Does infection with *Chlamydia trachomatis* induce long-lasting partial immunity? Insights from mathematical modelling

Ryosuke Omori,1,2,3 Hiam Chemaitelly,3 Christian L Althaus,4 Laith J Abu-Raddad3,5,6

**ABSTRACT**

**Objectives** To explore whether existence of long-lasting partial immunity against reinfection with *Chlamydia trachomatis* is necessary to explain *C. trachomatis* prevalence patterns by age and sexual risk, and to provide a plausible estimate for the effect size, defined here as a reduction in susceptibility to reinfection.

**Methods** A population-based mathematical model was constructed to describe *C. trachomatis* natural history and transmission dynamics by age and sexual risk. The model was parameterised using natural history, and epidemiological and sexual behaviour data, and applied for UK and US data. Sensitivity analyses were conducted to assess the robustness of predictions to variations in model structure and to examine the impact of alternative assumptions for the mechanism underlying partial immunity.

**Results** Partial immunity against reinfection was found necessary to explain observed *C. trachomatis* prevalence patterns by age and sexual risk. The reduction in susceptibility to reinfection was estimated at 93% using UK data (95% uncertainty interval (UI)=88%–97%) and at 67% using US data (95% UI=24%–88%). The model-structure sensitivity analyses affirmed model predictions. The immunity-mechanism sensitivity analyses suggested a mechanism of susceptibility reduction against reinfection or a mechanism of infectious-period duration reduction upon reinfection.

**Conclusions** A strong long-lasting partial immunity against *C. trachomatis* reinfection should be present to explain observed prevalence patterns. The mechanism of immunity could be either a reduction in susceptibility to reinfection or a reduction in duration of infection on reinfection. *C. trachomatis* infection appears to naturally elicit a strong long-lasting immune response, supporting the concept of vaccine development.

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**INTRODUCTION**

*Chlamydia trachomatis* is a common bacterial STI. Untreated *C. trachomatis* infection is associated with pelvic inflammatory disease, infertility and ectopic pregnancy among women, and causes urethritis among men. Most genital *C. trachomatis* infections are asymptomatic. The WHO estimates that 4.2% of the population aged 15–49 years is infected.

An understanding of *C. trachomatis* natural history and its implications on transmission dynamics is needed to guide public health strategies for its control. Its infection is characterised by a prolonged interval between infection acquisition and spontaneous cessation of shedding. In a study among 82 women followed for >5 years, 46% of infections were persistent at 1 year, 18% at 2 years and 6% at 4 years. *C. trachomatis* immunity appears to take at least months to acquire.

*C. trachomatis* control has focused on early detection and treatment, but the effectiveness of such strategy is subject to debate. Despite widespread testing of young asymptomatic adults and treatment of infected individuals, *C. trachomatis* prevalence in the targeted age group has not changed markedly. It is argued that *C. trachomatis* early detection and treatment hinder the development of an adequate immune response, thereby increasing susceptibility to reinfection at the individual level, reducing herd immunity at the population level and counteracting reductions in prevalence.

Since *C. trachomatis* infection is curable, there are ethical constraints to conducting studies that directly assess existence/strength of a protective immunity against reinfection. There is, nonetheless, evidence from animal models suggesting short-term complete immunity and long-term partial immunity. Partial immunity can take different forms, such as reduction in susceptibility to reinfection, reduction in infectious-period duration on reinfection and/or reduction in infectiousness upon reinfection (lower organism load). Indirect evidence from human studies supports the concept of protective partial immunity. The evidence includes rapidly declining prevalence with age, similarity in prevalence despite high variability in sexual risk, lower organism load with age and repeat infection, reduction in concordance rate in couples with age, and an apparent treatment attenuation of protective immunity.

Against this background, we present a novel hypothesis-generation approach to assess the existence, and to provide a plausible effect-size estimate, of the partial immunity against reinfection. The approach rests on the concept that natural history effects at the individual level have manifestations at the population level. Starting from population-level measures, we used mathematical modelling to provide the link between these measures and natural history effects.

