Chlamydia Public Health Programs and the Epidemiology of Pelvic Inflammatory Disease and Ectopic Pregnancy

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Background. Many countries have witnessed a disturbing increase in cases of Chlamydia trachomatis infection despite enhanced control programs. Since the goal of Chlamydia control is to prevent reproductive complications such as pelvic inflammatory disease and ectopic pregnancy, an understanding of recent trends in these conditions is needed to fully evaluate the effect of control efforts.

Methods. We analyzed 2 provincial, comprehensive health services administrative databases (encompassing hospitalizations and all physician-delivered services) for pelvic inflammatory disease and ectopic pregnancy trends from 1992 through 2009 in women of reproductive age in British Columbia, Canada. Trends were compared to provincial Chlamydia surveillance data by time-series analysis, using the cross-correlation function method and Granger causality testing.

Results. Chlamydia cases substantially increased from 1992 through 2009. Inpatient, outpatient, and total diagnoses of pelvic inflammatory disease and ectopic pregnancy declined from 1992 through 2003. After 2003, pelvic inflammatory disease rates continued to fall, while ectopic pregnancy rates significantly increased. The male Chlamydia urethritis rate increased from 39.4 to 173.6 cases/100,000 from 1996 to 2009.

Conclusions. In the context of increasing Chlamydia infection rates, the reproductive complications of Chlamydia infection in women are declining overall. A recent increase in rates of ectopic pregnancies is cause for concern.

Keywords. Chlamydia; PID; ectopic pregnancy; arrested immunity; public health programs.
[8–11]. A population-based assessment of Chlamydia infection trends that used data from five 2-year cycles of the National Health and Nutrition Examination Surveys from 1999 through 2008 estimated a 40% reduction in prevalence among participants aged 14–39 years [10]. However, this reduction did not occur in women aged 14–25 years, the target population for routine annual screening. Two recent studies reported trends among women 15–24 years of age attending Infertility Prevention Project clinics [9, 11]. Chlamydia positivity did not change from 2004 through 2008 among women attending family planning clinics [9] but declined from 2004 through 2009 (odds ratio, 0.93 per year) among women attending prenatal clinics [11]. However, 5 of the 7 regions reporting prenatal data showed flat rates, and 1 showed an increase. Only Region IV showed a decline, but this region dictated the overall trend.

Even if the prevalence of Chlamydia infection is stable or declining, the disease burden in a population includes incident (ie, new) and prevalent (ie, existing) cases [12, 13]. What is known about incident Chlamydia infection in the United States? Rates of new cases are increasing, but this is often ascribed to improved case finding [5, 6, 14] rather than to a real increase in incidence. Improved case finding might result from (1) higher diagnostic yield because nucleic acid amplification testing (NAAT) is more sensitive, (2) higher testing volumes because NAAT urine testing is more acceptable, or (3) better targeting of screening programs to high-risk populations [5]. To estimate Chlamydia infection incidence without the confounding bias of changes in screening, one can analyze male urethritis because men are not targeted for Chlamydia screening. In one Pacific Northwest managed care health plan, male urethritis rates increased 2.46-fold from 1997 through 2007, suggesting a true increase in incidence [1].

In British Columbia, improved case finding because of higher diagnostic yield does not account for rising rates (Figure 1) because NAAT was the predominant testing method throughout this period. As well, improved case finding from higher testing volumes does not fully explain increasing rates. From 1998 to 2009, the estimated volume of Chlamydia testing increased by 115,607 (from 186,169 tests to 301,776 tests), the percentage of tests yielding positive results (ie, the percentage positivity) increased by 1.1% (from 2.6% of tests to 3.7% of tests), and the number of cases increased by 6315 (from 4880 cases to 11,195 cases). If the percentage positivity had remained stable, expansion of the testing volume would have accounted for only 48% of the additional 6315 cases. However, percentage positivity increased by 1.1%.

Improved case finding in British Columbia from better targeting of screening is also unlikely. Despite the 62% increase in testing volume from 1998 through 2009, there is no evidence of changes among the group of individuals who were tested. The provincial screening strategy remained the same [15], and the demographic variables of test takers (age group, sex, patient address, and testing location) did not show a pattern of change that suggests better targeting [2].

