Laboratory Detection of First and Repeat Chlamydia Cases Influenced by Testing Patterns: A Population-Based Study

Microbiology Insights
Volume 12: 1–7
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DOI: 10.1177/1178636119827975

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ABSTRACT

OBJECTIVES: The purpose of this study was to describe and explore potential driving factors of trends in reported chlamydia infections over time in Manitoba, Canada.

METHODS: Surveillance and laboratory testing data from Manitoba Health, Seniors and Active Living were analysed using SAS v9.4. Kaplan-Meier plots of time from the first to second chlamydia infection were constructed, and Cox proportional hazards regression was used to estimate the risk of second repeat chlamydia infections in males and females.

RESULTS: Overall, the number of reported infections found mirrored the number of tests conducted. From 2008 to 2014, the number of first infections found among females decreased as the number of first tests conducted among females also decreased. Between 2008 and 2012, the number of repeat tests among females increased and was accompanied by an increase in the number of repeat positive results from 2009 to 2013. From 2008 to 2016, the number of repeat tests and repeat positive results increased steadily among males.

CONCLUSIONS: Chlamydia infection rates consistently included a subset composed of repeat infections. The number of cases identified appears to mirror testing volumes, drawing into question incidence calculations that do not include testing volumes.

SUMMARY BOX: 1) What is the current understanding of this subject? Chlamydia incidence is high in Manitoba, particularly among young women and in northern Manitoba.

2) What does this report add to the literature? This report suggests that incidence calculated using case-based surveillance data alone does not provide an accurate estimate of chlamydia incidence in Manitoba and is heavily influenced by testing patterns.

3) What are the implications for public health practice? In general, improving testing rates in clinical practices as well as through the provision of rapid services in non-clinical venues could result in higher screening and treatment rates. In turn, this could lead to a better understanding of true disease occurrence.

Keywords: chlamydia, sexually transmitted infection, repeat infection, recurrence, epidemiology, testing, nucleic acid amplification test, Manitoba

RECEIVED: December 22, 2018. **ACCEPTED:** December 28, 2018.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

In Manitoba, a chlamydia control programme was first introduced in 1987.[1] The introduction of this screening programme led to an initial reduction in reported incidence from 1988 to 1995. Subsequently, the number of cases detected began to trend upwards – a trend that was observed in many countries where screening programmes existed. Given this apparent global increase in the number of cases, much effort has been devoted to identify the factors underlying these trends. Chlamydia transmission is multifactorial and potentially influenced by socioeconomic and demographic characteristics of the population, patterns of risk behaviours, sexual network characteristics, the effects of treatment on immunity and susceptibility, and the variable effectiveness of public health disease prevention and control activities.[2-6]

A complicating factor is the coincident change in chlamydia diagnostics that has taken place within testing laboratories. In Manitoba, a notable increase in cases detected occurred from 2006 to 2008 as laboratory diagnosis transitioned to a more sensitive nucleic acid amplification test (NAAT) for all specimen types in June 2007. Prior to June 2007, a less sensitive nucleic acid probe assay was used for chlamydia testing of swab

specimens and NAAT was used only for urine specimens, predominantly collected from males.[6] Since 2007, the transition to NAAT has been associated with an increase in overall testing volumes and an increasing number of urine specimens from females, all of which may influence the number of cases detected. However, as only positive laboratory detections are typically reported to surveillance units, interpretation of trends is complicated by the lack of denominator information (ie, number of tests conducted). The objectives of the present study were to describe the trends associated with reported chlamydia cases over time in Manitoba with an emphasis on the role of repeat infections and to explore the relationship between the volume of reported chlamydia cases and the volume of laboratory testing conducted.

