Upsurge of Chlamydial Reinfection in a Large Canadian City: An Indication of Suboptimal *Chlamydia* Screening Practices?

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ABSTRACT

Objectives: Given the limited knowledge on chlamydial reinfection (CR) in Canada, we examined the extent and predictors of CR in Montréal, a large Canadian city.

Methods: We retrospectively studied all Montréal residents aged ≥10 years for whom ≥1 laboratory-confirmed chlamydial infection was reported to the public health department between 1988 and 2007 (n=44,580). Each person was passively followed for two years after baseline infection or until reinfection. Socio-demographic factors and histories of other notifiable diseases were examined as potential predictors. Cox multivariate regression was used to model the time to CR. Survival analyses were stratified by age group (<25 vs. ≥25 years).

Results: We estimated an overall two-year CR rate of 6.4%, an incidence density of 3.5 per 100 person-years, and a median time to reinfection of nine months. CR significantly increased over time. Among persons <25 years, reinfection was significantly more likely among females [adjusted hazard ratio (AHR): 1.58] and younger participants (10-14 years: AHR: 2.98; 15-19 years: AHR: 1.81). Residing within the South Central sector was deleterious for six months following initial infection after which it became protective. Among persons ≥25 years, a history of sexually transmitted infections increased the risk of reinfection (AHR: 1.79).

Conclusion: CR is a significant and growing problem in Montréal. The current recommendation for a single repeat screening six months post-treatment might be usefully complemented with additional screenings. Our results also underscore the importance of screening high-risk populations, particularly young women.

Key words: *Chlamydia trachomatis;* urban spatial distribution; epidemiologic determinant; public health; infectious disease reporting; survival analysis

La traduction du résumé se trouve à la fin de l'article.

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Sexually transmitted infections (STIs), particularly chlamydia, pose a serious threat to the health of Canadians and strain health care resources.[1-3] Chlamydial reinfections (CR) may significantly add to the existing burden. Indeed, relative to a single infection, recurrent *Chlamydia* infections have been demonstrated to increase the risk of ectopic pregnancy, pelvic disease[4] and female infertility.[5,6] Moreover, CR may be responsible for maintaining endemic rates of chlamydial infection. Finally, CR, a marker of persistent risk-taking, reflects the effectiveness of the STI prevention and management and therefore constitutes a useful monitoring indicator.

Updated in 2008, the Canadian Guidelines on STI are a valuable resource for clinical and public health professionals.[7] Several recommendations have been proposed to prevent CR, including 1) more intensive screening of young males, thought to be hidden reservoirs for reinfection of partners, and 2) repeat screening of all individuals with genital chlamydia six months post-treatment.[7,8]

Although CR is routinely observed in clinical practice, we know little about its frequency and distribution in Canada. Our knowledge lags behind in comparison with the United States, where several studies on CR have been conducted over the past years.[9-23] We have found only one published Canadian study that reported a high (i.e., 10%) and increasing CR rate among persons 15-50 years living in the greater Vancouver area passively followed for a 14-year period (1989-2003).[24] Given the scarcity of data on this silent epidemic in Canada, our goal in the present study was to determine the extent and main predictors of CR in a large Canadian city using a population database of individuals diagnosed at least once with chlamydial infection. We were particularly interested in examining the temporal trends of CR to stimulate critical reflection about current STI prevention practices.

METHODS

Settings

The study was conducted on the Island of Montréal from 1988 to 2007. The 2006 census enumerated 1.9 million inhabitants in Montréal. In 2003, the island's health services were divided into 12 Health and Social Services Centres responsible for promoting health and well-being within a given territory. To assess the intra-urban spatial variation of CR, we merged the 12 Centres into four geographic sectors – South Central, North Central, East and West (see Figure 1).

