

1 Towards more robust estimates of the transmissibility
2 of *Chlamydia trachomatis*

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Abstract

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There is a lack of a common concept on how to estimate transmissibility of *Chlamydia trachomatis* from cross-sectional sexual partnership studies. Using a mathematical model that takes into account the dynamics of chlamydia transmission and sexual partnership formation, we report refined estimates of chlamydia transmissibility in heterosexual partnerships.

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Summary

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This study provides improved estimates of the transmissibility of *Chlamydia trachomatis* in heterosexual partnerships, using a mathematical model that considers the dynamics of chlamydia transmission and sexual partnership formation.

31 Knowledge about the transmissibility of *Chlamydia trachomatis* (chlamydia) is important
32 for health professionals to be able to give accurate information to their patients and for those
33 investigating and implementing preventive interventions.¹ Estimates of transmission probabil-
34 ities are needed in research studies to parameterize mathematical and computational models,
35 which are used to study the transmission dynamics of chlamydia and the impact of public
36 health interventions such as screening programs.² Chlamydia is the most commonly diagnosed
37 bacterial sexually transmitted infection in many developed countries. Prevalence is high with
38 more than 2 million infected persons per year in the USA alone.³ It is, however, difficult
39 to obtain reliable estimates of chlamydia transmissibility from observational epidemiological
40 studies.

41 Empirical estimates of the transmissibility of chlamydia have usually been based on data
42 about the proportions of concordant and discordant pairs that are infected or uninfected with
43 chlamydia.⁴ Katz proposed an original approach for analyzing such couple data.⁵ The expected
44 numbers of concordant and discordant couples before transmission takes place can be calculated
45 if it is assumed that all couples in the population with at least one infected individual have
46 the same probability of observation and that sexual partnership formation is independent of
47 infection status. After sexual partnerships have formed, transmission can happen in discordant
48 partnerships resulting in a higher proportion of couples where both partners are positive.
49 Using data from heterosexual couples attending a sexually transmitted diseases (STD) clinic
50 in Indianapolis, Katz estimated the probabilities that transmission has occurred within a couple
51 at 0.395 from men to women and 0.323 from women to men. There are two major problems
52 with this approach, however. First, the infection status of the couples is observed during the
53 partnership and not at the end so the estimated transmission probabilities do not represent the
54 per partnership transmission probability; this frequently used concept implies the probability
55 of transmission by the end of the partnership. Second, it does not take into account the
56 natural history of chlamydia infection where spontaneous clearance and re-infection within
57 sexual partnerships can occur.⁶ These additional complexities need to be considered because
58 different assumptions about the infectious duration and re-infection in sexual partnerships can
59 affect the prevalence of chlamydia.^{7,8}

60 In this study, we apply a mathematical model to data from a cross-sectional partnership
61 study that has frequently been used as the source of estimates for chlamydia transmissibility.⁹
62 Mathematical models are a tool for explicitly describing the dynamics of sexual partnership

63 formation and transmission of chlamydia infection. The pair model framework has proven
64 useful for describing the transmission of chlamydia and other STIs.^{8,10-12} The model consid-
65 ers the formation of sexual partnerships or pairs (P) and their dissolution into singles (X).
66 Quinn et al. studied heterosexual couples attending two STD clinics in Baltimore.⁹ There were
67 comparable numbers of discordant couples where either the woman or man was infected, so
68 we made the simplifying assumption that the prevalence and the natural history of chlamydia
69 infection were the same in women and men. Assuming a SIS (susceptible-infected-susceptible)
70 structure, the pair formation and chlamydia transmission can be described by the following
71 set of ordinary differential equations:

$$\begin{aligned}\frac{dX_S}{dt} &= -\rho X_S + \gamma X_I + 2\sigma P_{SS} + \sigma P_{SI}, \\ \frac{dX_I}{dt} &= -\rho X_I - \gamma X_I + 2\sigma P_{II} + \sigma P_{SI}, \\ \frac{dP_{SS}}{dt} &= \frac{1}{2}\rho \frac{X_S^2}{X} + \gamma P_{SI} - \sigma P_{SS}, \\ \frac{dP_{SI}}{dt} &= \rho \frac{X_S X_I}{X} - f\beta P_{SI} + 2\gamma P_{II} - \gamma P_{SI} - \sigma P_{SI}, \\ \frac{dP_{II}}{dt} &= \frac{1}{2}\rho \frac{X_I^2}{X} + f\beta P_{SI} - 2\gamma P_{II} - \sigma P_{II}.\end{aligned}$$

