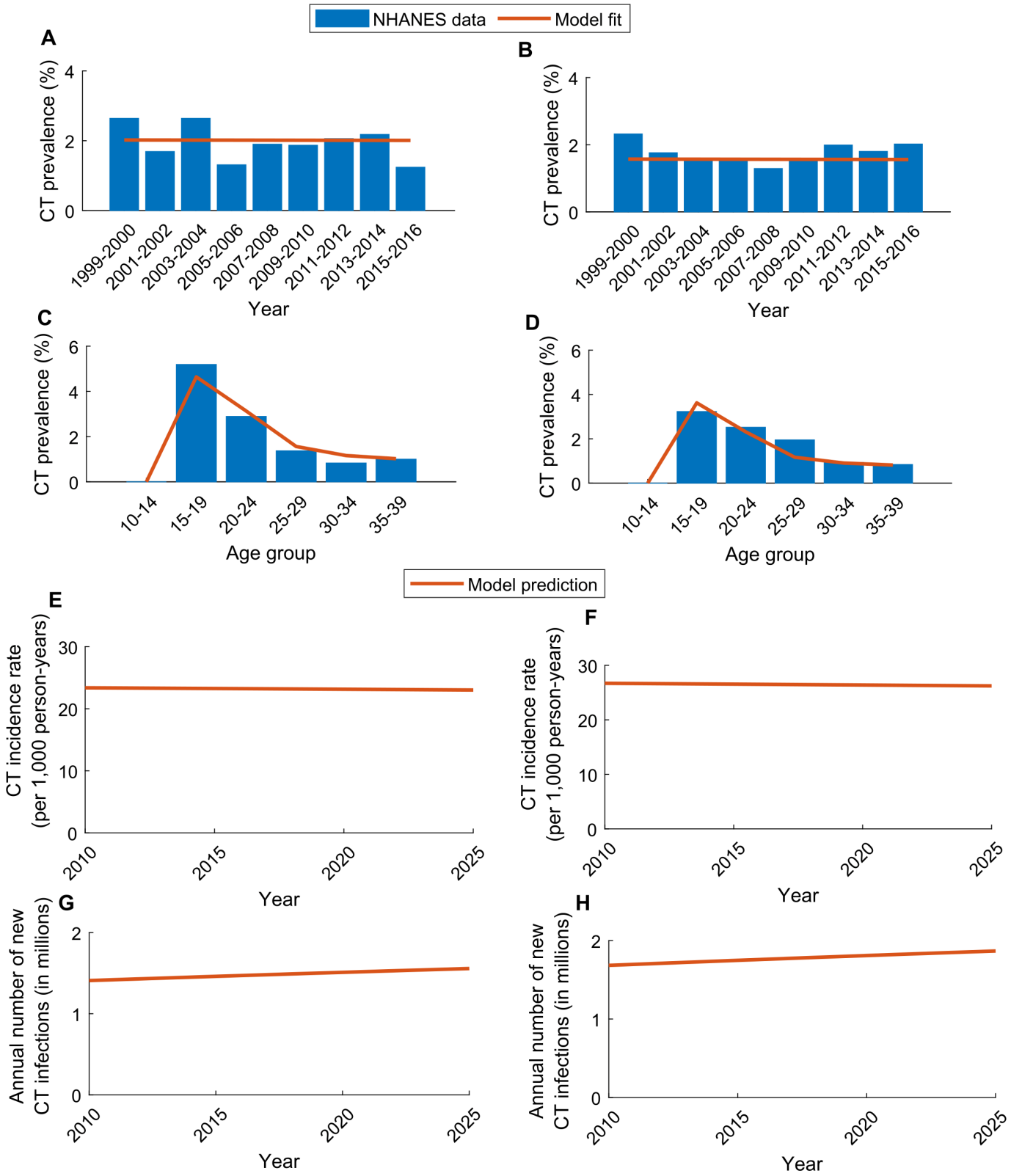

Figure 2 CT infection in women and men in the USA. Model fit of CT prevalence (A) among women and (B) men aged 15–39 years, compared NHANES data, 1999–2016. Model fit of the age-specific CT prevalence in (C) women and (D) men aged 15–39 years, compared with the pooled prevalence over NHANES rounds, 1999–2016. Model-estimated incidence rate among (E) women and (F) men aged 15–49 years. Model-estimated annual number of new CT infections among (G) women and (H) men. CT, *Chlamydia trachomatis*; NHANES, National Health and Nutrition Examination Surveys.

was assumed that once individuals lose vaccine immunity, which occurs after an average of 20 years in the main scenario, these individuals are revaccinated at the same vaccination rate. This assumption is based on the idea that maintaining long-term vaccine protection for bacterial infections, such as for 20 years, may require an initial vaccination series supplemented by periodic booster shots every few years. All vaccinations, whether for the primary series or booster vaccinations, are counted in the model, and all results presented in this study account for the number of implemented vaccinations.

Additional analyses

To determine the vaccine product characteristics that will lead to an optimal outcome, vaccine impact was assessed at various levels for VE_S, VE_I, VE_P and average duration of protection. Further analyses were conducted to examine the effect of variation in the average duration of immune protection of natural infection and the vaccine's potential effect of reducing the proportion of infected individuals who become symptomatic.