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Figure 1. Island of Montréal and geographic sectors

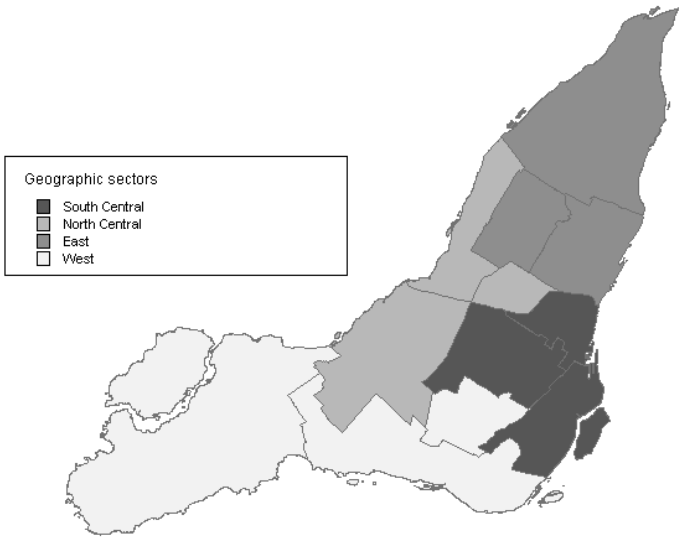
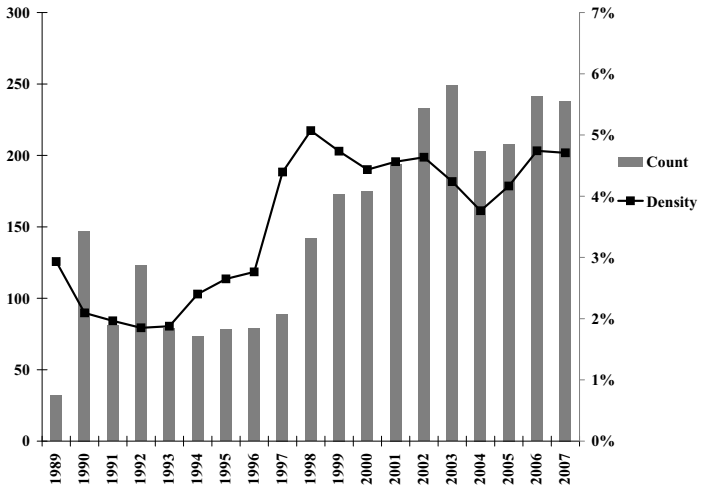


Figure 2. Counts and incidence density of chlamydial reinfection within two years of a first chlamydial infection in Montréal, 1989 to 2007 (n=44,580)



Note: Incidence density (%) = (Number of chlamydial reinfections/person-years) * 100.

Table 1. Baseline and Follow-up Characteristics of Cases with ≥1 Chlamydial Infection Reported to the Regional Public Health Department (n=44,580), by Residential Location Status (Available vs. Missing), Two-year Follow-up, Montréal, 1988-2007

Characteristics	Residential Location Available n (%)	Residential Location Missing n (%)
Baseline		
Sex		
Female	22,477 (73.6%)	9169 (65.2%)
Male	8043 (26.4%)	4891 (34.8%)
Age (years)		
10-14	343 (1.1%)	75 (0.5%)
15-19	8633 (28.3%)	3069 (21.8%)
20-24	10,482 (34.3%)	5223 (37.1%)
25-29	5577 (18.3%)	2726 (19.4%)
30-39	4146 (13.6%)	2173 (15.5%)
≥40	1339 (4.4%)	794 (5.6%)
Year		
1988-1995	13,844 (45.4%)	2279 (16.2%)
1996-2007	16,676 (54.6%)	11,781 (83.8%)
Geographic sector		
South Central	12,210 (40.0%)	
North Central	6275 (20.6%)	
East	7354 (24.1%)	
West	4681 (15.3%)	
History of other notifiable STIs*		
Yes	284 (0.9%)	124 (0.9%)
No	30,236 (99.1%)	13,936 (99.1%)
History of notifiable enteric infections*		
Yes	140 (0.5%)	52 (0.4%)
No	30,380 (99.5%)	14,008 (99.6%)
History of notifiable vaccine-preventable infections*		
Yes	43 (0.1%)	12 (0.0%)
No	30,477 (99.9%)	14,048 (99.9%)
Follow-up		
Chlamydial reinfection		
Yes	1952 (6.4%)	885 (6.3%)
No	28,568 (93.6%)	13,175 (93.7%)
Incidence density of chlamydial reinfection	3.5 per 100 person-years	3.5 per 100 person-years
Median time to chlamydial reinfection	273 days	271 days
Total	30,520 (100%)	14,060 (100%)

