Online Supplementary Material

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

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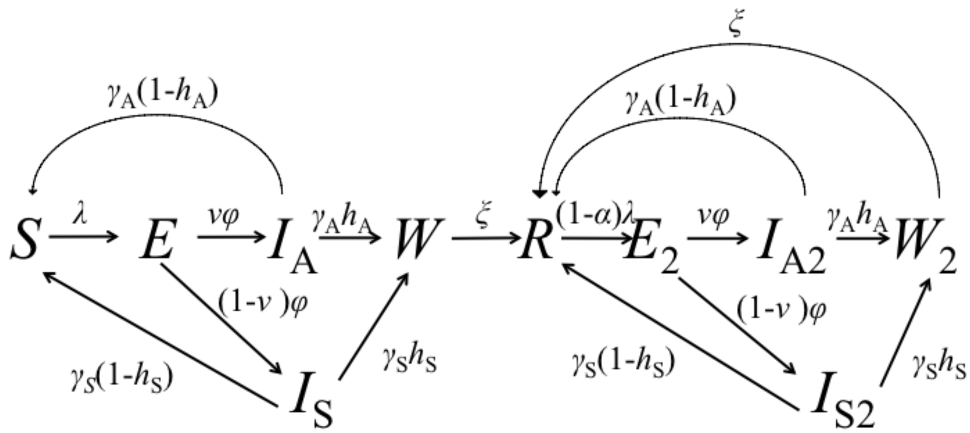
Model structure and description

We constructed a deterministic compartmental mathematical model to explore the role of long-lasting partial immunity in the epidemiology of *Chlamydia trachomatis* (*C. trachomatis*) infection. Figure S1 provides a schematic diagram of the model.

Figure S1 Schematic diagram of the mathematical model describing *Chlamydia trachomatis* natural history and its transmission dynamics in a population.



The model stratifies the population according to *C. trachomatis* infection status, immune status, age and sexual risk behaviour, and is described by the following set of differential equations:

$$
\begin{aligned}
\frac{dS_{x,y}}{dt} &= -\lambda_{x,y}S_{x,y} + \gamma_A(1-h_A)I_{A_{x,y}} + \gamma_S(1-h_S)I_{S_{x,y}} + f_{S_{x,y}}, \\
\frac{dE_{x,y}}{dt} &= \lambda_{x,y}S_{x,y} - (\varphi+\mu)E_{x,y} + f_{E_{x,y}}, \\
\frac{dI_{A_{x,y}}}{dt} &= v\varphi E_{x,y} - (\gamma_A+\mu)I_{A_{x,y}} + f_{I_{A_{x,y}}}, \\
\frac{dI_{S_{x,y}}}{dt} &= (1-v)\varphi E_{x,y} - (\gamma_S+\mu)I_{S_{x,y}} + f_{I_{S_{x,y}}}, \\
\frac{dW_{x,y}}{dt} &= \gamma_A h_A I_{A_{x,y}} + \gamma_S h_S I_{S_{x,y}} - (\xi+\mu)W_{x,y} + f_{W_{x,y}}, \\
\frac{dR_{x,y}}{dt} &= \xi(W_{x,y} + W_{2_{x,y}}) - \left[(1-\alpha)\lambda_{x,y} + \mu\right]R_{x,y} + \gamma_A(1-h_A)I_{A2_{x,y}} + \gamma_S(1-h_S)I_{S2_{x,y}} + f_{R_{x,y}}, \\
\frac{dE_{2_{x,y}}}{dt} &= (1-\alpha)\lambda_{x,y}R_{x,y} - (\varphi+\mu)E_{2_{x,y}} + f_{E_{2_{x,y}}}, \\
\frac{dI_{A2_{x,y}}}{dt} &= v\varphi E_{2_{x,y}} - (\gamma_A+\mu)I_{A2_{x,y}} + f_{I_{A2_{x,y}}}, \\
\frac{dI_{S2_{x,y}}}{dt} &= (1-v)\varphi E_{2_{x,y}} - (\gamma_S+\mu)I_{S2_{x,y}} + f_{I_{S2_{x,y}}}, \\
\frac{dW_{2_{x,y}}}{dt} &= \gamma_A h_A I_{A2_{x,y}} + \gamma_S h_S I_{S2_{x,y}} - (\xi+\mu)W_{2_{x,y}} + f_{W_{2_{x,y}}}.
\end{aligned}
\tag{S1}
$$

