The Unexpected Impact of a *Chlamydia trachomatis* Infection Control Program on Susceptibility to Reinfection

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**Background.** After the introduction of a program to control *Chlamydia trachomatis* infection in British Columbia, Canada, case rates fell from 216 cases/100,000 population in 1991 to 104 cases/100,000 population in 1997. Since 1998, rates have increased, and case counts now exceed those recorded before the intervention.

**Methods.** We used Cox proportional-hazards survival analysis and developed a compartmental mathematical model to investigate the cause of resurgence in chlamydia cases.

**Results.** Cox proportional-hazards survival analysis showed that the relative risk of *C. trachomatis* reinfection has increased 4.6% per year since 1989, with the increased risk greatest among the young and greater among women than men. A compartmental mathematical model of *C. trachomatis* transmission showed that a control strategy based on shortening the average duration of infection results in an early reduction in prevalence followed by a rebound in prevalence, reproducing the observed trends.

**Conclusions.** We speculate that a *C. trachomatis* infection control program based on early case identification and treatment interferes with the effects of immunity on population susceptibility to infection and that, in the absence of strategies to alter sexual networks, a vaccine will be needed to halt the spread of infection at the population level.

Worldwide, *Chlamydia trachomatis* infections are major causes of several sexually transmitted diseases and are prevalent in both industrialized and developing countries [1]. From a public health perspective, *C. trachomatis* infection in women is particularly important, since it can result in serious sequelae, such as pelvic inflammatory disease, ectopic pregnancy, tubal infertility, and chronic pelvic pain. Persistent or recurrent infection appears to be the major risk factor for these sequelae [2]. *C. trachomatis* infection also appears to facilitate the transmission of HIV [3] and to promote the development of human papilloma virus–induced neoplasia [4]. Because of its public health importance, *C. trachomatis* infection has been the focus of control programs that include case recognition and treatment, screening for asymptomatic infection, and tracing of sexual contacts [5]. The goal of such control programs is to reduce transmission by shortening the average duration of infection after antimicrobial treatment. Because the incidence of a communicable disease such as *C. trachomatis* infection depends on its prevalence, antimicrobial treatment represents an important approach to primary prevention [6].

Since 1994, *C. trachomatis* infection has been a notifiable infectious disease in the province of British Columbia, and there has been a sustained effort to control the transmission of the infection provincewide. In 1991, the case rate was 216 cases/100,000 population, and, by 1997, after the introduction of a control program, it had declined to 104 cases/100,000 population [7]. However, since 1998, chlamydia case rates have steadily increased, such that the number of new cases now exceeds the number of cases before the implementation of the control program. This trend in British Columbia has been seen throughout Canada and in other countries, such as Sweden [8]. Multiple reasons have been proposed for the increase in chlamydia case rates in the
C. trachomatis Reinfection Rates

Figure 1. Chlamydia trachomatis infection incidence rates in British Columbia from 1991 to 2003. Rates initially declined between 1991 and 1997 and have increased since then. The no. of cases in 2003 (8050) exceeds that in 1991 (7294).

We propose that C. trachomatis infection prevalence has increased because of a change in population susceptibility to re-infection, as a result of the C. trachomatis infection control program. This proposal rests on the hypothesis that treatment is occurring at increasingly earlier times after acquisition of infection and, thereby, interferes with the development of nat-

Figure 2. Transmission diagram of the natural history of (re)infection with Chlamydia trachomatis. See the Appendix, which appears only in the electronic edition of the Journal, for mathematical details.
ural immunity that is induced by infection [9]. This hypothesis is supported by the twin observations that natural immunity to C. trachomatis infection in women, as measured by the time to spontaneously clear infection, takes many months to occur [10, 11] and that early antimicrobial treatment interferes with the acquisition of immunity in a murine model of vaginal infection with C. muridarum [12]. Interestingly, Su et al. [12] suggested that their observations of the murine model could have an important impact on efforts to control human chlamydial infections.