Methods

Data sources

Data were obtained from 3 centralized databases of Manitoba Health, Seniors and Active Living: the Manitoba Health Insurance Registry, Manitoba Public Health Surveillance Data, and the laboratory test database of Cadham Provincial Laboratory (CPL). The Manitoba Health Insurance Registry contains a record for every individual eligible for universal health care in the Province of Manitoba. The health insurance registry captures the Manitoba residents who qualify for health coverage through Manitoba Health, Seniors and Active Living (98% of Manitoba residents).[7] Each record includes a personal health number, birthdate, residential postal code, and health coverage start and end dates.[8] The health insurance registry also provides a very accurate estimate of population size by year, sex, and age groups for Manitoba. This registry was linked, using scrambled personal health numbers, to chlamydia case reports contained within the Manitoba Public Health Surveillance Data and to chlamydia testing data from CPL for the purpose of verifying cases and for the calculation of a 'population at risk' denominator for chlamydia rate calculations for this study. Surveillance data were available for the period of 1993 to 2011. Reporting of all identified chlamydia cases is mandatory in the Province of Manitoba. Chlamydia testing data for the period of 2000 to 2016 were obtained. Cadham Provincial Laboratory data reflect virtually all chlamydia tests in Manitoba and include the age, sex, and postal code of residence of the individual tested, specimen type, test type, and specimen collection date.[9]

Chlamydia cases (chlamydia infection of the eye, nasopharynx, rectum, epididymitis, genitourinary sites, and pneumonia) were extracted from the Manitoba Public Health Surveillance database to generate a retrospective population-based cohort of Manitoba residents who had 1 or more chlamydia infections during the period of 1993 to 2011. Washout periods were applied to the surveillance dataset (1993-1997) and the laboratory dataset (2000-2007) to identify repeat reported infections in the post-washout periods. The washout periods were applied to avoid underestimating repeat reported infections during these earlier time periods.

The case definitions used were as follows: *First or only chlamydia case* – the earliest record of chlamydia in the surveillance database for a given individual, which has a corresponding positive chlamydia test result in the CPL data; *Repeat chlamydia case* – any chlamydia record with a corresponding positive test result, which occurred after an earlier record with a corresponding positive test result for the same individual. A repeat case must have specimen collection date that is more than 30 days after the specimen collection date for the earlier case, otherwise they are considered to be the same case.

Statistical analysis

Incidence of reported chlamydia infections per 100 000 population members was age-standardized to the 2001 Manitoba population, which was close in time to the midpoint of the dataset analysed. Cumulated chlamydia infection rates were calculated by combining all chlamydia infections in each year, including repeat infections, and dividing by the 'population at risk', calculated using the health insurance registry. The 95% confidence intervals (CIs) of rates were also calculated using 'population at risk'. Specifically, the population at risk for the first chlamydia infection was calculated as the entire population of each relevant group minus the number of individuals who had previously been diagnosed as infected (ie, during the washout period) and were still alive and registered in the provincial insurance registry. The population at risk for a repeat infection was calculated as only those who had had a first infection (during the washout period or after the washout period) and who had not (yet) had a subsequent diagnosed infection and were still alive and registered in the provincial insurance registry. Based on residential postal codes, data were grouped into 5 geographical regions corresponding to Manitoba's health administrative units (regional health authorities [RHAs]): Winnipeg RHA (encapsulating Manitoba's major urban centre, Winnipeg), Northern RHA, Southern Health-Santé Sud, Prairie Mountain Health (which includes the City of Brandon), and Interlake-Eastern RHA. Cases with a missing or unknown postal code or originating from outside of province were excluded from the region-specific analyses.

Rates of reported chlamydia infections were compared by sex, age group (<16, 16-17, 18-21, 22-29, 30+), geographic residential area category, and time period, and hazard ratios for repeat infections were calculated.

Repeat infections in each person were also identified and converted into a format suitable for survival analysis. We constructed Kaplan-Meier plots of time from the first to second chlamydia infection and performed Cox proportional hazards regression to estimate the risk of second repeat chlamydia infections adjusting for sex, age, and region of residence (at the time of first infection) in males and females separately. SAS v9.4 was used for all analyses.