72 The infection status is represented by the indices S and I for being susceptible or infected,
73 respectively. Singles X seek partners at rate ρ resulting in sexual partnerships with a concor-
74 dant (P_{SS} and P_{II}) or discordant (P_{SI}) chlamydia infection status. The duration of sexual
75 partnerships and infection are exponentially distributed with a mean duration of $1/\sigma$ and $1/\gamma$,
76 respectively. Within discordant partnerships, couples engage in heterosexual intercourse at rate
77 f and transmission happens with probability β per sex act. The per partnership transmission
78 probability p is defined as the probability that an infected individual transmits chlamydia to
79 his or her susceptible partner before the infection is spontaneously cleared or the partnership
80 breaks up ($p = f\beta/(\sigma + \gamma + f\beta)$).

81 We assumed that chlamydia infection in the population had approached steady-state, i.e.,
82 all derivatives can be set to zero. We then used maximum likelihood estimation (MLE)¹³ to fit
83 the model to the data from the study by Quinn et al.⁹ The study contains information about
84 chlamydia infection status and sexual activity in 494 heterosexual couples. The study reported
85 53 concordant chlamydia positive, 48 discordant and 393 concordant negative couples. The
86 median number of sex partners in the last 6 months was reported to be 1 in females and 2

87 in males. In the model, we account for a skewed distribution and vary the mean number of
88 partners during the previous 6 months for individuals in a partnership at steady-state between
89 1.5 and 3. The median number of episodes of sexual intercourse in the preceding 30 days
90 was reported to be 6, so we assumed one sex act every 5 days. Due to uncertainties in the
91 duration of sexual partnerships and infections, we generated 1000 parameter combinations by
92 sampling the mean partnership duration from a uniform distribution between 1 week and the
93 maximal duration that is consistent with the assumed number of partners in the last 6 months,
94 and the infectious duration from a uniform distribution between 6 and 12 months.⁷ Note that
95 infectious durations of more than 12 months resulted in poor descriptions of the data.

96 The pairs in the model represent the couples from the study by Quinn et al.⁹. The singles
97 can be interpreted as the population from which they are drawn. Assuming that the test data
98 are binomially distributed, we fitted the model to the overall positivity of all individuals in
99 couples (154 of 988) and to the positivity of partners of index patients that are either chlamydia
100 positive (53 of 77) or negative (24 of 417). Using the function `mle` from the R software
101 environment for statistical computing,¹⁴ we estimated the per sex act transmission probability
102 β from which we also derived the per partnership transmission probability p . Estimates that
103 resulted in per sex act transmission probabilities of more than 100% or low goodness of fit
104 based on the Akaike information criterion (AIC)¹⁵ were excluded.

105 We obtained model estimates of the per partnership transmission probability for different
106 values of the number of partners during the last 6 months (Fig. 1A). Higher number of partners
107 resulted in lower estimates of the per partnership transmission probability. However, partner
108 numbers of 3 or more during the last 6 months resulted in poor fits to the data. We therefore
109 consider 2 partners during the last 6 months as our baseline scenario for which the median
110 of the estimated per partnership transmission probability is 55.5% (interquartile range (IQR):
111 49.2% – 62.5%). The estimates of the per sex act transmission probability seemed to be less
112 affected by the assumed number of partners in the last 6 months (Fig. 1B). Most values were
113 around 10% with the median of the baseline scenario at 9.5% (IQR: 6.0% – 16.7%).

114 Our estimated range of chlamydia transmission probabilities in heterosexual partnerships
115 is higher than the baseline values reported by Katz.⁵ This is expected because we report the
116 probability of transmission taking place by the end of a partnership. The additional assumption
117 that chlamydia can be cleared spontaneously also results in higher estimates of the transmission
118 probability. Interestingly, our estimate is lower than what others have concluded from the same

119 data.⁹ Seventy per cent of female and 68% of male partners were infected with chlamydia if
120 their sexual partner was also chlamydia-positive. These values have often, but incorrectly,
121 been interpreted as the per partnership transmission probabilities.^{16,17} However, the direction
122 of transmission cannot be reliably determined from these raw percentages.⁶ This discrepancy
123 illustrates the importance of taking into account the natural history of chlamydia infection
124 and the dynamics of sexual partnership formation in estimating transmissibility from data of
125 chlamydia-positivity in couples.