To test the hypothesis, we conducted 2 types of analyses. We analyzed chlamydia case reports from Greater Vancouver, British Columbia, for the years 1989–2003 to determine the relative risk of and the risk factors for C. trachomatis reinfection. We also developed a mathematical model to evaluate the impact of treatment at different intervals after the acquisition of infection. Overall, the epidemiological data show that C. trachomatis reinfection rates have been increasing in British Columbia at 4.6% per year since the start of the control program. The mathematical model supports the hypothesis that early treatment of C. trachomatis infection increases population susceptibility to reinfection.

**METHODS**

**Study setting.** Greater Vancouver is Canada’s third-largest metropolitan area, with a 2001 population of 1,986,965 [13]. It is located in the southwestern corner of British Columbia, covering an area of 2,879 km². Over the past 2 decades, Greater Vancouver has experienced rapid growth and urbanization. The major economies of Greater Vancouver include retail trade, manufacturing, and health care. The ethnic composition of the population is very diverse; 37% are visible minorities.

**Data sources.** Since 1994, C. trachomatis infection has been a reportable infectious disease in British Columbia. All reported cases of chlamydia have been laboratory confirmed by culture, immunoassay, or polymerase chain reaction (PCR), depending on the year. Since 1998, all cases in the province have been recorded in an electronic surveillance database at the STD/AIDS Control Division of the British Columbia Centre for Disease Control (BCCDC) in Vancouver. Before 1998, cases were recorded in either paper or electronic format. In aggregate, these sources were compiled as the BCCDC Chlamydia surveillance database.

The rates of C. trachomatis infection in British Columbia between 1991 and 2003 are shown in figure 1. Despite a sharp downward trend between 1991 and 1996, C. trachomatis infection incidence has steadily increased since 1998, except for the year 2001. This may have been due to the use of mass treatment with single-dose azithromycin in 2000, which was undertaken in an attempt to control an outbreak of syphilis in Vancouver [14].

For analysis of reinfections, all individuals with chlamydia in Greater Vancouver who were 15–50 years of age and were reported in the database between 1989 and 2003 were included. We restricted the analysis to Greater Vancouver rather than the whole province, because data were available over a longer pe-