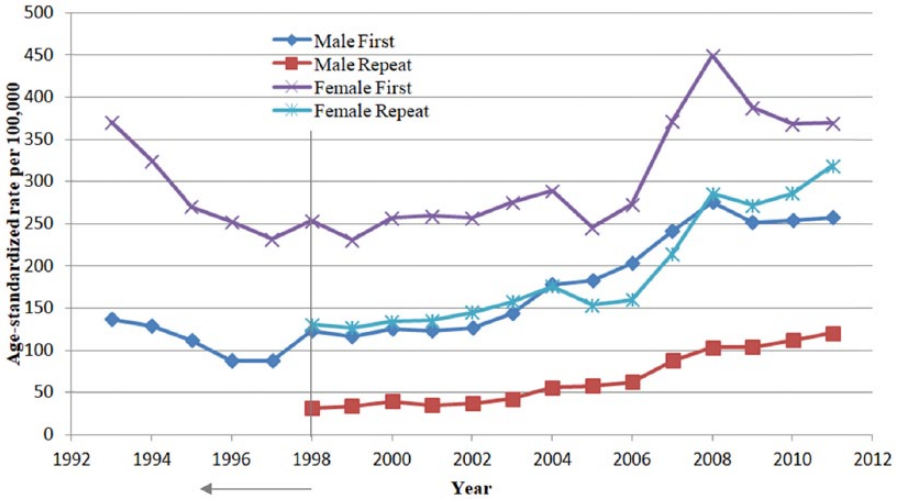

Figure 1. Trends of first and repeat chlamydia infections by sex.

Table 1. Demographic Characteristics and Hazard Ratios for Second Infections Among the Chlamydia-Infected Population in Manitoba (1998-2011).

		FIRST OR ONLY INFECTION		*SECOND INFECTIONS*		*ALL INFECTIONS*		*ADJUSTED HAZARD RATIO FOR 2ND REPEAT INFECTIONS**	
DEMOGRAPHIC FACTORS		*#*	*RATE /100,000*	*#*	*RATE /100,000**	*#*	*RATE /100,000*	*HR*	*95% CI*
Sex	Male	15246	190	3591	3728	20683	254	***Ref***	
	Female	25748	317	9147	4974	42014	502	***1.19***	***1.14-1.25****
Age Group	<16	2734	77	487	17516	3378	95	***5.84***	***5.31-6.42****
	16-17	6112	1317	1620	19075	8418	1773	***4.46***	***4.09-4.88****
	18-21	14349	1656	4549	10426	21703	2345	***2.60***	***2.39-2.83****
	22-29	12051	761	4520	3900	20639	1182	***1.55***	***1.41-1.69****
	30+	5748	59	1562	1428	8559	87	***Ref***	
Health Regions	Winnipeg RHA	21219	231	6187	4244	31610	337	***Ref***	
	Southern Health-Santé Sud	2909	130	665	3328	3875	171	***0.80***	***0.73-0.87****
	Prairie Mountain Health	4833	218	1155	3764	6528	289	***0.84***	***0.79-0.9****
	Interlake-Eastern RHA	3739	233	1095	4569	5586	342	1.04	0.98-1.12
	Northern RHA	8232	904	3625	7007	15024	1519	***1.44***	***1.38-1.51****
Time Period	1998-2002	10808	191	3148	4984	15732	274	***Ref***	
	2003-2007	14164	247	4124	4120	21081	359	***1.107***	***1.06-1.16****
	2008-2011	16022	339	5466	4673	25884	529	***1.28***	***1.21-1.35****
Total		40994	254	12738	4546	62697	380		

* Multiple predictor models were adjusted for all other variables listed in the table; event was the 2nd infection based on everyone who got the 1st infection.