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Although our approach uses an indirect method, mathematical modelling, its strength lies in that it provides an independent assessment of this effect that capitalises on existing quality population-based data. Specifically, we used two population-level distributions, prevalence by age and by sexual risk, to explore a population-level ‘signature’ of partial immunity. We also factored in the model different biological (eg, various forms of immunity and impact of treatment on immunity development) and behavioural (eg, impact of age on sexual behaviour and various forms of sexual mixing by age and risk behaviour) mechanisms that potentially may explain the observed patterns, irrespective of inclusion of an immunity effect. Accordingly, we aimed to answer two questions: (1) Is the existence of partial immunity against reinfection necessary to explain prevalence patterns by age and sexual risk? (2) How strong is the effect of partial immunity likely to be?

METHODS
We constructed a population-based deterministic compartmental model to assess the role of long-lasting partial immunity in C. trachomatis epidemiology. The model was developed based on a review of existing mathematical models for this infection.\(^{17}\)

The model stratified the population according to infection status, immune status, age and sexual risk behaviour, and to reduce complexity, sex was not included explicitly in the model, nor did the model explicitly distinguish between different forms of sexual transmission.

Mathematical model
Model description and C. trachomatis natural history
Online supplementary figure S1 shows a schematic diagram of the model. The model assumes full susceptibility to infection at birth. Following the first C. trachomatis exposure, infected individuals enter a non-infectious latent period of 14 days,\(^5\) followed by an infectious period that can be asymptomatic or symptomatic. We assumed that asymptomatic infections comprise 62.5% of all infections.\(^5\) The infectious period lasts for 300 days for asymptomatic infection,\(^5\) but only 35 days for symptomatic infection, on account of treatment-seeking behaviour.\(^5\)

We assumed that, by the time of infection clearance, asymptomatic individuals acquire short-term temporary (90 days) but full immunity against reinfection, per the recent Althaus et al model\(^5\) and as informed by animal model studies.\(^39\) This is followed by long-lasting partial immunity that reduces susceptibility to reinfection by a fraction \(\alpha.\)\(^17\) The latter mechanism is informed by a review of evidence from human studies that examined both biological (eg, markers of protective immunity) as well as epidemiological (eg, patterns in different populations) data.\(^17\)

Meanwhile, symptomatic individuals do not acquire immunity and revert back to the fully susceptible state after clearance by treatment—treatment shortens infection duration in symptomatic individuals, thus reducing their chance to develop an adequate immune response.\(^5\)

Details on model structure, equations and parameterisation are in the online supplementary materials.

Demography and sexual risk behaviour
The model assumes a stable population with a balance between births and deaths. It further incorporates 20 age groups, each of which describes a 5-year age band in the population. Demographics for the UK and the USA were drawn from the United Nations Population Division databases.\(^27\)

Sexual activity lifespan extends in the model from ages 15 to 74, with sexual activity declining with older age. For each 5-year age category, the model incorporates six sexual risk groups describing a hierarchy of sexual risk behaviour varying from low to high levels. Accordingly, the model accommodates for the broad behavioural heterogeneity that typically exists in a given population.\(^28\)–\(^30\)

Distribution of the population across risk groups is informed by data for the number of heterosexual partners during the last 12 months, as reported in the second UK National Survey of Sexual Attitudes and Lifestyles (Natsal-2).\(^21\)\(^31\) Distribution of the level of risk behaviour across risk groups follows a power-law function as informed by sexual partnership data\(^27\) and analyses of complex weighted networks.\(^13\)\(^–\)\(^16\) Partnership acquisition rate in each risk group varies with age as informed by the Natsal-2 data.\(^27\) Coital frequency also varies with age as informed by the US data.\(^28\)

The pattern of sexual mixing between sexually active individuals is determined by two mixing matrices describing the likelihood of a partnership to be formed based on age group or risk group.\(^30\)\(^39\)\(^40\) Each matrix describes a mixing continuum varying between proportionate mixing (no preferential bias based on age or risk group) and full assortativity (partnerships formed exclusively within the same age or risk group).

Details on the inclusion of demography and sexual behaviour in the model are in the online supplementary materials.

Data sources
The model was parameterised using available data for C. trachomatis natural history (online supplementary table S1) and sexual behaviour (online supplementary table S1 and S2). The key model parameters were based on the median value of the range that was used in published models.\(^5\)\(^21\)\(^–\)\(^26\) Empirical data describing the distribution of C. trachomatis prevalence by age were obtained from (1) a systematic review of studies assessing C. trachomatis prevalence in the UK\(^31\) and (2) the US Centers for Disease Control and Prevention (CDC) STI database.\(^42\) The distribution of C. trachomatis prevalence by sexual risk group was obtained through Natsal-2 data analysis.\(^21\)\(^31\)

Plan of analysis
We conducted analyses to explore the role of partial immunity in explaining observed C. trachomatis epidemiological patterns.