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Table 1. Baseline values and corresponding ranges of the parameters introduced in the mathematical model in figure 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Baseline value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1/j_{0}$</td>
<td>First infection incubation period</td>
<td>14 days</td>
<td>10–20 days</td>
</tr>
<tr>
<td>$1/p_{1}$</td>
<td>Duration between the early and intermediate stages of the first infection</td>
<td>105 days</td>
<td>50–150 days</td>
</tr>
<tr>
<td>$1/p_{2}$</td>
<td>Duration between the intermediate and final stages of the first infection</td>
<td>120 days</td>
<td>60–180 days</td>
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<tr>
<td>$1/p_{3}$</td>
<td>Recovery period</td>
<td>60 days</td>
<td>30–90 days</td>
</tr>
<tr>
<td>$1/p_{4}$</td>
<td>Duration of clearance with partial immune memory</td>
<td>60 days</td>
<td>30–90 days</td>
</tr>
<tr>
<td>$1/r_{1}$</td>
<td>Duration of clearance without immune memory for an exposed individual after early treatment</td>
<td>15 days</td>
<td>1–30 days</td>
</tr>
<tr>
<td>$1/r_{2}$</td>
<td>Duration of clearance without immune memory for an infected individual after early treatment</td>
<td>15 days</td>
<td>1–30 days</td>
</tr>
<tr>
<td>$1/r_{3}$</td>
<td>Duration of clearance with complete immune memory for an infected individual after treatment</td>
<td>15 days</td>
<td>1–30 days</td>
</tr>
<tr>
<td>$1/r_{4}$</td>
<td>Duration of clearance without immune memory for an infected individual without treatment</td>
<td>60 days</td>
<td>30–90 days</td>
</tr>
<tr>
<td>$1/\alpha_{1}$</td>
<td>Second infection incubation period</td>
<td>14 days</td>
<td>10–20 days</td>
</tr>
<tr>
<td>$1/\alpha_{2}$</td>
<td>Duration of clearance to a higher immune level after the second infection</td>
<td>300 days</td>
<td>100–400 days</td>
</tr>
<tr>
<td>$1/\alpha_{3}$</td>
<td>Duration of return to the same immune level after the second infection</td>
<td>300 days</td>
<td>100–400 days</td>
</tr>
<tr>
<td>$1/\alpha_{4}$</td>
<td>Recovery time to the full protection level</td>
<td>300 days</td>
<td>100–400 days</td>
</tr>
<tr>
<td>$1/\psi_{1}$</td>
<td>Third infection incubation period</td>
<td>14 days</td>
<td>10–20 days</td>
</tr>
<tr>
<td>$1/\psi_{2}$</td>
<td>Duration of clearance to a higher immune level after the third infection</td>
<td>300 days</td>
<td>100–400 days</td>
</tr>
<tr>
<td>$1/\psi_{3}$</td>
<td>Duration of return to the same immune level after the second infection</td>
<td>300 days</td>
<td>100–400 days</td>
</tr>
<tr>
<td>$1/\psi_{4}$</td>
<td>Recovery time to the full protection level</td>
<td>300 days</td>
<td>100–400 days</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Force of infection (calculated on the basis of other parameters; see [15])</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>$1 - z_{1}$</td>
<td>Fraction of the population removed from $E_{1}$ by early treatment</td>
<td>0</td>
<td>0–0.9</td>
</tr>
<tr>
<td>$1 - z_{2}$</td>
<td>Fraction of the population removed from $E_{2}$ by early treatment</td>
<td>0</td>
<td>0–0.9</td>
</tr>
<tr>
<td>$1 - z_{3}$</td>
<td>Fraction of the population removed from $E_{3}$ by early treatment</td>
<td>0</td>
<td>0–0.9</td>
</tr>
<tr>
<td>$Z$</td>
<td>Vaccine coverage</td>
<td>0%</td>
<td>0%–90%</td>
</tr>
</tbody>
</table>
iod (1989–2003) and were more completely reported. We also reasoned that the Greater Vancouver area is more likely than the entire province to share a common or overlapping sexual network through which *C. trachomatis* spreads.

Duplicate entries in the chlamydia surveillance database were removed on the basis of name, sex, and date of birth. The time interval between *C. trachomatis* infections was calculated where applicable. A reinfection was defined as a second infection in the same individual, confirmed by a positive chlamydia test result >30 days after the last infection. By linking the surveillance database with a treatment database, we determined that 89% of individuals with confirmed chlamydia received antimicrobial treatment and 78% received a recommended regimen; for 11% of individuals, we were unable to determine the treatment received. These percentages were virtually identical for those with and without reinfection. Age-standardized rates were calculated using population data from provincial sources. From January 1989 to December 2003, a total of 33,917 individuals with *C. trachomatis* infection in Greater Vancouver who were 15–50 years of age were reported to the STD/AIDS Control electronic surveillance database. Of these, 3394 individuals (10%) had a second infection. The number and rate of second infections over time were calculated.

**Analysis of reinfection rates.** Time to reinfection was defined as the number of days between the first and second infection and was analyzed by a Cox proportional-hazards model. Those without a second infection were censored at 31 December 2003. Predictors of the relative risk of reinfection that were entered into the survival analysis included sex, age, an interaction term between sex and age, and the time of infection expressed in years. The linearity of the first infection predictor was checked both visually and by a series of polynomial contrasts. Both approaches suggested that a linear relationship was appropriate for analysis. The proportional-hazards assumption was checked, and no serious deviation was detected. Given the size of the study (33,917 first infections, 3394 of which were associated with a second infection), statistical significance was extremely high, and insignificance was not due to a lack of power. In fact, we observed that each evaluated effect was either extremely significant or not significant at all.