Here, S denotes the fully susceptible population, E denotes the infected but not yet infectious population (latently infected but not yet infectious), I_A denotes the asymptomatic *C. trachomatis* infected population, I_S denotes the symptomatic *C. trachomatis*infected population, W denotes the recovered population who is protected by temporary immunity, R denotes the recovered population protected by long-lasting partial immunity, E_2 denotes the re-infected population that is not yet infectious (latently reinfected but not yet infectious), I_{A2} denotes the asymptomatic *C. trachomatis* reinfected population, I_{S2} denotes the symptomatic *C. trachomatis* reinfected population, and W_2 denotes the recovered population who is protected by temporary immunity following the clearance of reinfection. We assume that individuals in the temporary immunity stages W and W_2 cannot be reinfected.

The model parameters include:

- λ, describing the force of infection. The model calculates λ using the partnership acquisition rate, *C. trachomatis* transmission probability per coital act, *C. trachomatis* prevalence in the population and the patterns of sexual mixing. Further details can be found in the 'Details on model parameterization' section below.
- $\frac{1}{\varphi}$, describing the latency period where the individual is infected but not yet infectious.
- ν, describing the fraction of infections that become asymptomatic among all *C. trachomatis* infections.
- $\frac{1}{\gamma_A}$ and $\frac{1}{\gamma_S}$, describing the infectious periods for the asymptomatic and symptomatic *C. trachomatis* infections, respectively.
- h_A and h_s, describing the fractions of those recovered from infection that develop immunity against reinfection following asymptomatic and symptomatic *C. trachomatis* infections, respectively.
- $\frac{1}{\xi}$, describing the duration of temporary immunity.
- α, describing the fractional reduction in susceptibility to reinfection (long-lasting partial immunity to reinfection) induced following clearance of *C. trachomatis* infection and passing through the temporary immunity stage, if any. We also examined, through sensitivity analyses, other immune response mechanisms that could potentially be

induced following clearance of *C. trachomatis* infection including reduction in infectious-period duration and reduction in infectiousness. These are described in detail in the 'Sensitivity analyses with respect to alternative immune response mechanisms' section below.

- f_{status} terms, describing demographic population flow into each population compartment. Further details related to the parameterization of these f_{status} terms can be found in the 'Model parameterization' section below.

Similar to other sexually transmitted infections, *C. trachomatis* infection transmission is driven by the sexual contact network in the population. We assumed that the sexual activity lifespan starts at age 15 and lasts up to age 74, but the intensity of sexual activity varies by age. We divided the population into 20 age groups of 5-year age bands. For each age group, individuals were distributed over six sexual risk groups describing a hierarchy of sexual risk behaviour varying from low to high levels.

In our model, the subscript indices 'x' and 'y' denote the individual's age group and sexual risk group assignment, respectively.

Model parameterization

a) Demography of population flow

The demography of population flow is described by the parameter f_{status} which is given by:

$$f_{status_{x,y}} = \begin{cases} \sum_j \mu_j N_{j,y} - \mu_1 S_{1,y} - \eta S_{1,y} & \text{for susceptible first age group } S_{1,y} \\ 0 & \text{for non-susceptible first age group } z_{1,y} \\ -\mu_x z_{x,y} + \eta(z_{x-1,y} - z_{x,y}) & \text{for age groups 2-19 } z_{x,y} \\ -\mu_{20} z_{20,y} + \eta z_{19,y} & \text{for age group 20 } z_{20,y} \end{cases} . \quad \text{(S2)}$$

Here, Z stands for any subpopulation compartment in this population. Meanwhile, μ_j denotes the natural mortality rate for the *j*-th age group, $N_{j,y}$ denotes the population size of the *j*-th age group and the *y*-th risk group, and η denotes the rate of ageing from one age bracket to the next. We assumed that mortality rate varies with age, with infants (aged 0-4 years; that is x =1) and older adults (aged 70+ years; that is x = 16-20) having higher mortality rates than the rest of the population. For simplicity, we assumed a stable population where total mortality

$$\sum_j \mu_j N_{j,y}$$

is equal to total births. We also assumed full susceptibility to *C. trachomatis* at birth. The values for these model parameters are shown in Table S1.