* Notifiable STIs included gonorrhea, syphilis, hepatitis B, hepatitis C, lymphogranulomatosis and human T-lymphotropic virus (HTLV) infections, but excluded HIV infections, since these are not usually reported nominally in Québec. Notifiable enteric infections included salmonellosis, shigellosis, giardiasis, yersiniosis, cryptosporidiosis, cyclosporosis, campylobacteriosis, amebiasis and *Escherichia coli* infections. Notifiable vaccine-preventable infections included mumps, measles, rubella, whooping cough and *Haemophilus influenzae* type b infections.

For the past two decades in the province of Québec, it has been mandatory for laboratories and physicians to report all cases of chlamydial infection to regional public health departments (PHD). Data were extracted from the regional Maladies à déclaration obligatoire (MADO) registry. The registry stores data on all reportable diseases and minimally provides, for each episode reported, a unique identification number (i.e., personal identifier based on name, birth date and residential address) as well as the socio-demographic characteristics and residential address of the individual affected, the diagnosis and report date.

Study population

We performed a longitudinal analysis of all persons ≥10 years old (at the time of their first diagnosis) with at least one laboratory-confirmed chlamydial infection reported to the PHD from October 1988 (date of implementation of the reportable disease database) to the end of 2007. Entry into the study was defined as an Island of Montréal resident's date of first notification of chlamydial infection during the study period. The sample included 44,580 individuals.

Measures

CR was defined as a chlamydial infection reported 60 to 730 days (two years) following a first infection for the same individual during the study period. Only the first reinfection, in case of multiple reinfections, was considered. For each subject, passive follow-up ended at the first of the following events: 1) reinfection, 2) December 31, 2007 (end of study period), or 3) end of the two-year period since entry. As clearly demonstrated elsewhere, most repeated chlamydial infections, particularly those diagnosed several weeks after initial diagnosis, are reinfections (i.e., new incident infections) rather than persistence without treatment or with treatment failure.[25] However, since many recent studies observed that most CR occur within two years, follow-up was limited to two years after

Table 2. Univariate Survival Analyses of Time to Chlamydial Reinfection, by Baseline Characteristics, for Persons <25 Years and ≥25 Years (n=30,520), Two-year Follow-up, Montréal, 1988-2007

Baseline Characteristics	<25 Years			≥25 Years		
	Reinfections n (%)	Total n	Log rank p-value	Reinfections n (%)	Total n	Log rank p-value
Sex						
Female	1376 (8.7%)	15,790	<0.0005	256 (3.8%)	6687	0.2
Male	173 (4.7%)	3668		147 (3.4%)	4375	
Age (years)						
10-14	58 (16.9%)	343	<0.0005			
15-19	900 (10.4%)	8633				
20-24	591 (5.6%)	10,482				
25-29				207 (3.7%)	5577	0.6
30-39				143 (3.4%)	4146	
≥40				53 (3.9%)	1339	
Year						
1988-1995	479 (5.4%)	8848	<0.0005	122 (2.4%)	4996	<0.0005
1996-2007	1070 (10.1%)	10,610		281 (4.6%)	6066	
Geographic sector						
South Central	454 (6.5%)	6968	<0.0005	179 (3.4%)	5242	0.2
North Central	373 (8.9%)	4156		93 (4.4%)	2119	
East	451 (8.9%)	5079		79 (3.5%)	2275	
West	271 (8.3%)	3255		52 (3.7%)	1426	
History of other notifiable STIs						
Yes	7 (7.3%)	107	0.8	13 (7.3%)	177	0.004
No	1542 (6.5%)	19,351		390 (3.5%)	10,885	
History of notifiable enteric infections						
Yes	12 (16.4%)	73	0.008	5 (7.5%)	67	0.1
No	1537 (7.9%)	19,385		398 (3.6%)	10,995	
History of notifiable vaccine-preventable infections						
Yes	8 (19.0%)	42	0.006	0 (0%)	1	0.8
No	1541 (7.9%)	19,416		403 (3.6%)	11,061	
Overall	1549 (8.0%)	19,458		403 (3.6%)	11,062	

initial infection to increase the number of CR identified while reducing the probability of loss to follow-up due to death or emigration.[17,22,23,25]