Partial immunity and age-specific and sexual risk-specific distributions of C. trachomatis prevalence
We generated model predictions for the age-specific and sexual risk-specific distributions of C. trachomatis prevalence in the UK at different strengths for the partial immunity, and compared these distributions with empirical data. The comparison was conducted to assess whether the existence of immunity yields enhanced agreement between model predictions and empirical data.

Estimation of the strength of partial immunity against reinfection
The strength of the long-lasting partial immunity against reinfection (\(\alpha\)) was estimated by fitting model predictions to data from the following surveys: (1) UK age-specific\(^41\) and sexual risk-specific\(^21\)\(^31\) C. trachomatis prevalence distributions, and (2) US age-specific\(^24\) C. trachomatis prevalence distribution. No fitting was done for the US sexual risk-specific C. trachomatis distribution, as such distribution was not available for the used CDC data. The fitting was implemented by minimising the residual
Table 1  Summary of description and results of the sensitivity analyses with respect to variations in model structure

<table>
<thead>
<tr>
<th>Sensitivity analysis</th>
<th>Description</th>
<th>Result</th>
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<tbody>
<tr>
<td>1. Variation in the distribution of risk behaviour across risk groups.*</td>
<td>Explored the impact of variation in the distribution of risk behaviour across risk groups by varying (in univariate analysis) the parameter ( \sigma ) of the distribution of risk behaviour (online supplementary materials), but fixing ( \alpha ) at its model-predicted baseline value.</td>
<td>The predicted age-specific Chlamydia trachomatis prevalence distribution was largely invariable despite the variation in the distribution of risk behaviour across risk groups (online supplementary figure S2A).</td>
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<td>2. Variation in the sexual mixing by age.*</td>
<td>Explored the impact of variation in sexual mixing by age (in univariate analysis) across the full spectrum starting from proportionate mixing-up to fully assortative mixing. This was done by varying ( \epsilon_e ), the parameter describing the degree of assortativity in mixing by age (online supplementary materials).</td>
<td>The predicted age-specific C. trachomatis prevalence distribution was largely invariable despite the variation in the sexual mixing by age (online supplementary figure S2B).</td>
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<tr>
<td>3. Variation in the sexual mixing by risk.*</td>
<td>Explored the impact of variation in sexual mixing by risk (in univariate analysis) across the full spectrum starting from proportionate mixing-up to fully assortative mixing. This was done by varying ( \epsilon_h ), the parameter describing the degree of assortativity in mixing by risk (online supplementary materials).</td>
<td>The predicted age-specific C. trachomatis prevalence distribution was largely invariable despite the variation in the sexual mixing by risk (online supplementary figure S2C).</td>
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<td>4. Temporal variation in risk behaviour.</td>
<td>Explored the impact of temporal variation in risk behaviour on our estimated partial immunity strength by assuming that 10% of individuals change their risk group every year.</td>
<td>( \alpha ) for the UK data was estimated at 93% (95% UI: 89%–95%) with an uncertainty analysis median of 93%—similar to the original estimate.</td>
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<td>5. Removal of latent period in C. trachomatis natural history.</td>
<td>Explored the impact of removing the latent period in C. trachomatis natural history.</td>
<td>( \alpha ) for the UK data was estimated at 93% (95% UI: 88%–97%) with an uncertainty analysis median of 93%—similar to the original estimate.</td>
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<tr>
<td>6. Inclusion of partial immunity for the symptomatically infected individuals.</td>
<td>Explored the impact of inclusion of partial immunity for the symptomatically infected individuals.</td>
<td>( \alpha ) for the UK data was estimated at 93% (95% UI: 89%–96%) with an uncertainty analysis median of 93%—similar to the original estimate.</td>
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<tr>
<td>7. Variation in the duration of the short-term temporary but full immunity.</td>
<td>Explored the impact of varying the duration of the short-term temporary but full immunity over a range of 0–100 days.</td>
<td>Variation in the short-term temporary immunity had limited impact on the estimated effect size of partial immunity (online supplementary figure S3).</td>
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All sensitivity analyses were applied to the model fit of the UK data.