Three additional analyses were also conducted to examine how the number of vaccinations needed to avert one CT infection varies with vaccine coverage, to assess whether the estimated vaccine impact may have been influenced by an underestimation of CT incidence and the proportion of women diagnosed and treated in the USA, and to assess the potential impact on the study results of setting the male-to-female transmission probability of CT infection per sex act at two times that of the female-to-male transmission probability. Finally, an additional analysis was conducted by assessing vaccine impact in a modified version of our model excluding revaccination for individuals with waned vaccine protection.

Uncertainty analyses

A multivariable uncertainty analysis was performed to examine the impact of model parameter uncertainty on the number of vaccinations required to prevent one CT infection, by deriving the 95% uncertainty interval (UI). Latin Hypercube sampling[63 64] was used to generate parameter distributions, assuming ±30% uncertainty around the point estimates (online supplemental table 2). The parameters included in the analysis were the duration of infection, duration of natural immunity, treatment rates for symptomatic and asymptomatic infections, proportion of infected individuals becoming symptomatic, proportion of individuals becoming immune after treatment, degree of assortativeness for risk group and age group mixing, transmission probability per coital act, frequency of coital acts and the exponent parameter in the power law function for the distribution of sexual risk behaviour. The model was run 500 times with randomly selected parameter values and refitted in every run to determine vaccine impact.

Role of the funding source

The Biomedical Research Programme at Weill Cornell Medicine-Qatar supported this study. The funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

RESULTS

Model fitting and CT prevalence and incidence

The model fitted the total and age-specific population sizes of females and males between 1950 and 2100 (online supplemental figure 2),[57] time-series of NHANES CT prevalence in women and men aged 15–39 years[47] (figure 2A,B), and pooled age-specific CT prevalence across NHANES rounds in women and men aged 15–39 years[47] (figure 2C,D).

CT prevalence in women and men remained relatively stable over time, with approximately 2.0% prevalence in women and 1.6% in men (figure 2A,B). Prevalence rapidly increased following sexual debut and peaked at 4.6% and 3.6% in women and men aged 15–19 years, respectively, before declining to 1.0% and 0.8% in women and men aged 35–39 years (figure 2C,D). The incidence rate of CT infection remained relatively stable over time, with an estimated 23 and 26 new cases per 1000 person-years in women and men, respectively (figure 2E,F). Despite the stable incidence rate, the annual number of new infections increased due to population growth, resulting in an estimated 1 539 000 and 1 844 000 new infections in 2023 in women and men aged 15–49 years, respectively (figure 2G,H).

Vaccine impact on CT prevalence and incidence and number of vaccinations needed to avert one infection

Figures 3–5 demonstrate the impact of the primary scenario, which involves introducing a vaccine in 2025 and scaling it up to achieve 80% coverage by 2035 among persons 15–49 years of age. When a vaccine with $VE_S = 50\%$ was introduced, CT prevalence was reduced by 36.3% by 2035, while CT incidence rate and annual number of new infections were reduced by 38.8% and 35.8%, respectively. The vaccine was estimated to avert 11 346 000 infections by 2035 and 31 427 000 by 2050. The number of vaccinations required to avert one infection decreased over time, from 17.7 by 2035 to 12.0 by 2050 (figure 6A).

When instead a vaccine with $VE_I = 50\%$ was introduced, CT prevalence was reduced by 26.5% by 2035, while CT incidence rate and annual number of new infections were reduced by 28.6% and 26.1%, respectively. The vaccine was estimated to avert 7 583 000 infections by 2035 and 22 410 000 by 2050. The number of vaccinations required to avert one infection decreased from 26.5 by 2035 to 16.8 by 2050 (figure 6A).

When a vaccine with $VE_P = 50\%$ was introduced, CT prevalence was reduced by 42.1% by 2035, while CT incidence rate and annual number of new infections were reduced by 24.1% and 21.9%, respectively. The vaccine