The following baseline characteristics were investigated as potential predictors of CR: sex, age, year, geographic sector, and history of other notifiable diseases including other STIs, enteric infections and vaccine-preventable infections (see Table 1 for details about infections included in each category). Continuous variables (age and year) were categorized using clinically relevant cut-offs. We created six age groups: 10-14, 15-19, 20-24, 25-29, 30-39, and ≥40 years. Dates of initial chlamydial infection were categorized as follows: 1988-1995 and 1996-2007. This cut-off point was chosen based on the increasing trend in observed STI cases since the mid-1990s in Canada.[1-3,26] For each individual, the geographic sector (North Central, South Central, East, or West) was determined according to the residential address provided at first notification. History of notifiable diseases was defined as having had a disease reported under Quebec's Public Health Act prior to the first episode of *Chlamydia* infection reported during the study period.

Analysis

First, we examined temporal trends in CR by computing annual incidence density (i.e., number of CR per 100 person-years) for the full sample (n=44,580). Since preliminary analyses showed that about a third of residential addresses were missing, we compared baseline characteristics of persons with and without residential information. Subsequent analyses were restricted to persons with residential addresses (n=30,520). Survival functions of time to reinfection were estimated using the Kaplan-Meier method. Log-rank tests were used to compare reinfection curves according to baseline characteristic. The proportional hazards assumption was verified for each baseline characteristic using graphical log-minus-log and Schoenfeld weighted residuals tests. Survival analyses were stratified by age (<25 vs. ≥25 years), as the proportional hazards assumption was not valid between these two age groups. Stratification was also supported by the clinical relevance of addressing the issue of CR among younger and older persons separately. Then, Cox proportional hazards regression was used to model the time to reinfection, using baseline characteristics as potential predictor variables. Only variables significantly associated with CR ($p<0.05$) were retained in final models. We decided to transform the "geographic sector" variable into a time-dependent variable given that the proportional hazards assumption was not met for this variable (i.e., hazard ratio not constant over time). Hence, we attempted to model the interaction of geographic sector with time using clinically meaningful time intervals (<6 vs. ≥6 months after baseline infection). Final multivariate models were used to estimate adjusted hazard ratios (AHR) and corresponding 95% confidence intervals (CI) for relationship between predictor variables and time to reinfection. All analyses were conducted using SPSS version 12.0 (SPSS Inc., Chicago, Illinois).

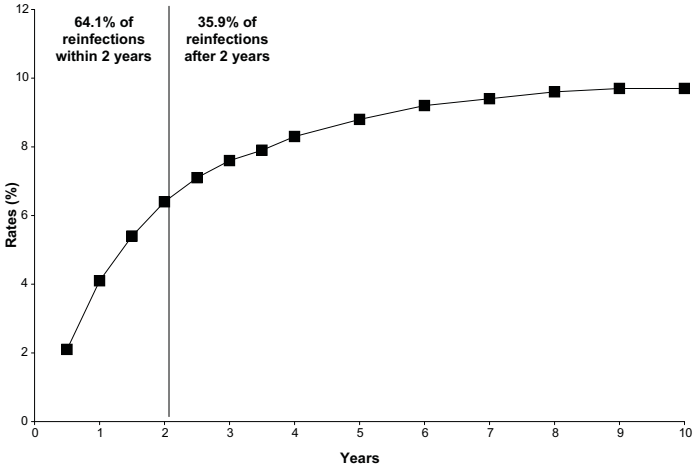
RESULTS

In our study, 2,837 (6.4%) persons were reinfected with *Chlamydia* within two years of first infection. From 1989 to 1994 in Montréal, the annual counts and incidence density of CR remained low and then rose sharply (Figure 2).