b) Sexual risk behaviour

1. *Distribution of sexual risk groups in the population*

The distribution of the population across sexual risk groups is informed by data for the number of sexual partners during the last 12 months as reported in the United Kingdom (UK) National Survey of Sexual Attitudes and Lifestyles (NATSAL 2000).[1 2]

2. The effective sexual partnership acquisition rate

The risk of *C. trachomatis* infection in the population is dependent on the individual's sexual contact network. The parameter $\rho_{x,y}$ describes the *effective* sexual partnership acquisition rate for an individual in the *x*-th age group and *y*-th risk group. This measure is representative of the number of new sexual partners that an individual in a specific age group and a specific risk group would acquire taking into account other factors that may increase the risk of infection such as level of concurrency and clustering within the sexual network.[3-6]

The distribution of $\rho_{x,y}$ was assumed to follow a power law function.[7] This function is motivated by the topology and clustering observed in empirical sexual contact networks and analyses of complex networks.[7-12] The mathematical expression describing the distribution of $\rho_{x,y}$ is given by

$$\rho_{x,y} = C l_x y^{\sigma}. \qquad \text{(S5)}$$

Here, l_x is the mean rate of sexual partners for individuals in age group 'x'. In this expression, σ is the exponent parameter that determines the level of variability in the effective partnership acquisition rate across the y risk groups, and C is a constant determined by the average effective acquisition of sexual partners for individuals in the *x*-th age group and the *y*-th risk group.

We parameterized l_x using the age-dependent mean acquisition rate of sexual partners obtained from analysing the UK NATSAL data as described by *Choi et al.* (2010).[13] C was determined through fitting the model to the age-specific *C. trachomatis* prevalence observed in UK empirical studies.[1 14] Specifically, C was calculated by fitting a *C. trachomatis* prevalence of 3% among those aged 15-29 years.[1 14] The values for these parameters can be found in Table S1. Since we assumed a 15-74 year sexual activity life span, $\rho_{x,y} = 0$ for age groups 0-4, 5-9, 10-14, 75-80, 85-89, 90-94 and 95+.

3. Sexual mixing

The pattern of sexual mixing between individuals is determined by two mixing matrices describing the likelihood of a sexual partnership to be formed between two individuals belonging to different age groups (mixing matrix G) and to different risk groups (mixing matrix H), respectively. The mathematical expressions defining these mixing matrices are given by

$$\begin{aligned} G_{x,j} &= e_G\, \delta_{x,j} + (1-e_G) \frac{\sum_k \rho_{j,k} N_{j,k}}{\sum_j \sum_k \rho_{j,k} N_{j,k}} \\ H_{y,k} &= e_H\, \delta_{y,k} + (1-e_H) \frac{\sum_j \rho_{j,k} N_{j,k}}{\sum_j \sum_k \rho_{j,k} N_{j,k}} \end{aligned} \quad . \tag{S6}$$

Here, $\delta_{i,j}$ is an element of the identity matrix, and e_G and e_H describe the degree of assortativity (assortativity coefficient) in the mixing between age and sexual risk subgroups, respectively. Assuming an extreme scenario where $e_G = 0$ and $e_H = 0$ results in a proportionate mixing where an individual's choice of a sexual partner is independent of the age or risk group of that partner. On the other hand, when $e_G = 1$ and $e_H = 1$, the mixing is fully assortative that is the sexual partner is always selected from the individual's own age group and sexual risk group.[8 15] The values for the parameters described in these equations can be found in Table S1.