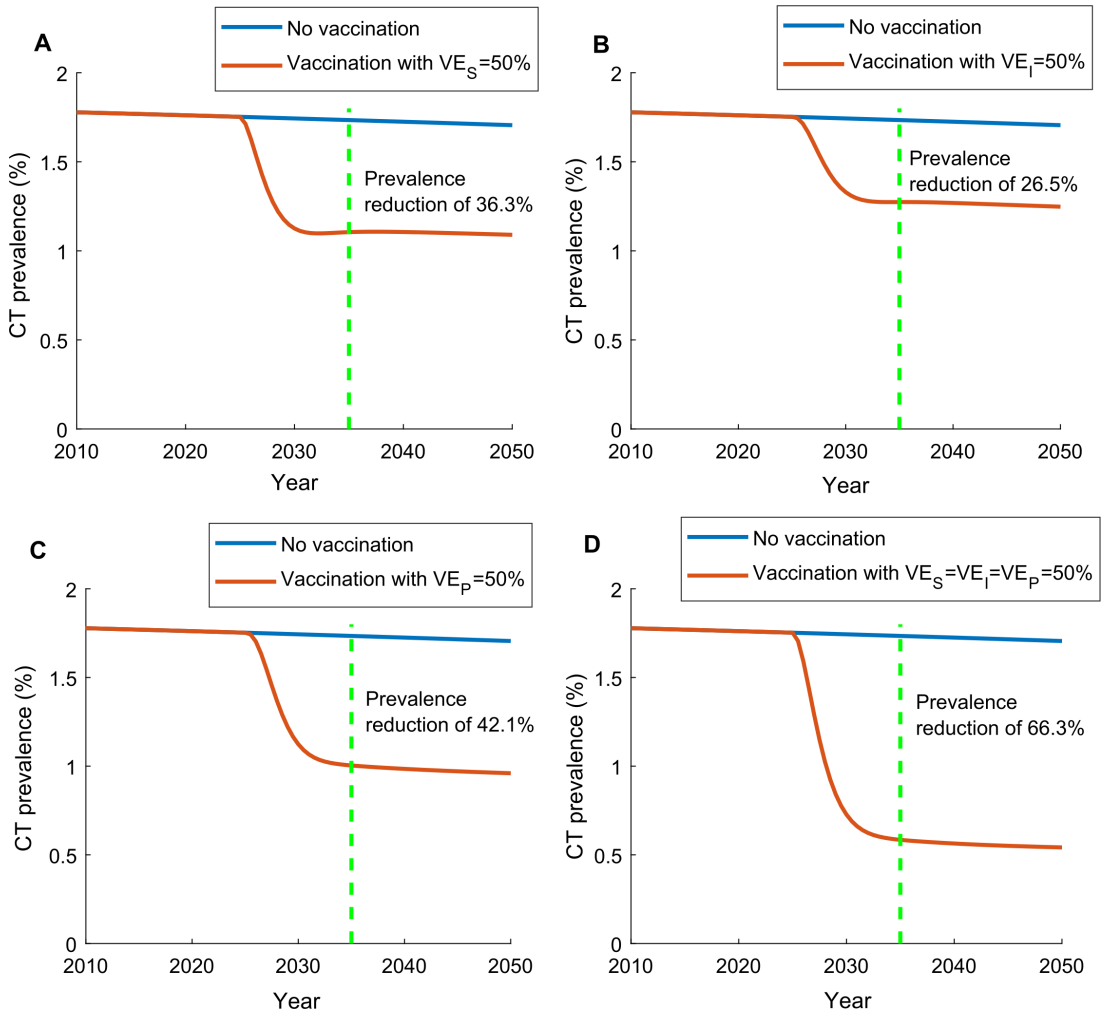

Figure 3 Impact of *Chlamydia trachomatis* (CT) vaccination on CT prevalence among persons aged 15–49 years in the USA. Impact of the vaccine at (A) VE_S = 50%, (B) VE_I = 50%, (C) VE_P = 50% and (D) VE_S = VE_I = VE_P = 50%. Average duration of vaccine protection is 20 years. The vaccine is introduced in 2025, with its coverage being scaled up to 80% by 2035.

was estimated to avert 6 012 000 infections by 2035 and 18 517 000 by 2050. The number of vaccinations required to avert one infection decreased from 33.4 by 2035 to 20.3 by 2050 (figure 6A).

The vaccine's impact was obviously greatest when the three efficacies were combined (ie, VE_S = VE_I = VE_P = 50%), reducing CT prevalence by 66.3% by 2035, CT incidence rate and annual new infections by 61.0% and 58.3%, respectively. The vaccine averted 16 898 000 infections by 2035 and 49 989 000 by 2050. The number of vaccinations required to avert one infection decreased from 12.0 by 2035 to 7.7 by 2050 (figure 6A).

Impact of adolescent vaccination

If the vaccine was limited to adolescents aged 10–14 years instead of the 15–49 years age group, the impact (on the 15–49 years age group) was lower, but still substantial (online supplemental figure 3). With VE_S = 50%, the reduction in prevalence was 22.5% by 2035, compared with 36.3% for the broader age group, and 27.4% versus 36.0% by 2050.

Impact of population prioritisation

To prevent one infection, the number of vaccinations required varied depending on the population group targeted by the vaccine. The age group of 15–19 years needed the lowest number of vaccinations with a value of 7.7 by 2035 (figure 6B), while the age group of 45–49 years required the highest number of vaccinations, with a value of 59.0. The second-lowest number of vaccinations required was in the age group of 10–14 years with a value of 11.2.

High-risk groups (who proxy the subpopulations experiencing the highest force of infection in the population such as female sex workers and men who have sex with men) required the lowest number of vaccinations to prevent one infection, with a value of approximately 2 (figure 6C). In contrast, the general population with the lowest risk required the highest number of vaccinations, with a value of 605.7. There was no significant difference in the number of vaccinations needed to prevent one infection when targeting either women or men (figure 6D).