CR for individuals with missing addresses did not differ from the others. Both groups had an overall incidence density of 3.5/100 person-years. However, there were more women and older persons among individuals with missing addresses (Table 1).

Univariate survival analyses showed that among persons <25 years, reinfection was more likely among females, adolescents (10-14 years), people initially infected after 1995, those living outside the South sector, and those with a history of notifiable enteric or vaccine-preventable infections (Table 2). By contrast, for people ≥25 years, risk of CR was higher among those whose first chlamydial infection occurred post-1995 or who had a history of other notifiable STIs.

Figure 3. Chlamydial reinfection rates using different cut-offs for follow-up of persons with ≥1 chlamydial infection reported to the regional public health department (n=44,580), Montréal, 1988-2007



Note: Maximal rate, using an uncensored follow-up period (i.e., up to 19 years), was 9.9%.

Table 3. Multivariate Cox Regression Analyses of Time to Chlamydial Reinfection, by Baseline Characteristics, for Persons <25 Years and ≥25 Years (n=30,520), Two-year Follow-up, Montréal, 1988-2007

Baseline Characteristics	<25 Years Adjusted HR (95% CI)	≥25 Years Adjusted HR (95% CI)
Sex		
Female	1.58 (1.34-1.85)	
Male	1.00 (Referent)	
Age (years)		
10-14	2.98 (2.28-3.91)	
15-19	1.81 (1.63-2.01)	
20-24	1.00 (Referent)	
Year		
1988-1995	1.00 (Referent)	1.00 (Referent)
1996-2007	2.06 (1.85-2.30)	2.07 (1.67-2.56)
Geographic sector		
<180 days		
South Central	1.46 (1.22-1.76)	
Other areas	1.00 (Referent)	
≥180 days		
South Central	0.71 (0.62-0.82)	
Other areas	1.00 (Referent)	
History of other notifiable STIs		
Yes		1.79 (1.03-3.12)
No		1.00 (Referent)

Table 3 displays Cox multivariate regression models for persons <25 years and for those ≥25 years. Among people <25 years, independent risk factors for CR included being female, <20 years old, and having a first infection after 1995. Furthermore, the association between CR and geographic location indicated that residing in the South Central sector was deleterious in the first six months following initial infection but protective after this period. By contrast, only two factors positively predicted CR among persons ≥25 years: a history of other STIs, and first infection after 1995.

DISCUSSION

Our study complements others by demonstrating that some predictors are specific to younger or older individuals. This finding is important as it emphasizes the need to adapt preventive strategies to socio-demographic factors such as sex, age and place of residence. Our findings also provoke critical examination of the relevance of currently proposed recommendations in the Canadian Guidelines on STI, and the time- and space-dependent contextual conditions that may shape the risk of CR.

The two-year CR rate of 6.4% observed among Montréal residents was slightly inferior to the 10% rate found in Vancouver.[24] The higher rate observed in Vancouver might be explained by a longer follow-up period (up to 14 years), which allowed more time for reinfection. Indeed, in our study, extending follow-up to the complete study period (1988-2007) would result in a 9.9% CR rate (Figure 3).

Our estimate of the median time between the initial and the following chlamydial infection (nine months) is consistent with the existing literature. Indeed, median time estimates across studies have continually been superior to six months.[22,23,27] If all physicians were to implement Canadian guidelines recommending repeat testing of individuals with chlamydial infection six months post-treatment,[7] over half of reinfected cases would not be diagnosed and reported.