Thus, the higher percentage positivity and additional Chlamydia cases in British Columbia may be best explained by increased incidence due to more-risky behavior or higher reinfection rates. There is no consistent evidence of increased sexual risk behavior. Gonorrhea cases remained low from 1996 through 2009, increasing from 13.3 to 30.3 cases/100,000. Infectious syphilis cases increased from 1997 through 2006, plateaued at around 300 cases/year from 2004 to 2008, and declined significantly afterward [2]. New cases of positive HIV test results have declined steadily [2]. Finally, sexual health surveys from 1998 to 2008 of 30,000 adolescent students in grades 7–12 at 50 of 59 British Columbia school districts showed declining rates of sexual activity, increasing age at onset of sexual activity, increasing condom use, declining self-reported sexually transmitted infections (STIs) among sexually active students, and stable rates of pregnancy among teenagers [16].

Therefore, by elimination, the association of arrested immunity with higher reinfection rates may be the most likely cause of, or a significant contributor to, increased Chlamydia infection incidence, reflected in a higher percentage positivity among Chlamydia tests and rising rates of Chlamydia infections.

Strikingly, recent increases in Chlamydia infection and reinfection rates have not been accompanied by a corresponding increase in Chlamydia-associated reproductive complications. Most locales, including ours, have experienced declining or stable complication rates during this period, especially for...
pelvic inflammatory disease (PID) and ectopic pregnancy (EP) [1, 5, 17–28]. On the basis of these observations, we hypothesize that, in addition to arresting the acquisition of natural immunity to Chlamydia reinfection, the seek-and-treat Chlamydia control program may also be arresting the underlying immune-mediated pathological processes that cause PID and EP.

To document Chlamydia infection, PID, and EP trends, we used 3 approaches to analyze 2 unique data sources from a Canadian province with universal healthcare, standardized and accessible Chlamydia laboratory testing, and stable clinical diagnostic criteria for PID and EP. We conducted a descriptive analysis of cases, analyzed trends for statistical significance, and used time-series analysis to determine cross-correlation of trends.

**METHODS**

**Data Sources**

We analyzed 2 sources of health services administrative data housed with the British Columbia Ministry of Health Services: Medical Services Plan (MSP) data and the provincial Discharge Abstract Database (DAD). The MSP insures medically required services provided by physicians (for both inpatient and outpatient settings, including emergency departments), supplementary healthcare practitioners, laboratory services, and diagnostic procedures [29]. Virtually 100% of residents are covered under the MSP, which includes billings submitted by physicians for services provided to unique patients, featuring International Classification of Diseases codes (Table 1) and accompanying patient demographic data.

The DAD contains demographic, administrative, and clinical data for hospital discharges (inpatient short-term care, long-term care, and rehabilitation hospitals) and outpatient surgeries from all British Columbia hospitals [30]. Trained coders review discharge records to assign a corresponding ICD code and a diagnosis most responsible for the hospitalization [30]. We prepared deidentified MSP and DAD data extracts, including demographic (age and sex) and ICD-coded diagnosis data. Individuals are recognized by a unique provincial health number (PHN) in both data sets; for this analysis, a unique study ID was substituted for the PHN for each individual, allowing for identification of repeat MSP services or hospital discharges over time and characterization of overlap between the 2 databases. Chlamydia infection case reports including male urethritis were extracted from the provincial surveillance database housed at the British Columbia Centre for Disease Control (BCCDC).