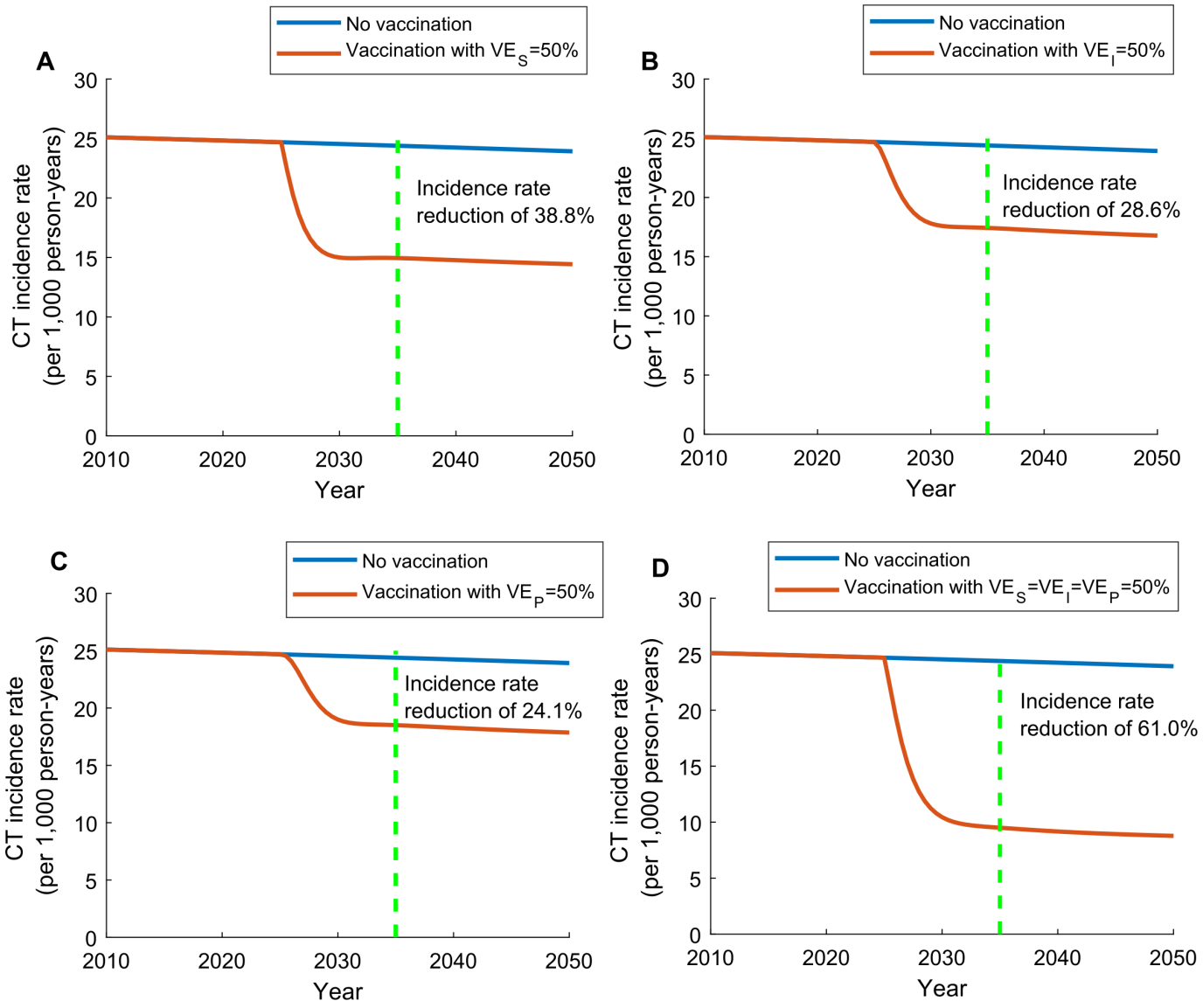

Figure 4 Impact of *Chlamydia trachomatis* (CT) vaccination on CT incidence rate among persons aged 15–49 years in the USA. Impact of the vaccine at (A) $VE_S = 50\%$, (B) $VE_I = 50\%$, (C) $VE_P = 50\%$ and (D) $VE_S = VE_I = VE_P = 50\%$. Average duration of vaccine protection is 20 years. The vaccine is introduced in 2025, with its coverage being scaled up to 80% by 2035.

Additional analyses and results

Online supplemental figures 4–7 show the impact of the vaccine across the entire range of vaccine efficacies for VE_S, VE_I and VE_P, and for an average duration of vaccine protection spanning from 1 week to 30 years. The vaccine's impact was particularly sensitive to the duration of vaccine protection, especially when the vaccine efficacy was high.

Vaccination could (theoretically) decrease the proportion of infected individuals who develop symptoms, resulting in increased transmission of the infection as asymptomatic carriers may not be diagnosed and treated.[65] However, online supplemental figure 8 indicates that this scenario is unlikely to lead to an overall negative vaccine impact, provided that the vaccine has at least moderate efficacy (online supplemental figure 8).

The average duration of protection against reinfection after a natural infection is not well-established,[16] but it could have implications for the vaccine impact. According to the results presented in online supplemental figure 9, vaccine impact is greater when the duration of natural immunity is shorter, but the impact of the vaccine is overall not affected by this duration as long as it lasts for at least 10 years. The number of vaccinations needed to prevent one CT infection was found to decrease, although at a relatively slow rate, with increasing vaccine coverage (online supplemental figure 10).