* Conducted in view of the fundamental ambiguity in defining ‘sexual risk’,

and done on the prediction for the age-specific C. trachomatis prevalence distribution, since this distribution is the most prototypical pattern in C. trachomatis epidemiology. UI, uncertainty interval.

sum of squares between data points and model predictions. Analyses were conducted assuming endemic equilibrium.

The uncertainty intervals (UIs) for estimates were calculated through multivariate uncertainty analyses with respect to variations in the model’s sexual behaviour structure. This was done using Monte Carlo sampling from (conservatively) uniform probability distributions, assuming 20% uncertainty around the parameters’ point estimates, as informed by the range of available data and previous modelling studies. Each new set of parameters was used to refit C. trachomatis prevalence distributions, and accordingly estimate \( \alpha \). We implemented 500 uncertainty runs for each estimation and determined the median and mean and associated 95% UI.

Sensitivity analyses with respect to variations in model structure

Several sensitivity analyses were conducted with respect to variations in model structure. These are summarised in table 1.

Sensitivity analyses with respect to alternative assumptions for the mechanism of partial immunity

We assumed, for theoretical simplicity, that the partial immunity mechanism is a reduction in the susceptibility to reinfection. However, there is ambiguity about the exact mechanism(s). Accordingly, we conducted sensitivity analyses exploring the impact of two alternative mechanisms on the predicted age-specific C. trachomatis prevalence distribution: a reduction in infectious-period duration upon reinfection and a reduction in C. trachomatis infectiousness upon reinfection (lower organism load).

Methodological details of these analyses are in the online supplementary materials.

RESULTS

Figure 1A shows the predicted age-specific C. trachomatis prevalence distribution for the UK data at different \( \alpha \) (the fractional reduction in susceptibility to reinfection). With no immunity (\( \alpha = 0\% \)), it was not possible to generate the typically observed distribution where the prevalence is highest in those aged 15–24 years and declines to <1% by age 30. \( \alpha \) must be large enough, in the range of 70%–90%, to reproduce this prototypical C. trachomatis empirical pattern. Moreover, it was not possible to generate the distribution without incorporating the age dependence of sexual behaviour.

Figure 1B shows the predicted age-specific C. trachomatis prevalence distribution at different \( \alpha \), but assuming no variation in sexual behaviour with age—absence of this variation did not lead to a good fit of empirical data.

Figure 1C shows the predicted risk-specific C. trachomatis prevalence distribution for the UK data at different \( \alpha \). With \( \alpha = 0\% \), the prevalence in high-risk populations was much higher than that in low-risk populations, in contrast to empirical data that suggest a more even distribution by risk. In order to generate such more even distribution, \( \alpha \) must be large enough to substantially lower C. trachomatis prevalence in high-risk populations, who are more likely to experience reinfections. Notice that the outlier for risk group 4 may be due to sampling variation or to the ambiguity of defining ‘sexual risk’;

R E S U L T S

Figure 1A shows the predicted age-specific C. trachomatis prevalence distribution for the UK data at different α (the fractional reduction in susceptibility to reinfec-

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Figure 1  Chlamydia trachomatis (CT) prevalence in the UK by age and
by sexual risk under different assumptions for the effect size of partial
immunity against reinfection (α). Model predictions for (A) age-specific
distribution of CT prevalence at variable levels of α and assuming age
dependence of sexual behaviour, (B) age-specific distribution of CT
prevalence at variable levels of α but with no age dependence of sexual
behaviour, and (C) sexual risk-specific distribution of CT prevalence
at variable levels of α for those 18–44 years of age. Empirical data
(illustrated by ‘*’) were provided from reference 41 for CT prevalence
by age and from references 21 31 for CT prevalence by sexual risk.
Distribution of the population across risk groups was based on the
reported number of heterosexual sex partners during the last 12 months
in the second National Survey of Sexual Attitudes and Lifestyles.21 31

Table 1 shows the results of the sensitivity analyses with
respect to variations in model structure. The analyses indicated
that the estimated $\alpha$ is not likely to be affected appreciably by the ambiguity in defining sexual risk nor by lack of detailed knowledge of sexual networking in a population.

Figure 3 shows the predicted age-specific Chlamydia trachomatis prevalence distribution under three distinct assumptions for the mechanism of partial immunity: susceptibility reduction (our baseline assumption; figure 3A), infectious-period duration reduction with reinfection or (C) infectiousness reduction with reinfection. Empirical data (illustrated by '*') were provided from reference. That the estimated $\alpha$ is not likely to be affected appreciably by the ambiguity in defining sexual risk nor by lack of detailed knowledge of sexual networking in a population.