**Descriptive Analysis**

We analyzed MSP and DAD data from 1992 through 2009 for females 15–44 years of age for PID and EP and 15–39 years for Chlamydia infection (because of existing age categories used for historic surveillance data). All records with an International Classification of Diseases, Ninth Revision (ICD-9), or International Classification of Diseases, Tenth Revision (ICD-10), code matching our provincial classification of PID or EP were included. This classification was developed by 2 authors (M. G. and D. M.) through review of ICD classifications used in other jurisdictions and consideration of clinical diagnostic and management practices in British Columbia. For PID, records in DAD were identified on the basis of the most responsible diagnosis; for EP, records with any diagnosis matching provincial ICD codes were retrieved. We defined annual cases of PID and EP as the number of identified unique females having at least 1 MSP billing or hospitalization related to PID or EP (repeat billings or hospitalizations within the same year were excluded). PID and EP rates (stratified by MSP billings alone, hospitalizations alone, and billings and

![Table 1. International Classification of Diseases Diagnostic Codes Assigned for Pelvic Inflammatory Disease and Ectopic Pregnancy, British Columbia, Canada, 1992–2009](image)

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>ICD-9 Codes</th>
<th>ICD-10 Codes</th>
</tr>
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<tbody>
<tr>
<td>Pelvic inflammatory disease</td>
<td>- Salpingitis and oophoritis (614, 614.0–614.2)</td>
<td>- Salpingitis and oophoritis (N70, N70.0–N70.9)</td>
</tr>
<tr>
<td></td>
<td>- Parametritis and pelvic cellulitis/peritonitis (614.3–614.5, 614.7)</td>
<td>- Parametritis and pelvic cellulitis/peritonitis (N73.0–N73.9)</td>
</tr>
<tr>
<td></td>
<td>- Other or unspecified inflammatory disease of female pelvic organs and tissues (614.8, 614.9)</td>
<td>- Other or unspecified female pelvic inflammatory disease (N73.8, N73.9)</td>
</tr>
<tr>
<td></td>
<td>- Inflammatory diseases of uterus except cervix (615, 615.0–615.9)</td>
<td>- Inflammatory diseases of uterus except cervix (N71, N71.0–N71.9)</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>- Ectopic pregnancy (633)</td>
<td>- Ectopic pregnancy (O00)</td>
</tr>
<tr>
<td></td>
<td>- Abdominal pregnancy (633.0)</td>
<td>- Abdominal pregnancy (O00.0)</td>
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<tr>
<td></td>
<td>- Tubal pregnancy (633.1)</td>
<td>- Tubal pregnancy (O00.1)</td>
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<tr>
<td></td>
<td>- Ovarian pregnancy (633.2)</td>
<td>- Ovarian pregnancy (O00.2)</td>
</tr>
<tr>
<td></td>
<td>- Other or unspecified ectopic pregnancy (633.8, 633.9)</td>
<td>- Other or unspecified ectopic pregnancy (O00.8, O00.9)</td>
</tr>
</tbody>
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Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.


* b Data are from the Discharge Abstract Database 2001–2009.
hospitalizations combined) and the number of Chlamydia infections per 100 000 females of reproductive age were calculated. We also analyzed male Chlamydia urethritis reports from 1996 through 2009.

**Analysis of Trends**
To determine whether the visually evident change in the declining EP rates around 2003 was statistically significant, we performed an analysis for trends [31], using the statistical software Joinpoint, version 3.5 (Surveillance Research, US National Cancer Institute).

**Time-Series Analysis**
Total case rates. We used annual, trimestral, and monthly time-series data for Chlamydia infection, PID, and EP case rates to investigate the cross-correlation of their temporal trends, using the cross-correlation function method [32]. First, we fitted ARMA time-series models to each Chlamydia time-series data set to remove any significant autocorrelation and nonstationarity within them. We then filtered (“prewhitened”) the PID and EP data with the corresponding Chlamydia ARMA model. Next, we compared the cross-correlation between the Chlamydia ARMA model residuals and the corresponding PID- and EP-filtered data. Finally, we performed Granger causality tests between the Chlamydia model residuals and the corresponding PID- and EP-filtered data.

Case rates by age and age-specific case rates by year. We used annual and trimestral case rates to investigate each 2-way cross-correlation for Chlamydia infection and PID in women aged 20–24 years and for EP in women aged 25–29 years. These age intervals correspond to the peaks of age-specific case rates for most years. Finally, we performed Granger causality tests between the Chlamydia model residuals and the corresponding PID- and EP-filtered data.

**Ethics Approval**
An existing memorandum of understanding between the BCCDC and the British Columbia Ministry of Health permits use of deidentified data for population public health surveillance purposes without individual consent.