Laboratory testing data for the period of 2000 to 2016 were obtained, and the period of 2000 to 2007 was used to establish testing histories for the purpose of identifying repeat infections and to avoid confounding due to the change in test type in 2007. First tests were defined as the first known test for a given individual. Repeat tests were defined as any test known to have occurred after a first test for a given individual and may have occurred in the same year as

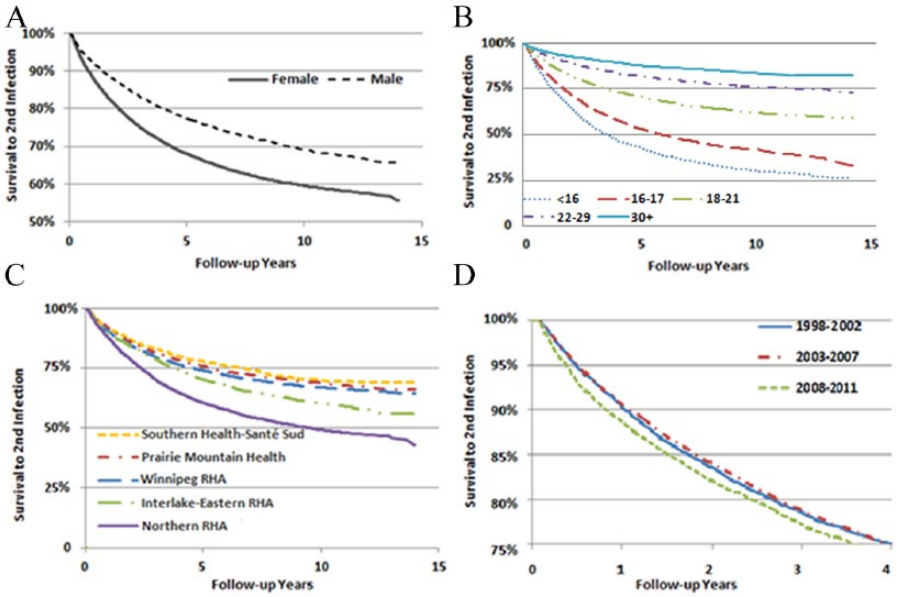

Figure 2. Kaplan-Meier estimates of occurrence of second chlamydia infection over the 14 follow-up years (1998-2011): (A) by sex, (B) by age group, (C) by region of residence, and (D) by time period.

the first test or in a subsequent year. The number of first tests and first infections was calculated by year separately for males and females. Similarly, the number of repeat tests and repeat infections was calculated by year separately for males and females.

Approval for the use of anonymized administrative health data was obtained from the Health Research Ethics Board of the University of Manitoba.

Results

Trends in reported chlamydia infections

A total of 76 891 reported infections were identified among 52 510 individuals in the surveillance dataset spanning 1993 to 2011. The majority of individuals – 68% of females and 79% of males – appeared only once in this dataset (ie, had only 1 reported chlamydia infection). Excluding cases from the wash-out period (1993-1997), the mean age of the first reported chlamydia infection in the period 1998-2011 was 21.6 ± 6.7 years for females and 24.6 ± 8.0 years for males.

From 1998 to 2011, the age-standardized rates of first and repeat reported chlamydia infections, respectively, were consistently higher among females than among males (Figure 1). The rate of first reported infections in females remained relatively steady until 2007, before increasing to a peak of 457 reported infections per 100 000 in 2008 following implementation of the more sensitive NAAT assay. The rate of first reported infections in males remained relatively steady until approximately 2003, when it began to increase and reached a peak in 2008 of 276 reported infections per 100 000.

The rate of repeat reported infections mirrored first infections from 1998 to 2008, particularly among females, but continued to show an increasing trend from 2009 to 2011 during a period when the rate of first reported infections among females was decreasing and/or stabilizing.

As presented in Table 1, during the time period of 1998 to 2011, the rate of reported chlamydia infections was substantially higher among females (502 per 100 000) compared with males (254 per 100 000). The rate of first reported infections was 190 per 100 000 for males and 317 per 100 000 for females, and among these individuals, the rate of a second reported infection was 3591 per 100 000 among males and 9147 per 100 000 among females. Females had significantly more repeat reported infections compared with males.