Figure 3 shows the predicted age-specific C. trachomatis prevalence under three distinct assumptions for the mechanism of partial immunity: susceptibility reduction (our baseline assumption; figure 3A), infectious-period duration reduction with reinfection or (C) infectiousness reduction with reinfection. Empirical data (illustrated by '*') were provided from reference.41 That the estimated $\alpha$ is not likely to be affected appreciably by the ambiguity in defining sexual risk nor by lack of detailed knowledge of sexual networking in a population.

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Epidemiology

Limitations may have affected this study. Although an elaborate model was used to capture the complexity of *C. trachomatis* transmission dynamics, the results may depend on the used model. We used a frequency-dependent model, but this type of model may overestimate immunity effects. The model depends on availability and representativeness of input data—the estimate for the USA had a wide UI, as the sexual risk-specific prevalence distribution was not available for the used CDC data. The sexual risk-specific prevalence distribution for the UK data was based on the number of sexual partners, which alone may not sufficiently capture sexual risk. This distribution, however, was influential in estimating such a strong α for the UK data. If the shape of this distribution was less even, we would still have estimated strong immunity, but with a smaller α (figure 1).

We assumed that symptomatically infected persons do not develop partial immunity because of treatment-seeking behaviour—a reasonable assumption but with undetermined validity. Lastly, for sexual mixing, we assumed a specific mix of proportionate and assortative mixing since the actual mixing in the population is not known.

Despite these limitations, the model was sufficiently complex to incorporate the main factors that can affect our research questions, and produced robust fits for *C. trachomatis* prevalence by age and by risk. None of the biological and behavioural factors suspected to affect the study outcome affected the study conclusions, and the different sensitivity analyses affirmed our findings. We conducted multivariate uncertainty analyses with respect to variations in model structure, rather than using maximum likelihood methods, to account for broader uncertainty in the estimated effect size. Although the exact effect size of *C. trachomatis* immunity is yet to be determined with precision, and there was a difference between the UK-based and US-based estimates, calculated results confirmed a strong effect of partial immunity. With sampling variation affecting *C. trachomatis* prevalence distributions in population-based surveys, and in the context of fundamental ambiguity in defining ‘sexual risk’, the presented approach is not best suited to provide an exact effect size, but is sufficient to demonstrate the likely existence of a strong partial immunity effect.

In conclusion, we explored the existence of partial immunity against *C. trachomatis* reinfection using an indirect, but novel hypothesis-generation approach. Our results indicated that a strong immunity effect should be present to explain observed *C. trachomatis* prevalence patterns. These findings are suggestive of a strong natural immune response against *C. trachomatis* infection, which, upon elucidation of its detailed biological mechanisms, may have implications for vaccine development.

Acknowledgements The authors gratefully acknowledge Professor Nicola Low from the University of Bern for valuable insights and rich discussions and critically reviewing this study. The authors also gratefully acknowledge the fine support of Ms Adona Canlas in the conduct of this study. The authors are further grateful for infrastructure support provided by the Biostatistics, Epidemiology, and Biomathematics Research Core at Well Cornell Medicine-Qatar.

Contributors RO conceived the study, developed the mathematical models and conducted the analyses. HC contributed to data analysis and wrote the first draft of the article. CLA provided technical input. LIA-R led the study design and analyses. All authors contributed to results generation and interpretation and to writing of the article.

Funding RO acknowledges the support of Precurious Research for Embryonic Science and Technology (PRESTO) grant number JPMJPR15E1 from Japan Science and Technology Agency (JST), and Japan Society for the Promotion of Science (JSPS), Grant-in-Aid for Young Scientists (B) 15K19212. This publication was made possible by NIH grant number S-572-3-177 from the Qatar National Research Fund (a member of Qatar Foundation). The findings achieved herein are solely the responsibility of the authors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data statement Model equations and parameters are provided in the online supplementary materials.

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Handling editor Katy M E Turner

Key messages

► Partial immunity against Chlamydia trachomatis reinfection can explain the observed prevalence patterns by age and sexual risk.

► C. trachomatis infection appears to elicit a strong natural immune response that reduces substantially the susceptibility to reinfection.

► Immunity mechanism can be either a reduction in susceptibility to reinfection or a reduction in infectious-period duration upon reinfection, or a combination of both.


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