**Mathematical model.** A dynamic mathematical model for *C. trachomatis* transmission was developed and is schematically depicted in figure 2. This compartmental model, which is based on the natural history of *C. trachomatis* infection [9, 10, 11], specifically incorporates multiple reinfections during the course of an individual’s sexually active life. Before being exposed to *C. trachomatis*, all individuals are assumed to be in the susceptible class, $S$. After being exposed to infection, a susceptible individual will move to the exposed class, $E$, in which the individual is assumed to be infected but not yet infectious. At the end of incubation period, the exposed person moves to the infectious class, $I$. To test the hypothesis regarding whether the
Timing of antibiotic intervention has an impact on the dynamics of *C. trachomatis* infection rates, we incorporated 3 different infectious classes (I₁–I₃), each with distinct immune response characteristics. During the natural course of infection and in the absence of treatment, individuals gradually move from the I₁ class to the I₂ class to the I₃ class and may experience 3 different outcomes, as a result of the diversity in immune responses: they may move to the recovered class, R, in which complete protection against reinfection is guaranteed; they may return to the susceptible class, S₁, if the individual does not develop protective immunity; and, finally, they may move to a less susceptible class, S₂, in which individuals have developed partial immunity against *C. trachomatis*, although the immunity is not sufficient to provide complete protection against reinfection. Reinfection is incorporated in the model by including a second susceptible class, S₂; a second exposed class, E₂; and the second infectious class, N. Similarly, the second and third reinfections are incorporated in the model by including the S₃, E₃, F and the S₄, R classes, respectively. Other possibilities for reinfected individuals are shown in figure 2 as different arrows emanating from these compartments. We assume that ≥4 infections ultimately generate adequate immune responses that protect individuals against further infection. All parameters related to the models are shown in table 1.

The sexually active population is also stratified by age and behavioral pattern [15]. On the basis of the age of infection extracted from the chlamydia surveillance database, we considered 5 age brackets: 15–19, 20–24, 25–29, 30–39, and 40–49 years. We also consider 3 groups characterized by different behavioral patterns: a group with occasional partner change, a group with active partner change, and a core group comprising highly sexually active individuals, including commercial sex workers [16]. Mathematical details related to the model are presented in the Appendix, which appears only in the electronic edition of the *Journal*.

**RESULTS**

*C. trachomatis* reinfection rates in British Columbia. From January 1989 to December 2003, a total of 33,917 individuals 15–50 years of age who resided in Greater Vancouver were reported to the STD/AIDS Control Division electronic surveillance database. Of these individuals, 3394 (10%) had a second infection, 562 (1.7%) had 3 infections, and 110 (0.3%) had ≥3 reinfections. The survival analysis included only the time to the first reinfection; data were censored at 31 December 2003 if no reinfection was recorded. The number and rate of repeat infections are shown in figure 3. Between the years of 1989 and

![Figure 4. Log₁₀ relative risk of *Chlamydia trachomatis* reinfection, which has increased in a linear manner between 1989 and 2003. The no. of first infections each year is superimposed on the individual year effects; the solid line represents the linear effect.](image-url)
1995, when chlamydia prevalence rates were declining, the reinfection rate was steady, at 1.3–2.6 cases/100,000 population. Since 1996, the reinfection rate has consistently increased, from 9.7 cases/100,000 population in 1996 to 53.2 cases/100,000 population in 2003.