Our model parameterisation, based on the WHO STI model parameterisation for global analyses,[1 53] could have underestimated the proportion of women who receive diagnosis and treatment in the USA.[8] This underestimation is due to the large CT screening and treatment programmes available to women. Online supplemental figure 11 illustrates the vaccine impact when the probability of asymptomatic women receiving treatment is increased from 0.07 to 0.56, representing an eightfold

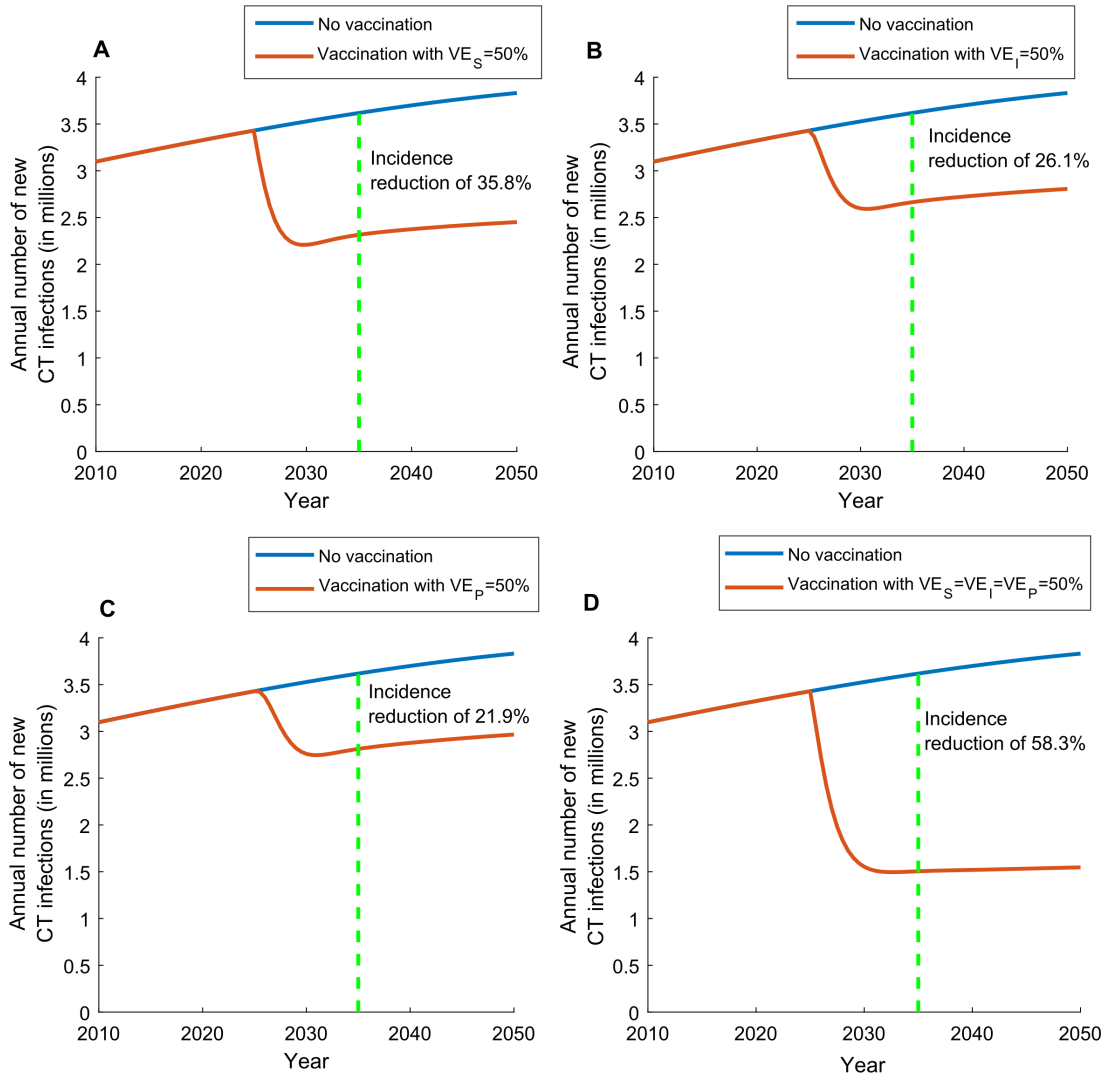

Figure 5 Impact of *Chlamydia trachomatis* (CT) vaccination on the annual number of new CT infections among persons aged 15–49 years in the USA. Impact of the vaccine at (A) $VE_S = 50\%$, (B) $VE_I = 50\%$, (C) $VE_P = 50\%$ and (D) $VE_S = VE_I = VE_P = 50\%$. Average duration of vaccine protection is 20 years. The vaccine is introduced in 2025, with its coverage being scaled up to 80% by 2035.

increase and resulting in nearly a million women being treated for CT annually. This adjustment in model parameterisation had a limited effect on the estimated vaccine impact (online supplemental figure 11 compared with figures 3–5).