The greatest rate of first reported infections occurred among individuals between the ages of 16 and 21 (Table 1). Among those who had a first reported infection under the age of 16, the rate of a second reported infection was quite high, and comparable to the rate of a second reported infection among those aged 16 to 17 - in the range of 17 516 to 19 075 per 100 000. Indeed, those in the <16 and 16 to 17 age group had a significantly higher risk of repeat reported infections compared with those in the 18 to 21 age group, and this was particularly high for those under the age of 16.

While the largest absolute number of reported chlamydia infections occurred among those residing within the Winnipeg RHA, the rate of reported infections, particularly for first reported infections, was the highest in the north rural health region (Table 1). Compared with those residing in the Winnipeg RHA, individuals living within the Northern RHA had significantly greater risk of repeat reported infections, and individuals living within Southern Health-Santé Sud and Prairie Mountain Health had significantly lower risk of repeat reported infections.

The rate of reported chlamydia infections and first/only reported infections was highest in the latest time period of 2008 to 2011 (529 per 100 000 and 339 per 100 000, respectively).

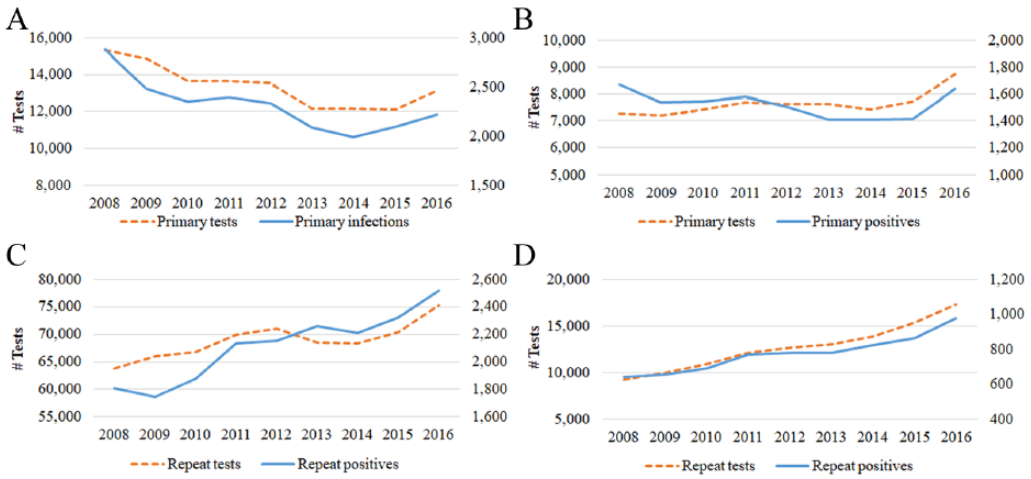

Figure 3. Comparison of number of tests conducted and number of infections identified by year, sex, and infection type (first infection or repeat infection): (A) first tests and infections, females; (B) repeat tests and infections, females; (C) first tests and infections, males; and (D) repeat tests and infections, males.

Survival analysis

The Kaplan-Meier plots of time to second reported chlamydia infection (Figure 2) demonstrated the divergence by sex, age group, and geographical region. Repeat reported infections occurred at a rate of 3728 and 4974 per 100 000 person-years after the first reported infection for males and females, respectively. A quarter of females had a second reported infection within 3 years (95% CI, 2.9-3.1), whereas it took 6 years (95% CI, 5.7-6.5) after the first reported infection for a quarter of the males to have a second reported infection. As shown in Figure 2, it took much less time for females, people in younger age groups, and people living in the Northern health region to become infected for the second time as compared with their counterparts. The rate of repeat reported infections was consistently higher for younger age groups after the first reported infection (17 516, 19 075, 10 426, 3900 per 100 000 person-years in the age groups of <16, 16-17, 18-21, 22-29 vs 1428 per 100 000 person-years in the age group 30+) and those residing in the Northern RHA (7007 vs 3328-4569 per 100 000 in other health regions). Particularly, a quarter of people living in the Northern RHA had a second reported infection within 2.4 years (95% CI, 2.2-2.5), whereas it took over 3.9 (95% CI 3.4-4.3) to 6.8 (95% CI 5.6-7.6) years after the first reported infection to have a second reported infection in other health regions.