4. The force of infection

The force of infection (λ) is given by:

$$\lambda_{x,y} = \rho_{x,y} \sum_{j=1}^{20} \sum_{k=1}^{10} G_{x,j} H_{y,k} \left(\frac{\rho_{j,k} q_{I_{A_{x,y}}} \left(I_{A\, j,k} + I_{A2\, j,k} \right) + \rho_{j,k} q_{I_{S\, x,y}} \left(I_{S\, j,k} + I_{S2\, j,k} \right)}{\rho_{j,k} N_{j,k}} \right). \qquad \text{(S7)}$$

Here, q describes *C. trachomatis* transmission probability per partnership between an asymptomatic ($I_{A_{x,y}}$) or a symptomatic ($I_{S_{x,y}}$) *C. trachomatis* infected individual and a susceptible individual in the population:

$$\begin{aligned} q_{I_{A_{x,y}}} &= 1-(1-p)^{m_{I_A} n_{x,y} \tau}, \\ q_{I_{S\, x,y}} &= 1-(1-p)^{m_{I_S} n_{x,y} \tau}. \end{aligned} \qquad \text{(S8)}$$

In these expressions, p denotes the *C. trachomatis* transmission probability per coital act, m_{I_A} and m_{I_S} denote the coefficients describing the relative variability in the frequency of coital acts between asymptomatic and symptomatic cases, respectively, with respect to uninfected individuals, $n_{x,y}$ describes the frequency of coital acts for uninfected individuals in the *x*-th age group and *y*-th sexual risk group per unit time, and τ describes the partnership duration. The values for these model parameters can be found in Tables S1 and S2.

We parameterized the age-specific distribution of the frequency of coital acts in the population using empirical data, which suggested an approximately negative linear correlation between age and the frequency of coital acts per week (Table S2).[16]

Sensitivity analyses with respect to alternative immune response mechanisms

In this study, we assessed the epidemiological impact of susceptibility-reduction long-lasting partial immunity against *C. trachomatis* reinfection as described above. We have also, through sensitivity analyses, assessed the impact of two other alternative mechanisms of partial immunity against *C. trachomatis* reinfection: 1) reduction in the duration of infection for those reinfected with *C. trachomatis*, and 2) reduction in infectiousness for those reinfected with *C. trachomatis*. The reduction in infectious period immunity effect was examined by reducing the infectious period for those reinfected with *C. trachomatis* through the expressions:

$$\frac{1}{\gamma_A} \rightarrow \frac{1-\alpha}{\gamma_A}$$ (among those asymptomatically infected)

and

$$\frac{1}{\gamma_S} \rightarrow \frac{1-\alpha}{\gamma_S}$$ (among those symptomatically infected).

Here, α, the immunity effect parameter, describes the fractional reduction in infectious period among those reinfected with *C. trachomatis*.

Meanwhile, the reduction in infectiousness immunity effect was examined by altering the force of infection (λ) using the expression:

$$\lambda_{x,y} = r_{x,y} \sum_{j=1}^{20} \sum_{k=1}^{6} \mathbf{G}_{x,j} \mathbf{H}_{y,k} \left(\frac{q_{I_{A_{x,y}}} \left(I_{A_{j,k}} + (1-\alpha) I_{A2_{j,k}} \right) + q_{I_{S_{x,y}}} \left(I_{S_{j,k}} + (1-\alpha) I_{S2_{j,k}} \right)}{N_{j,k}} \right).$$

where α, the immunity effect parameter, describes here the fractional reduction in infectiousness of those reinfected with *C. trachomatis*.

Table S1 Description and values of model parameters.

Symbol	Description	Value	References
$1/\varphi$	Duration of the non-infectious latent infection	14 days	Based on previously published models along with their parametrization.[2 17-22] This baseline value is the median value of the range that was used in previous modelling studies
ν	Fraction of infections that become asymptomatic among all *Chlamydia trachomatis* infections	62.5%	Based on previously published models along with their parametrization.[2 17-22] This baseline value is the median value of the range that was used in previous modelling studies
$1/\gamma_A$	Infectious period for an asymptomatic infection	300 days	Based on previously published models along with their parametrization[2 17-22] This baseline value is the median value of the range that was used in previous modelling studies
$1/\gamma_S$	Infectious period for a symptomatic infection	35 days	Based on previously published models along with their parametrization[2 17-22] This baseline value is the median value of the range that was used in previous modelling studies
$1/\xi$	Duration of the temporary full immunity	90 days	An assumption based on the Althaus *et al.* model parametrization[17]
μ	Age-specific mortality rates		
	0-4 years old (age group 1)	0.04	Parameterized to generate the observed survival curve and life expectancy of the current United Kingdom and United States populations, as provided by the database of the Population Division of the United Nations Department of Economic and Social Affairs.[23]
	5-69 years old (age group 2-14)	0.0026	
	70+ years old (age group 15-20)	0.0998	
η	Rate of ageing	1/5	5 year age bands
σ	Power law exponent for the variability in the effective sexual partnership acquisition rate across sexual risk groups	3 4	Model fitting (UK data fit) Model fitting (US data fit)
e_G	Assortativity coefficient for age group mixing	0.7	[24]
e_H	Assortativity coefficient for sexual risk group mixing	0.3	[3]
p	*Chlamydia trachomatis* transmission probability per coital act	0.0375	[2 22]
τ	Partnership duration	6 months	Reasonable value of no consequence on the model results