Online supplemental figure 12 shows the impact on the study results of setting the male-to-female transmission probability of CT infection per sex act at twice that of the female-to-male transmission probability. This adjustment in model parameterisation had a limited effect on the estimated vaccine impact (online supplemental figure 12 compared with figures 3–5).

Online supplemental figure 13 compares vaccine impact in the baseline model, including revaccination for individuals with waned vaccine protection, to the modified model, excluding revaccination for those with waned vaccine protection. Inclusion or exclusion of revaccination had a generally small effect on vaccine impact up to 2050, whether on prevalence, incidence rate, annual number of new infections or the number of vaccinations needed to avert one infection. As expected, the differences between these two models were minimal in the short-term and increased in the long-term, as more individuals lost their vaccine protection over time.

Vaccination and the reproduction number of CT infection

Online supplemental figure 14 illustrates the relationship between the basic reproduction number of CT infection in a fully vaccinated population (R_0^V), relative to the basic reproduction number in a fully non-vaccinated population (R_0), and VE_S, VE_I, VE_P, and $VE_S = VE_I = VE_P$. This ratio decreased linearly with VE_S and VE_I, but non-linearly with VE_P and $VE_S = VE_I = VE_P$. R_0^V declined rapidly with increasing VE_P.

Uncertainty analysis

Online supplemental figure 15 presents the results of the uncertainty analysis. Despite low precision in model

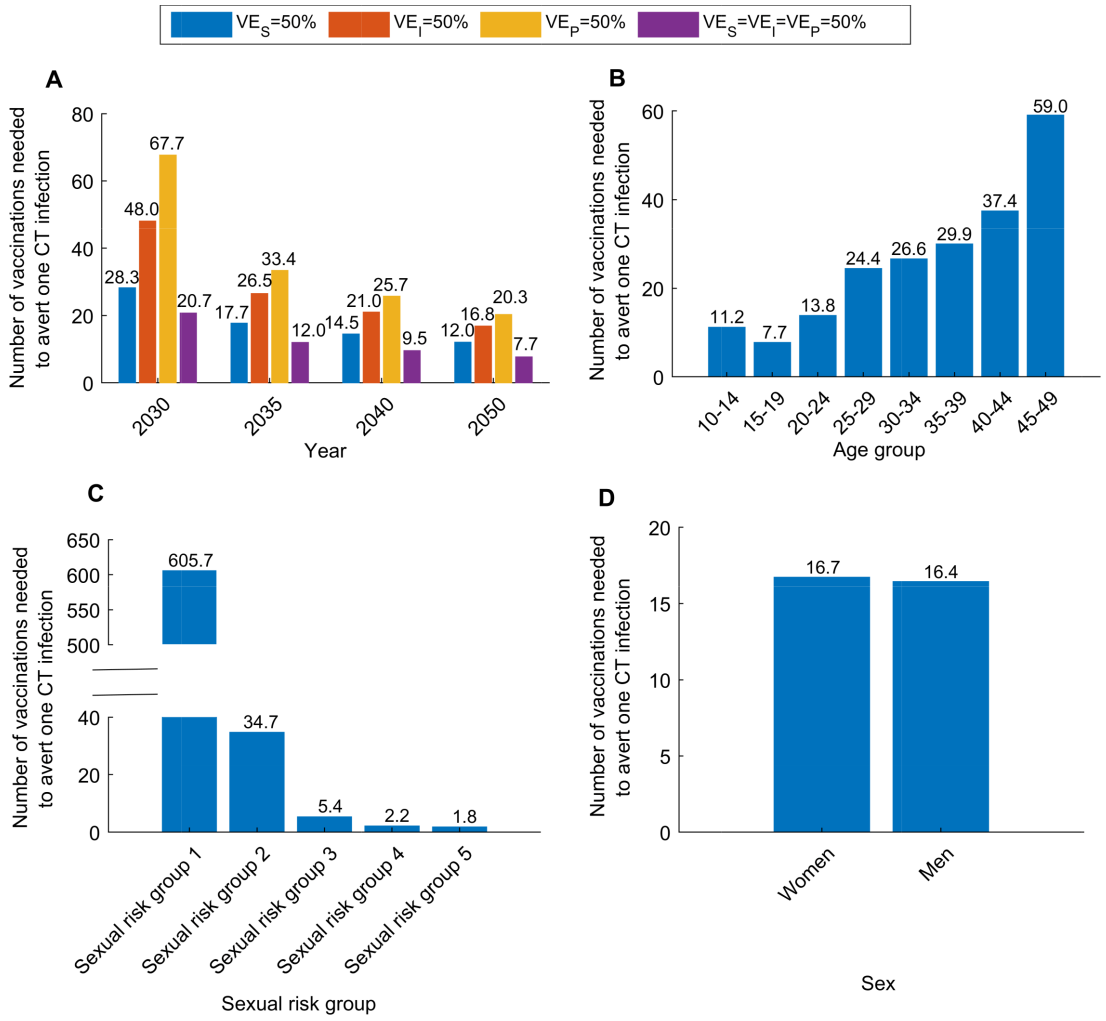

Figure 6 Vaccine prioritisation and number of vaccinations needed to avert one *Chlamydia trachomatis* (CT) infection. Number of vaccinations needed to avert one CT infection (A) versus time and type of vaccine efficacy, (B) by age group prioritisation in 2035, (C) by sexual risk group prioritisation in 2035 and (D) by sex prioritisation in 2035. Average duration of vaccine protection is 20 years. The vaccine is introduced in 2025, with its coverage being scaled up to 80% by 2035. In B, C and D, $VE_S = 50\%$.

parameters such as those relating to natural history of infection and sexual behaviour in the population, the overall predicted impact of the vaccine is not expected to be significantly affected by this uncertainty.