To correct for the growing pool of individuals in the chlamydia surveillance database who are identifiable as having reinfection, a survival analysis based on the Cox proportional-hazards model, in which the time to reinfection was defined as the number of days between the first and the second infection, was used to analyze the data. The predictors of the relative risk of reinfection were sex, age, and the main variable of interest—time of first infection expressed in years (figure 4). The relative risk is a ratio of the probability of reinfection at one instant in time divided by the probability of reinfection exactly 1 year prior. On the basis of the data, we estimated the relative risk to be 1.0464, or an increase in the probability of reinfection of 4.64% per year (95% confidence interval, 3.27%–6.03%). The relative risk of reinfection was also greater at younger ages and was greater for women than for men (figure 5). No significant interaction between time of first infection and either sex or age was found. Indicators of other interventions, like the time of introduction of single-dose azithromycin therapy or reportability of chlamydia, were also evaluated but were found to be nonsignificant predictors (data not shown).

These analyses were based on defining a reinfection as 2 laboratory-confirmed infections separated by ≥30 days. We repeated the analyses, using 3 and 6 months as the intervals between 2 positive tests to define a reinfection. On the basis of the 3-month definition, there were 2937 reinfections; on the basis of the 6-month definition, there were 2536 reinfections. The analyses yielded results that were qualitatively similar to those found when the 1-month definition was used, with the relative risk of infection increasing by 4.7% per year when the 3-month interval was used and by 5.4% per year when the 6-month interval was used.

**Model simulation.** We simulated the transmission dynamics of *C. trachomatis* infection, using the demographic profile of sexually active individuals in Greater Vancouver [15]. We varied the parameters in the model to study the impact of different demographic and behavioral factors as well as various intervention scenarios. We performed a sensitivity analysis to evaluate the robustness of the results. The impact of 2 intervention scenarios—antimicrobial treatment and immu-
Figure 6. Impact of control strategies on the prevalence of cases of infection, showing before-intervention endemic equilibrium (blue), prevalence after the early treatment of 80% of the infected individuals (beginning at year 20) (green), and prevalence after vaccination of 80% of the individuals (red). We assumed that the vaccine is 100% efficacious and provides long-term (10 years) immunity.

Immunization—is summarized in figure 6. Each simulation was performed over a 45-year span after the introduction of the first infected individual within the population. After a transient period, the prevalence of infection reached an equilibrium level, which is depicted by the horizontal segment at the left end of the curves. In the absence of an intervention and if all demographic and behavioral parameters remain constant, the endemic equilibrium is sustained. However, if early treatment (at $E_i$ or $I_i$ in figure 2) of 80% of individuals begins (at year 20), the prevalence will initially decrease dramatically but will be followed by a rebound within a few years. This phenomenon is in good qualitative agreement with the temporal variation of cases observed in British Columbia, as shown in figure 1. The 80% coverage rate corresponds to an ideal treatment program, and, in most cities, the actual coverage rate is unlikely to reach this level. Therefore, the simulation was repeated, varying treatment coverage over a wide range. The analysis showed the same rebound phenomena, even when coverage rates were as low as 20% (data not shown).

As an alternative intervention to case detection and antimicrobial treatment, the scenario in which 80% of individuals are vaccinated by a 100% efficacious chlamydia vaccine, which is assumed to provide long-term (10 years) immunity, was considered. Figure 6 shows that, under this scenario, *C. trachomatis* infection can be eradicated within 5 years after widespread introduction of the vaccine into the population. In general, the success of immunization intervention depends on both vaccine efficacy and vaccination coverage. The analysis showed that, when the multiplication of vaccine efficacy and vaccine coverage exceeded the critical threshold value of 60%, *C. trachomatis* infection could be eliminated from the population with the sexual mixing pattern examined (data not shown).