**RESULTS**

**Chlamydia Infections**
From 1997 to 2009, new reports of genital Chlamydia infection in 15–39-year-old females in British Columbia increased from 2960 (401.7 cases/100 000 population) to 6923 (934.6 cases/100 000) (Figure 1). This followed a decline from 1993 to 1996. Male Chlamydia urethritis cases increased from 761 (39.4 cases/100 000) in 1996 to 3837 (173.6 cases/100 000) in 2009 (Figure 2).

**Rates of PID**
PID rates decreased from 1992 through 2009 (Figure 1). PID hospitalizations decreased 80%, from 1214 (150.1 hospitalizations/100 000) to 273 (30.1 hospitalizations/100 000) (Figure 3). Physician billings decreased 70%, from 6234 (771.0 cases/100 000) to 2225 (245.7 cases/100 000) (Figure 3).

**Rates of EP**
EP rates decreased from 1992 through 2003 but have increased slightly since then (Figure 1). EP hospitalizations decreased 50%, from 987 (122.1 hospitalizations/100 000) to 501 (55.3 hospitalizations/100 000) (Figure 3). Physician billings decreased from 1597 (197.5 cases/100 000) to 979 (110.5 cases/100 000) but subsequently increased to 1365 (150.7 cases/100 000) in 2009 (Figure 3).

**Outpatient Visits**
To check for changes in practice patterns, we calculated the proportion of PID and EP cases managed in the outpatient setting from 1992 to 2009. For PID, the proportion of unique women aged 15–44 years with a physician billing but no hospitalization increased slightly, from 82.5% to 87.6%. For EP, this proportion increased considerably, from 43.8% to 62.3%. This may reflect the increasing outpatient EP management with methotrexate.

**Analysis of Trends**
Using Joinpoint, we found a significant trend change in 2003 ($P = .0002$) for EP (Figure 4) but not PID.

**Time-Series Analysis**
Cross-correlation function analysis found significant cross-correlation between Chlamydia infection and EP total case rates in the annual and monthly models and between Chlamydia infection and PID in the annual, trimestral, and monthly models. Cross-correlation function analysis also
demonstrated cross-correlation between the incident age group peaks of Chlamydia infection and EP case rates for annual (Figure 5) and trimestral data. In aggregate, Chlamydia infection and EP rates were cross-correlated in 4 of 5 models, and Chlamydia infection and PID were cross-correlated in 3 of 5 models. Finally, we found evidence of a significant ecological causality between Chlamydia infection and EP in the total case rate monthly series (Chlamydia Granger causes EP, \( P = .045 \)). Results of all other Granger causality tests were nonsignificant.

Age-Related Trends
The analysis of age-related trends confirmed that the overall Chlamydia infection, PID, and EP trends seen in Figure 2 occurred in all age groups (Figure 6). Over time, the peak age for Chlamydia infection and EP shifted to older age groups.

DISCUSSION
We analyzed population-based trends for inpatient, outpatient, and total diagnoses of PID and EP in unique 15–44-year-old females in a Canadian province with universal healthcare, unchanged diagnostic criteria, and consistent ICD coding procedures. Since Canadian STI Guidelines, a clinician’s primary reference for PID and EP, have changed little over the past 15 years, our data include virtually every medical encounter consistent with a stable definition of PID and EP for 18 years during which Chlamydia infection rates initially declined (1993 through 1996) and subsequently increased (1997 through 2009). Male Chlamydia urethritis rates increased from 1996 through 2009. The study demonstrates 5 findings from British Columbia that may inform a general understanding of the epidemiology of Chlamydia control: (1) population-based rates of inpatient, outpatient, and total PID diagnoses have substantially declined over the last 2 decades; (2) population-based rates of inpatient, outpatient, and total EP diagnoses declined from 1992 through 2003 but have significantly increased since then; (3) male Chlamydia urethritis rates have increased substantially from 1996 through 2009, suggesting increased Chlamydia infection incidence; (4) Chlamydia infection and EP rates and Chlamydia infection and PID rates are cross-correlated; and (5) a Granger causality link exists between Chlamydia infection and EP monthly rates.