As observed by other researchers, we also found that young females were at increased risk for reinfection.[9,13,15,18] These results support the Canadian recommendation to increase screening of young males, the hidden reservoir; this specific measure is regarded as a promising strategy to reduce infections and reinfections among young females.[28]

Similar to Vancouver, we observed a significant increase in reinfections in 1996-2007 versus 1988-1995 that coincides with an increase in STIs.[24,26] Several factors may explain the simultaneous upsurge of chlamydial infections and reinfections, including changes in sexual risk behaviour, diagnostic test and reportable disease surveillance.[29-32] Innovations in HIV therapy in the mid-1990s led to treatment optimism and reduced risk awareness.[7] Moreover, more acceptable, more sensitive and less specific screening tests (i.e., nucleic acid amplification tests)[33] became widely available in the last decade in Montréal. Alternatively, the increase in CR may be due to causes specific to reinfection, such as the arrested immunity hypothesis which posits that early treatment of *Chlamydia* interferes with the development of protective immune response.[34]

Contrary to expectations, hospital-diagnosed reproductive sequelae, such as pelvic inflammatory disease and ectopic pregnancy, have steadily declined since the mid-90s in Montréal (results not shown) and elsewhere.[30,31,35,36] The fact that an increase in reinfections did not parallel trends in associated complications suggests that frequent infections are not as damageable to reproductive health as long-lasting untreated infections. If this hypothesis were true, intensive screening of CR, rather than prevention, would be a first priority.

Our study is subject to limitations. First, one third of the full sample was missing residential address and was excluded from survival analyses; however CR rates were calculated using data from the full sample. The remaining individuals differed from those excluded with regard to age, sex, and possibly other unmeasured factors. Second, our sample is only representative of the population using health care services. Thus, our estimated rates may only represent the "tip of the iceberg". Third, persons were only passively followed, which precluded being informed of their vital and migration statuses. Subsequent chlamydial infections diagnosed among persons who had moved outside of Montréal may have resulted in an underestimation of CR rates. Similarly, we were only able to investigate the influence of residential location at baseline, although it may have changed over time. Fourth, our measurement of CR (i.e.,

second episode >60 days following initial episode) may, in some instances, reflect persistence of previous infection left untreated or ineffectively treated rather than true reinfection. Finally, our choice of predictors was limited to those available in the MADO registry.

Our results support frequent targeted re-screenings during the first year following initial *Chlamydia* infection, with particular focus on young women. We question the current recommendation of a single repeat screening six months post-treatment in light of our finding that most reinfections may occur later than six months following initial infection.

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RÉSUMÉ

Objectifs : Étant donné les connaissances limitées sur la récidive de chlamydiose au Canada, nous avons examiné son ampleur ainsi que ses déterminants dans une grande ville Canadienne.

Méthodes : Nous avons inclus dans cette étude rétrospective tous les résidents de Montréal ≥10 ans avec ≥1 épisode de chlamydiose confirmé en laboratoire et rapporté à la Direction de santé publique entre 1988 et 2007 (n=44 580). Chaque personne a été suivie passivement pour une période de deux ans suivant l'infection initiale ou jusqu'à la récidive. Les facteurs sociodémographiques et les antécédents d'autres maladies à déclaration obligatoire ont été examinés en tant que déterminants. Une régression multivariée de Cox a été utilisée pour modéliser le temps jusqu'à la récidive. Les analyses de survie ont été stratifiées selon le groupe d'âge (<25 contre ≥25 ans).

Résultats : Nous avons estimé un taux de récidive sur deux ans de 6,4 %, une densité d'incidence de 3,5/100 personne-années, et un temps médian de récidive de neuf mois. Parmi les personnes <25 ans, la récidive était significativement plus fréquente chez les femmes [ratio de risque ajusté (RRA) : 1,58] et chez les adolescents (10-14 ans : RRA : 2,98; 15-19 ans : RRA : 1,81). Vivre dans le secteur centre-sud était délétère au cours des six premiers mois suivant l'infection initiale puis devenait par la suite un facteur protecteur. Chez les personnes ≥25 ans, un antécédent d'infection transmise sexuellement augmentait le risque de récidive (RRA : 1,79).

Conclusion : La récidive de chlamydiose est un problème préoccupant et grandissant à Montréal. La recommandation actuelle de répéter le dépistage six mois suivant une première infection gagnerait à être accompagnée de dépistages additionnels. Nos résultats supportent aussi le dépistage des populations à haut risque, particulièrement les jeunes femmes.

Mots clés : *Chlamydia trachomatis;* distribution spatiale; déterminants de la santé; santé publique; maladies à déclaration obligatoire; analyse de survie