DISCUSSION

Successful control or eradication of *C. trachomatis* infection ranks among the top public health priorities for Canada [17]. In British Columbia, interventions have been undertaken to control *C. trachomatis* infection among the sexually active population, including case identification, antibiotic treatment, and contact tracing. Despite these efforts, the incidence of infection has not demonstrated a significant long-term decrease. On the contrary, the data show that initial success in decreasing case rates between 1991 and 1996 has been followed by an upward
trend in the number of reported cases since 1998. Of concern, the data also demonstrate that the rate of C. trachomatis reinfection has increased over the past 14 years. Because the database contains an expanding pool of individuals identified as having had a prior infection, we used survival analysis to calculate the relative risk of reinfection, counting individuals who were and were not reinfeected. The Cox proportional-hazards analysis showed that the relative risk of reinfection is truly increasing, at nearly 5% per year over the course of the C. trachomatis infection control program. Furthermore, the relative risk of reinfection was greater for younger individuals and was greater for women than for men. These latter findings are similar to the risk factors for C. trachomatis reinfection that have been identified in other studies [18–20].

In aggregate, the results suggest that the era of the C. trachomatis infection control program has been associated with enhanced susceptibility to reinfection at the population level. We hypothesized that the enhanced population susceptibility may be due to interference in the development of immunity to natural infection after early case detection and antimicrobial treatment. Antimicrobials have clearly been shown to blunt the development of immunity to C. muridarum in mouse rechallenge models [12]. Natural immunity to C. trachomatis in humans, although incompletely defined, appears to depend on Th1 cells that secrete interferon-γ and on B cells that secrete neutralizing and opsonizing antibodies [9]. Importantly, human immunity takes some time to acquire [21, 22], and spontaneous clearance of C. trachomatis infection takes many months to occur [10, 11]. Thus, antimicrobials, through early clearance of the infection, may impede the time-dependent acquisition of an immunological set point necessary for C. trachomatis immunity.

To test the potential impact of early treatment on C. trachomatis control, we developed a mathematical model based on demographic data for the sexually active population in Greater Vancouver. Results from the model suggested that the lack of development of immunity against reinfection with C. trachomatis at the individual level can result in an increase in the number of infected and reinfeected individuals at the population level. Although early treatment reduces the prevalence of infection in the short term, prevalence reaches and can even exceed the before-treatment level, in the form of a rebound. Sensitivity analysis showed that the timing and duration of the rebound depends on the parameters introduced in the model. Nevertheless, under a wide range of parameter estimation, the rebound effect always occurs after early intervention. Importantly, the model reproduced the general trend in C. trachomatis infection rates seen after the introduction of the control program in British Columbia.

The model assumed that demographic and behavioral forces remain unchanged after the introduction of the C. trachomatis infection control program. In fact, this is one of the reasons why rates rebound after the introduction of an antimicrobial-based control program—that is, treated individuals re-enter unchanged sexual networks as susceptible and contribute to enhanced transmission [23, 24]. Although changing sexual networks is a long-term goal for sexually transmitted disease control programs [25, 26], how to make effective and sustained changes in such networks is not currently clear. Accordingly, the mathematical model also evaluated the potential effect of a vaccine on C. trachomatis transmission dynamics. The model simulation suggested that the most efficient way to control or eradicate chlamydia in the absence of changing sexual networks is to develop a vaccine that induces long-term immunity against C. trachomatis.

Although the epidemiological and mathematical model data reported in this study are consistent with the interpretation that C. trachomatis infection control based on antimicrobial treatment may enhance population susceptibility to C. trachomatis infection, further evidence to test predictions of the hypothesis are needed. For instance, it may be possible to determine whether the proportion of individuals infected with C. trachomatis who lack detectable immune responses to the organism at the time of initial infection may be increasing over time and whether such individuals are at increased risk of reinfection. Furthermore, detailed study of the estimated duration of infection from time of acquisition to time of treatment may show that this interval is decreasing. These and other studies may help to determine whether treatment-based control programs, such as the one for C. trachomatis infection, have an inherent weakness, in terms of disease control at the population level. Nevertheless, we conclude that, with the data in hand, research and development of a vaccine remains an important and perhaps the necessary solution to halt the spread of C. trachomatis infection at the population level.

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References


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