Laboratory testing data

Laboratory testing data were available for the period of 2000 to 2016 and, as presented in Figure 3, the number of infections found post-washout period (2000-2007) mirrored the number of tests conducted for both males and females. From 2008 to 2014, the number of first infections found among females decreased as the number of first tests conducted among females also decreased (Figure 3A). In 2015 and 2016, there was an increase in the number of first tests and first positive test results among females. There had also been an increase in the number of first tests conducted and first positive test results among males in 2015 and 2016 (Figure 3C).

Between 2008 and 2012, the number of repeat tests among females increased and was accompanied by an increase in the number of repeat positive results from 2009 to 2013 (Figure 3B). Similar to first tests and results, there had been an increase in the number of repeat test and repeat positive results among females in 2015 and 2016. For the entire data period of 2008 to 2016, the number of repeat tests and repeat positive results increased relatively steadily among males (Figure 3D).

Discussion

A high rate of reported chlamydia infection, particularly among females, those aged 16 to 21, and those residing in the Northern RHA, was identified, consistent with national surveillance data.[10] The rate of repeat infections was high particularly among individuals <18, females, and those residing in the Northern RHA and Southern Health-Santé Sud compared with the Winnipeg RHA. Survival analysis indicated that females became reinfected in a much shorter time period than males. Similarly, the time to reinfection was shorter for those in the north and in younger age groups compared with other regions and older age groups. These results are consistent with other findings[1,4,11-14] and suggest that females, younger age groups, and individuals in the north who have had a previous infection should have follow-up testing recommended by their health care provider at 6 months and have additional opportunities for testing provided at every visit to their health care provider.

The number of reported infections largely mirrored the number of tests conducted for both males and females, and the calculated rates of reported chlamydia achieved new higher levels following the implementation of NAAT in 2007,[6] though the change in test sensitivity may not completely explain this increase.[11] In 2010 and 2011, the number of first tests and infections both went down and the number of repeat

tests and infections both went up. These coincident changes in first and repeat testing patterns can at least partially explain why the difference in the calculated rates of first and repeat infections became smaller. Also, the sudden drop in first tests and first positive results in 2013 may reflect the change in cervical cancer screening guidelines which resulted in fewer opportunities for convenience screening for sexually transmitted infections (STIs) among females.[15,16] This suggests that incidence calculated using case-based surveillance data alone does not provide an accurate estimate of chlamydia incidence in Manitoba and is heavily influenced by testing patterns. As in many other jurisdictions, Manitoba's public health surveillance system is limited by the fact that it does not routinely have access to laboratory testing data. To have a better understanding of the epidemiology of chlamydia and other infectious diseases, it is imperative that linkages are made between laboratory data management systems and public health surveillance units. This recommendation is consistent with one of the goals of the 2015-2019 Manitoba Sexually Transmitted and Blood-Borne Infections Strategy, which is to 'strengthen and support the surveillance, reporting, and research of sexually transmitted and blood-borne infections in Manitoba'.[17]