Hospital and outpatient diagnoses of PID in the United States have also declined over the last 3 decades, while the Chlamydia infection case rate increased from 6.5 cases/ 100 000 (in 1984) to 401.3 cases/100 000 (in 2008) [1, 17, 18]. By use of the National Hospital Discharge Survey, the Centers for Disease Control and Prevention (CDC) tracks annual PID hospitalizations in women 15–44 years of age, with data broken down by acute/unspecified and chronic ICD-9 codes. Hospitalizations in these categories declined throughout the 1980s and 1990s and remained fairly constant from 2000 through 2006 [1]. The CDC also monitors physicians’ offices for PID, using the National Disease and Therapeutic Index. Initial PID visits in this database also declined from 2000 through 2008 [1]. EP hospitalizations declined during the

Figure 3. Inpatient (based on hospitalizations [hosp]) and outpatient (based on Medical Services Plan [MSP] billings) case rates of pelvic inflammatory disease (top) and ectopic pregnancy (bottom), British Columbia, Canada, 1992–2009. Abbreviations: PID, pelvic inflammatory disease; EP, ectopic pregnancy.


Figure 5. Rate unique women – hosp, Rate unique women – MSP, Rate unique women – MSP or hosp.
The proportion treated medically rather than surgically increased [19]. Similar data have been reported from Sweden, United Kingdom, Europe, and Australia [6, 20–28]. A cross-national comparison of rates of Chlamydia infection, PID, EP, and infertility in women aged 15–39 years from 1999 through 2008 involving Australia, Denmark, the Netherlands, New Zealand, Sweden, and Switzerland was recently published [28]. Chlamydia test positivity was similar in all countries with available data and increased over time. Increasing Chlamydia positivity rates were associated with decreasing PID rates in Denmark and Sweden and with decreasing EP rates in Denmark, New Zealand, and Sweden.

If the ecologic association of rising Chlamydia infections and declining reproductive complications are related, what might be the underlying mechanism? We interpret the epidemiological findings as suggesting that the Chlamydia control program is altering the underlying immunobiology of infection. Case rates may be rising because early treatment interferes with the acquisition of protective immunity. Shortening the duration of infection is the root cause behind the arrested immunity hypothesis. We find that the infection prevalence increased by 46% between 1997 and 2009. Because prevalence equals incidence times duration (and assuming that duration has been shortened by 50%), then incidence should be measurably increased by ≥3-fold. Indeed, male Chlamydia urethritis rates in British Columbia rose 4.4-fold from 1997 through 2009 [1]. Together, these results support the hypothesis that a true rise in disease incidence has occurred during the era of Chlamydia control.

The immune response to Chlamydia is also involved in disease pathogenesis. Epidemiological and animal model data suggest that tissue-damaging effects of Chlamydia can be linked to either reinfection [34–36] or to persistent infection [37], with the inflammatory responses triggered via the innate [38] or adaptive [36] immune system being the underlying mechanism. Thus early treatment may also be arresting immunopathology triggered by persistent infection. This appears to be the best explanation for the steady decline in PID case rates. To support the arrested immunopathology hypothesis, the effect of antimicrobial treatment on cellular and humoral immunity to C. trachomatis should be evaluated.

The magnitude of the PID and EP declines that we observed were greater than expected on the basis of estimates of the etiologic fraction of cases due to Chlamydia. This raises 2 questions. First, is the proportion of PID and EP caused by Chlamydia greater than previously thought? Second, what additional factors may be contributing to these declines?
A synthesis of published studies implicates Chlamydia in approximately 30% of acute PID cases, as measured by detection of C. trachomatis at the cervix at the time of PID [39]. However, trials of Chlamydia screening to prevent PID that were performed in Seattle, Denmark, and London resulted in larger than expected decreases in incident PID of 57%, 55%, and 32%, respectively [40]. In interpreting these results, one needs to consider that earlier studies were performed when gonorrhea was more prevalent and less sensitive Chlamydia tests were commonly used.