h_A	Fraction of those asymptomatically infected who develops protective immunity against reinfection	1	[17]
h_S	Fraction of those symptomatically infected who develops protective immunity against reinfection	0	[17]
m_{I_A}	Relative frequency of coital acts among asymptomatically *Chlamydia trachomatis* infected persons with respect to uninfected individuals (baseline)	1	Reasonable value given lack of symptoms
m_{I_S}	Relative frequency of coital acts among symptomatically *Chlamydia trachomatis* infected persons with respect to uninfected individuals (baseline)	0.645	Reasonable value informed by coital data among HIV-infected persons[25]

Table S2 Age-specific coital frequency and sexual partnership acquisition rate in the population.

Age groups	Description	Frequency of coital acts per week ($n_{x,y}$)[16]	Mean sexual partnership acquisition rate per year (l_x)[13]
1-3	0-14 years	0.00	0.000
4	15-19 years	3.90	0.850
5	20-24 years	3.50	1.200
6	25-29 years	3.20	0.610
7	30-34 years	2.90	0.330
8	35-39 years	2.50	0.250
9	40-44 years	2.20	0.190
10	45-49 years	1.90	0.140
11	50-54 years	1.50	0.095
12	55-59 years	1.20	0.065
13	60-64 years	0.87	0.045
14	65-69 years	0.53	0.033
15	70-74 years	0.20	0.025
16-20	75+ years	0.00	0.000

Table S3 Model fit of *Chlamydia trachomatis* prevalence by age group for the United Kingdom data.

Age group (years)	15-19	20-24	25-29	30+
Prevalence of *Chlamydia trachomatis* (%)				
Empirical data[14]	4.8	3.2	1.5	0.8
Model prediction	4.3	3.3	1.1	0.4

Table S4 Model fit of *Chlamydia trachomatis* prevalence by sexual risk group for the United Kingdom data.

Sexual risk group	1	2	3	4	5	6
Prevalence of *Chlamydia trachomatis* (%)						
Empirical data[2]	0.3	1.1	2.6	7.8	4.8	6.0
Model prediction	0.2	1.2	2.6	3.7	4.8	6.6

Table S5 Model fit of *Chlamydia trachomatis* prevalence by age group for the United States data.

Age group (years)	15-19	20-24	25-29	30-34	35-39	40-44
Prevalence of *Chlamydia trachomatis* (%)						
Empirical data[26]	2.1	2.5	1.0	0.5	0.2	0.1
Model prediction	2.1	2.5	1.0	0.4	0.2	0.1

Figure S2 Sensitivity analyses of the impact of variations in sexual-risk-behaviour structure on the model-predicted age-specific *Chlamydia trachomatis* (CT) prevalence in the United Kingdom. Sensitivity analyses with respect to A) variation in the distribution of sexual risk behaviour across the different risk groups (parametrized by σ and discussed in the "Model parameterization" section above), B) variation in the pattern of sexual mixing by age (parametrized by e_G and discussed in "Model parameterization" section above), and C) variation in the pattern of sexual mixing by sexual risk (parametrized by e_H and discussed in "Model parameterization" section above). Empirical data (illustrated by '*') were provided from reference[41].