Our results imply that case-based surveillance data alone should not be used to measure and track chlamydia prevalence in the population because the number of detected cases is at least partially influenced by testing volume. In the absence of a vaccine, 1 potential intervention may therefore be to increase the volume of testing. Many jurisdictions recommend testing a large proportion of the sexually active population, though this is rarely achieved. The proportion of the Manitoba population tested for chlamydia is similar to values seen in other countries with comparable screening methods, including Australia[18] and England.[19] Most RHAs in Manitoba tested 10% to 15% of young women aged 14, to 19% and 30% of women aged 20 to 29, with little change in testing rates during 2000 to 2016 (unpublished data). In 2016, most RHAs tested between 2% and 4% of young men aged 14 to 19, and between 5% and 10% of those in older age groups (unpublished data). Unlike women, there has been a steady increase over time in the percentage of the male population being tested in Manitoba. Targeted testing with an emphasis on maintaining regular contact with individuals at high risk of chlamydia infection and greater screening at extragenital sites – which are not routinely screened[20] – even in the absence of genital chlamydia infection may be effective alternatives to current approaches. Staff training and the use of computer prompt reminders may help to better target testing in family practices.[21,22] In addition to interventions within family practices, making chlamydia testing available through non-clinical venues or networks may also improve testing uptake and offer a means of connecting with individuals who do not regularly attend a family medical practice. Offering testing through appropriately targeted and accessible services at venues such as malls[23] or through amateur sports clubs,[24] for example, may improve testing rates. The use of rapid or point of care tests may also improve testing uptake and the likelihood that an individual receives their result and any necessary treatment.[25-28] Technology such as this, performed in non-clinical settings with self-sampling and utilizing a building, vehicle, or privacy shelter for sample collection,[29] may increase screening by accessing individuals who may not present to medical practices. Improving testing rates could lead to a better understanding of true disease prevalence. Notably, chlamydia infection rates consistently include a subset of repeat infections. The number of first and repeat cases identified mirrors testing volumes, drawing into question incidence calculations that do not include overall testing data. There is a need for a subsequent study to formally test the extent to which test volume accounts for observed patterns of chlamydia incidence. In future, greater effort should be placed on obtaining data on all tests, both positive and negative, performed for chlamydia, to improve our understanding of true disease incidence and aid in interpretation of changes in case numbers over time.

While improved screening could lead to a better understanding of true disease prevalence, in the absence of other strategies it is not likely to reduce chlamydia prevalence. There is a need to improve case management with improvements to partner notification, prevention of reinfection by providing advice on behaviour change and condom use, and timely retesting.[30] Expedited partner therapy has been found to be acceptable to health care providers and patients[31] and is more effective at reducing repeat infections than referring partners to the health care system.[32] In Manitoba, STIs are managed by physicians and nurse practitioners through their offices and through public health offices and community health centres, depending on where the client sought care and was diagnosed with the STI. Due to the high volume of chlamydia cases, universal case and contact follow-up is not possible and rather a targeted programme allows for public health interaction for cases and contacts most likely to experience sequelae, service access barriers, or otherwise be most likely to benefit from interaction with public health.[33] A variety of STI prevention strategies have been developed and implemented by individual RHAs and by Manitoba Health, Seniors and Active Living over the years. The provincial recommendation is annual testing among young sexually active men and women (<25 years of age) and more frequent testing among 'high risk populations', with repeat testing recommended for all cases 6 months post-treatment.[34] Routine programme monitoring and evaluation is deemed a high priority for effective STI surveillance and evidence-driven programme implementation. An educational poster has recently been developed by Manitoba Health, Seniors and Active Living for health care practitioners to inform them of the ongoing syphilis, gonorrhoea, and hepatitis B and C outbreaks and remind them of case management protocols and referral pathways.[35]

As this study used centralized population-level data, these results are generalizable to Manitoba's population during the

study period. However, undiagnosed chlamydia infections are not included in the datasets. This study did not include an assessment of behavioural and social network characteristics that may offer insights into the context of repeat infections. Laboratory results are limited by the sensitivity and specificity of the test used, and the sensitivity is known to have increased with the implementation of NAAT in June 2007. The use of a washout period to more accurately calculate repeat reported infection and repeat laboratory tests reduced the time period included in the analysis. Comparison of laboratory testing data and reported case data was limited by the different time periods of the available laboratory testing data compared with available surveillance data, which resulted in a relatively short period of overlap between the two datasets (2008-2011). Given the observation that calculated incidence mirrored laboratory testing volumes, a subsequent study is recommended to empirically test the hypothesis that calculated incidence is highly influenced by laboratory testing volumes.

Author Contributions

NY conceived of this project. LHT wrote the manuscript with guidance from NY. ZN performed the data analysis for this project. JLW, CL, PVC, and JFB all reviewed and provided feedback on manuscript drafts. All authors reviewed and approved the final manuscript.

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