DISCUSSION

Vaccination against CT can significantly reduce infection rates in the USA, even if the vaccine has a moderate efficacy of only 50% and does not provide sterilising immunity. The vaccine's benefits become apparent within a few years of its launch, and its impact increases with time. With the relatively small number of vaccinations needed to prevent one infection, the vaccine may have the potential to be cost-effective (if not cost-saving) under plausible scenarios, even at moderate efficacy and significantly costly vaccine, in line with a health economics analysis.[66] By 2035, 18 vaccinations can prevent one infection, and this number could drop to just 12 by 2050. Vaccination against CT should be considered a priority public health measure to control its spread and reduce the disease and economic burdens associated with it.

To optimise the cost-effectiveness of the vaccine, it can be targeted towards specific population groups. Vaccinating the 15–19 age group is the most effective, with only eight vaccinations needed by 2035 to prevent one infection. Adolescents between the ages of 10 and 14 are also a good target group, with only 11 vaccinations needed to prevent one infection. Populations at high risk of infection, such as female sex workers and men who have sex with men, can benefit greatly from vaccination, with only two vaccinations needed to prevent one infection.

It is expected that the CT vaccine will be developed to prevent acquisition of the infection with a specific value for VE_S. However, breakthrough infections among vaccinated individuals are likely to have a modified natural history. For instance, vaccinated individuals who acquire SARS-CoV-2 experience lower viral load and shorter duration of infection.[67–69] It is plausible that the CT vaccine will have additional biological effects that are

related to the mechanisms of action behind its VE_S, such as reducing the infectiousness (VE_I) and duration (VE_P) of the infection, as supported in laboratory studies on animal models.[26 45 62] The study findings indicate that these 'breakthrough' effects could be as impactful as the conventional vaccine effect against infection acquisition, confirming earlier findings.[45] A CT vaccine developed to protect against acquisition of the infection is likely to have a larger population impact than expected based solely on the measured value of VE_S. These findings emphasise the importance of measuring, in vaccine trials, the effects of the vaccine on bacterial load and duration of infection in addition to its effect on acquisition of the infection.

The impact of the three efficacies, VE_S, VE_I and VE_P, was generally comparable, but with some differences. VE_P had a smaller impact on incidence of infection (figures 4 and 5), but a larger impact on prevalence (figure 3), due to shorter duration of infection. This shorter duration may decrease the likelihood of serious disease sequelae, such as PID,[45] making VE_P particularly important for public health. VE_I had an overall smaller impact than VE_S, but targeting the vaccine to those under 20 years old and populations at highest risk may increase its impact since they have higher rates of secondary transmissions (online supplemental figure 3).

The study has limitations due to uncertainties and assumptions in modelling CT infection. The validity and generalisability of input data are important for our model estimations, but the natural history and transmissibility of this infection are still inadequately understood.[16 17 34 70 71] This challenge primarily arises due to the ethical complexities associated with conducting studies to directly measure these aspects, given the treatable nature of CT infection. Consequently, researchers often resort to indirect methods to estimate these parameters, resulting in varying results among different studies. Nonetheless, vaccine impact assessment relies on metrics that gauge relative changes, making it less susceptible to the constraints imposed by an incomplete understanding of the infection's natural history and transmissibility. This is evident in the different additional analyses conducted with varying assumptions for the model parameters, where the resultant vaccine impact estimate displayed generally minimal variations.

The model calibration relied on nine publicly available NHANES rounds, and recent rounds were not included, although this is unlikely to affect the predictions given the largely stable prevalence of CT in the USA.[47 72–74] We did not consider possible risk behaviour changes that may occur after vaccination due to the absence of concrete evidence supporting this possibility.[75] The definition of a 'sexual risk group' is somewhat ambiguous,[40 76 77] making the results for vaccine effectiveness among these groups approximate.

The model did not explicitly account for the effects of CT testing and treatment programmes. This approach is rooted in the debate surrounding whether CT testing and treatment programmes have had a considerable impact on CT prevalence.[2] However, in practice, we indirectly account for the effects of testing and treatment programmes. This is accomplished through our model's calibration to observed prevalence rates, which inherently reflects the dynamics of CT transmission in the presence of testing and treatment.