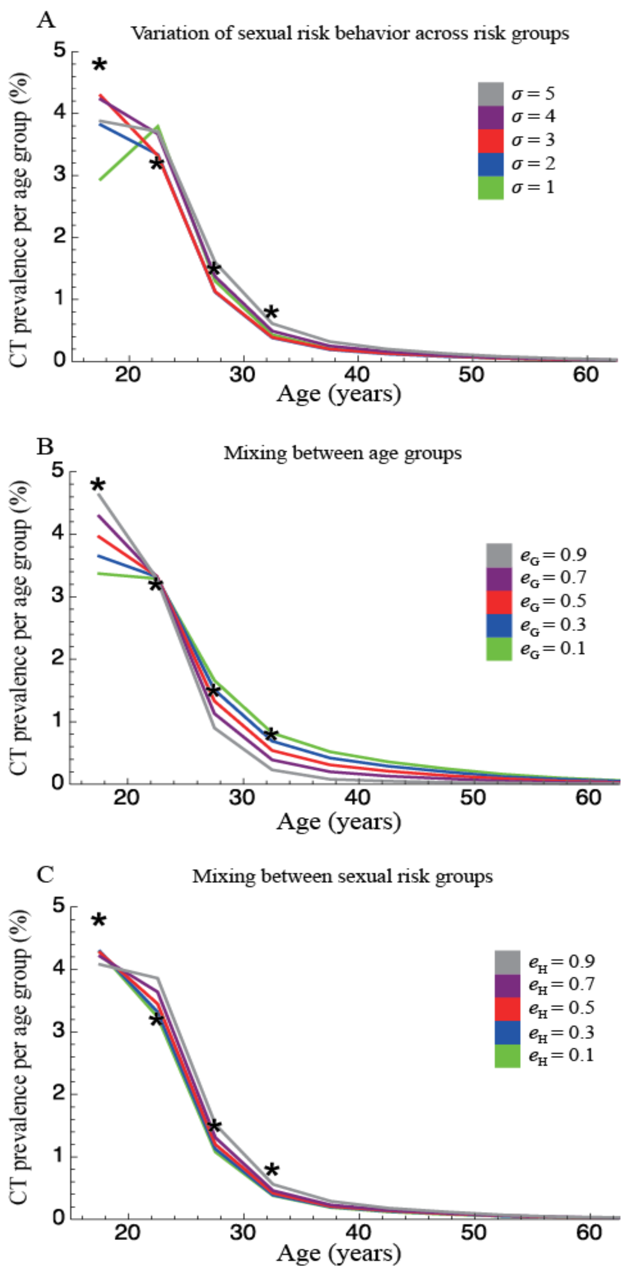
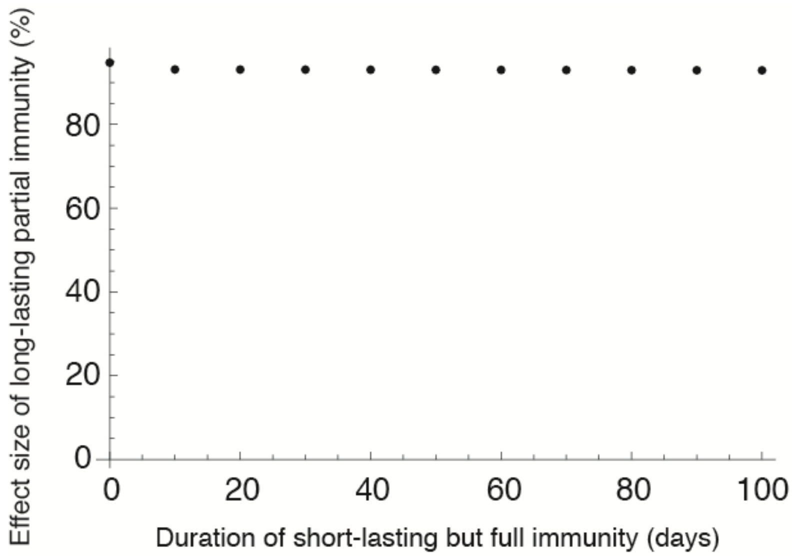


Figure S3 Sensitivity analysis of the impact of varying the duration of the short-term temporary (but full) immunity over a range of 0-100 days, on the estimated effect size of *Chlamydia trachomatis* long-lasting partial immunity against reinfection.



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