126 The estimates of the per sex act transmission probability for chlamydia are consistent
127 with those obtained or used in other modeling studies^{18–20}. While the estimates are lower
128 than for *Neisseria gonorrhoeae*,^{4,21} they are considerably higher than the per heterosexual
129 sex act transmission probability for HIV.^{22,23} Our estimates of the per sex act transmission
130 probability are limited by the lack of information on the number of unprotected episodes
131 of heterosexual intercourse in the couples. While one episode of intercourse every 5 days on
132 average is in good agreement with population-based data of sexual activity,^{24,25} the proportion
133 of unprotected episodes is unknown. An additional limitation is that we could not investigate
134 differences between women and men. Different female-to-male and male-to-female transmission
135 probabilities and a higher proportion of symptomatic cases in men could result in sex-specific
136 differences in the transmission and prevalence of chlamydia. As already noted, however, the
137 data from Quinn et al. showed a strikingly similar chlamydia positivity pattern between women
138 and men.⁹ Ultimately, our estimates are derived from a single study population. While this
139 ensures consistency of our results, the per partnership transmission probability might differ
140 in the general population where partnership durations might be longer than in the study
141 population.

142 The framework described here does not take into account natural variability in chlamydia
143 transmission. For example, spontaneous resolution of chlamydia could confer a certain degree
144 of immunity,²⁶ resulting in heterogeneity of susceptibility and transmissibility in a population.
145 Tu et al. present a promising Bayesian framework using detailed longitudinal individual level
146 data about chlamydia infection status and the type and frequency of sexual intercourse in
147 women.²⁰ If such longitudinal data sets were matched to the women’s male partners’ infec-
148 tion status and sexual behavior, more detailed investigations of sex differences in chlamydia
149 transmissibility and its heterogeneity could be performed. In summary, we report the expected
150 ranges of the average per partnership and per sex act chlamydia transmission probability. Fur-

151 ther efforts will be needed to investigate the between-individual heterogeneity in susceptibility
152 and transmissibility of chlamydia.

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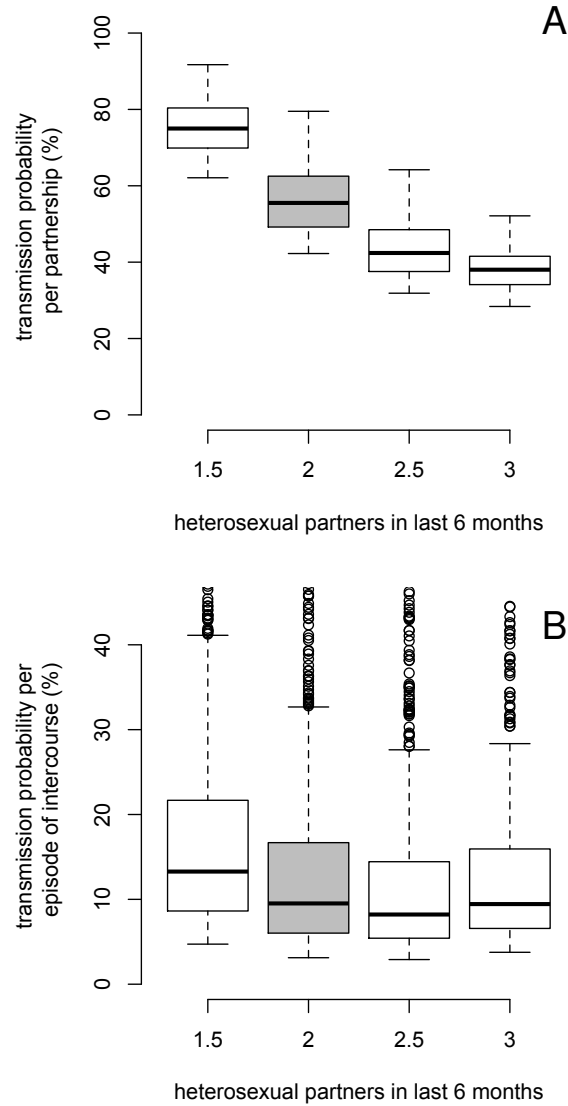


Figure 1: Estimated transmission probabilities for different values of the number of partners in the last 6 months. (A) Per partnership transmission probability of chlamydia. (B) Per sex act transmission probability of chlamydia. Each boxplot represents estimates from 1000 different parameter combinations. The baseline scenario, where it is assumed that individuals in a partnership at steady-state have on average 2 heterosexual partners during the previous 6 months, is in gray. It is assumed that individuals have one episode of heterosexual intercourse every 5 days.