Our estimated number of incident CT infections in women is lower than the most recent CDC model estimate[72] but comparable to the earlier CDC round estimate.[73] This difference may have arisen due to an underestimation of the proportion of women who receive diagnosis and treatment,[8] leading to effectively a longer duration of infection in the population than in reality. The number of women diagnosed and treated for CT annually in the USA[8] is substantially higher than what is implicit in our model assumptions and its baseline results. This difference with CDC estimates may have also occurred because of variations in the assumed natural history parameters for this infection, which remain inadequately characterised.[16 17 34 70 71]

However, while estimating incidence can be challenging, the same does not hold true for prevalence. Prevalence is reliably captured through the high-quality NHANES,[47] whereas incidence is generated indirectly through modelling estimations with additional assumptions. Our model was fitted to these NHANES prevalence estimates. As a result, our estimates related to vaccine impact on prevalence should be robust, while those pertaining to absolute incidence among women could be conservative. Notably, even when we increased the probability of asymptomatic women receiving treatment by eightfold, thereby indirectly considerably increasing estimated incidence, this adjustment had a limited effect on the estimated vaccine impact in terms of the relative reduction in incidence following vaccination.

Our modelling approach assumed a prophylactic vaccine with benefits directed toward individuals who have not previously been infected with CT. It is reasonable to assume that once a person has been infected with CT, the vaccine may not offer additional benefits. This assumption is supported by both human and laboratory animal data on CT immunity.[19–21] However, in the actual implementation of the vaccine, it may not be feasible to restrict vaccination to those who have not been exposed to the infection. Determining whether individuals with prior exposure can benefit from vaccination and whether the benefits outweigh potential risks may require empirical data. These factors should be taken into consideration in future research, especially when data become available for a specific CT vaccine and its indications and target populations. It is possible that CT vaccination will follow a model similar to the human papillomavirus vaccination programme,[75] targeting adolescents before their initial exposure to the infection.

The model operated under the assumption that individuals losing their vaccine protection would be revaccinated to maintain continuous immunity. Although this

assumption might appear idealised, it is grounded in the concept that sustaining long-term vaccine protection for such a bacterial infection could necessitate an initial vaccination series supplemented by periodic booster shots administered every few years. These boosters are typically administered according to a schedule, without relying on individualised laboratory testing to assess the waning of immunity. Notably, all vaccinations, including both the primary series and booster shots, were counted in the presented modelling scenarios. The results presented in this study, such as the number of vaccinations needed to avert one infection, also incorporate the total number of implemented vaccinations.

The durability of vaccine immunity and how this immunity will wane remain unknown. If 20-year vaccine protection can be achieved solely through the primary vaccination series, the model-estimated number of vaccinations, implicitly incorporating the count of booster vaccinations, exceeds the actual requirement. This overestimation stems from the model's assumption that the duration of protection follows an exponentially distributed pattern. Consequently, a significant portion of individuals would lose their vaccine protection within a few years of vaccination and would subsequently be revaccinated, while others would retain immunity for more than 20 years. The model's estimated absolute impact on prevalence and incidence would also be overestimated due to these revaccinations. It should be noted, however, that the inclusion or exclusion of these revaccinations had a generally small effect on vaccine impact up to 2050 (online supplemental figure 13).

This study was exclusively focused on evaluating the epidemiological impact of CT vaccination. It did not include a health economics analysis that takes into account various cost components, such as diagnosis, clinic visits, treatment for individuals with asymptomatic and symptomatic infections, management of women with PID, addressing women with ectopic pregnancies, and the expenses associated with individuals seeking assisted reproductive technologies due to infertility. A natural extension of this research involves gathering comprehensive cost information and conducting detailed health economics analyses, optimally when cost data related to the vaccine becomes available. This approach would provide a comprehensive perspective on the economic implications of CT vaccination, significantly augmenting our understanding of its epidemiological impact.

Ideally, it would have been best to use CIs or ranges for the parameters in the uncertainty analysis based on actual empirical values.[78] However, such confidence intervals or ranges are not available due to the inadequate understanding of the natural history and transmissibility of this infection. Therefore, we employed a commonly applied approach in the epidemiological modelling literature[44 59 79–82] of applying a uniform (±30%) uncertainty around the point estimates of the parameters.

This study has strengths. Our model was complex enough to account for the complexity of CT transmission and different vaccine characteristics, yet also tailored to the available data. The results are robust to a wide range of model assumptions and are not overly sensitive to imprecision in knowledge of the infection's natural history parameters. Our model generated conservative estimates. For instance, if the duration of protection against reinfection following natural infection is shorter than our assumption, the vaccine's impact is higher (online supplemental figure 9).

In conclusion, a moderately efficacious CT vaccine can significantly reduce infection rates and control the disease burden of this infection. The benefits of the vaccine become apparent within a few years of its launch and increase with time. With the relatively small number of vaccinations needed to prevent one infection, the vaccine may have the potential to be cost-effective, even at moderate efficacy levels. Targeting specific population groups can further maximise the vaccine cost-effectiveness, with adolescents and populations at high risk of infection benefiting greatly. The potential 'breakthrough' effects of the vaccine, namely reducing infectiousness and duration of infection, could further enhance its impact. Vaccine development and vaccination against CT should be considered a public health priority. To thoroughly understand a vaccine's impact, it is critical for vaccine trials to measure not only its effect on the acquisition of the infection but also its potential effects on bacterial load and duration of infection.

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