In British Columbia, however, gonorrhea rates have not risen to the same degree as Chlamydia infection rates over the period of declining PID rates [2], and the diagnostic criteria for Chlamydia infection, PID, and EP have not changed. Shifts to outpatient management are also unlikely contributors, because we captured data from both inpatient and outpatient settings. Overall, we conclude that the magnitude of PID and EP due to Chlamydia infection may be greater than previously estimated and that Chlamydia control programs may have a greater than anticipated effect on these outcomes.

The recent EP increase coincident with a PID decrease is disquieting. This is unlikely to be related to a shift to outpatient management because EP remains one of the most accurate diagnoses, whether ascertained in the outpatient or inpatient setting. The standard of care involves specific ultrasound findings plus serum β-human chorionic gonadotropin measurements that can detect 96% of ectopic pregnancies with a specificity of 100% [41]. Rising EP rates may, however, be influenced by increasing average age of pregnancy and by improved reproductive technologies that enhance opportunities for women with fallopian tube damage to become pregnant. However, the Granger causality test suggests that Chlamydia infection may increase EP risk. EP rates may be more closely linked than PID rates to reinfections, which increased in British Columbia from 9.7 cases/100,000 in 1996 to 53.2 cases/100,000 in 2003 [6]. C. trachomatis infection in women with EP is histologically associated with subclinical plasma cell salpingitis [42]. Thus, cervical reinfection may trigger an in situ fallopian tube immune-mediated inflammatory response that alters the myosalpinx contraction critical for egg transport [43]. In this scenario, PID may be more closely linked to long-term persistent infection and EP to reinfection, causing these 2 conditions to track differently.

There are several limitations in ecological studies like ours. The wide spectrum of PID severity may have affected diagnosis and monitoring, in contrast to the more specific spectrum

Figure 6. Case rates, by age, of Chlamydia trachomatis infection, pelvic inflammatory disease, and ectopic pregnancy, British Columbia, Canada, 1992–2009. Abbreviations: PID, pelvic inflammatory disease; EP, ectopic pregnancy.
of EP. However, any such bias would be unlikely to vary proportionally from year to year. There are no accepted standards for ICD coding of PID and EP. A sensitivity analysis using different combinations confirmed that the findings were robust with no change in trends (data not shown). Similarly, we found no difference with using the most responsible diagnosis or any diagnosis within DAD data. The ability of ICD codes to monitor true population trends in *Chlamydia* complications is unknown. When compared to the CDC case definition of PID and results of laboratory testing, ICD-9 codes in clinical practice have a poor positive predictive value [44]. Although the most common codes used in the MSP billing data were not specific (ICD-10 codes N70 Salpingitis and oophoritis and N71 Inflammatory disease of uterus, except cervix), these were not often used in DAD databases, likely reflecting the use of trained coders. We assume that PID and EP misclassifications did occur, particularly for MSP data; however, this bias should be relatively constant throughout the study period, given no major related changes to British Columbia’s healthcare system.

MSP fee-for-service billing information remained unchanged and has always used ICD-9 codes. In the DAD, the coding of PID and EP in ICD-9 and ICD-10 CA has remained consistent over the study period, as set out by the Canadian Coding Standards issued by the Canadian Institute for Health Information, and trends appear continuous before and after the change-over in 2001.

For the time-series analysis, the study period is relatively short to draw conclusions, particularly for annual data. Trimestral and monthly data were noisier and less reliable, particularly when stratified by age. Furthermore, although time-series analysis can identify potential correlations and ecological causation, little light can be shed on the nature of the relationship.

We conclude that this analysis provides evidence that *Chlamydia*-associated complications in women are declining overall and that reproductive health is improving during the era of *Chlamydia* control. The rise in EP since 2003 tempers this conclusion and may suggest that rising *Chlamydia* reinfection rates are contributing to rising EP rates. An immunological explanation for observed trends in *Chlamydia* epidemiology requires further study, as reinforced in a recent symposium on this subject [45]. Optimal control of *Chlamydia* appears to require a vaccine. If rising EP rates are the result of rising reinfection rates, patient-delivered and/or expedited partner therapy may prove an important strategy to enhance the reproductive health impact of *Chlamydia* control programs while a vaccine is awaited [46].

### Note

**Potential conflicts of interest.** All authors: No reported conflicts.