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Title: Estimating the test-adjusted incidence of *Chlamydia trachomatis* infections identified through Public Health Ontario laboratories in Peel region, Ontario, 2010–2018: a population-based study
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Reviewer 1: Dr. Stephanie Totten
General comments (author response in bold)

This is an interesting and important study, in light of the continued high and increasing rates of chlamydia infection in Canada. Determining potential reservoir populations may help direct public health and health care resources appropriately. Overall, it is very well written. I have the following comments for the authors, organized by manuscript section:

Methods
- What proportion of chlamydia tests conducted for Peel residents are available through PHO labs? Are any tests done at private labs and thus excluded from analysis?
Thank you for this comment, unfortunately we do not have data to understand the number of tests completed at public labs. We do however know the proportion of cases detected by PHO labs vs other labs and have added that proportion in to give more context.
Lines 226-227: "This accounted for 32% of all chlamydia cases identified in Peel region within this the study period."
Lines 444-445: "In Peel region, approximately 1/3 of cases were identified through a PHO laboratory during the study period."

- Population for intercensal and postcensal years are available from Statistics Canada, and typically used for rate calculation in surveillance data. Is there a reason why the authors chose to develop their own estimates, and are the results markedly different than those created by StatCan?
Thank you for this suggestion, however we were unable to find intercensal and postcensal population estimates broken down by age at the municipal level so we feel the methods used were appropriate for this study.

- If available, reason for test (asymptomatic screening vs. symptoms or contact tracing/partner notification) would be a useful variable to include in the analysis.
This would be a very interesting and useful variable to include, however, due to data limitations we do not have this information.

Results

- It appears as though there were no cases missing both age and sex, is this accurate?
Yes this is correct, we had age information for all cases within our study group, however, there were some missing sex, and those therefore were excluded.

- Please describe, if possible, the representativeness of tests and cases obtained through public health labs/clinics. What % of total cases in the study period are included in the analysis?

Out of our full dataset (including both public and private lab cases), public lab cases represent 32% of all cases. Unfortunately, we do not have access to private lab testing data. This information as been added.
Lines 226-227: "This accounted for 32% of all chlamydia cases identified in Peel region within this the study period."
Lines 444-445: "In Peel region, approximately 1/3 of cases were identified through a PHO laboratory during the study period."

- Incidence patterns by age and sex reflect those seen in national level surveillance data.
Yes, this is true, thank you for this comment. We have added that into our interpretation section (lines 368-369).
"This study found that chlamydia incidence in Peel region followed national trends where females and younger age groups have higher rates of cases (20)."

Interpretation

- You mention STI testing in private labs; can you quantify the proportion of tests/cases these may represent and estimate impact on results?
Thank you for this comment, we have added this information to give the reader more context.
Lines 226-227: "This accounted for 32% of all chlamydia cases identified in Peel region within this the study period."
Lines 444-445: "In Peel region, approximately 1/3 of cases were identified through a PHO laboratory during the study period."

- Specimen source/site (swab vs. urine) is not discussed; is there a differential test sensitivity that may impact results (as females are more likely to be swabbed during routine care, vs. males being more likely to be offered urine testing)?
With the use of NAATs, test sensitivity is very high for all methods of collection (between 95-100%) and we did not believe this would be an issue of note.

Overall, with minor revisions to address representativeness of data as indicated above, I am recommending this manuscript for publication.

Reviewer 2: Dr. Ann Jolly
General comments (author response in bold)

Adjusting for differential testing: Estimating the incidence of Chlamydia trachomatis infections identified through Public Health Ontario laboratories in Peel region, Ontario, 2010–2018

In this paper the authors use the testing rate for Chlamydia trachomatis in people from Peel Region Ontario to estimate chlamydia infection incidence. A major challenge in describing the burden of chlamydia infections and improving prevention programs is that testing for the organism varies greatly by age and sex which they address. First, they use data from public health laboratories to estimate testing rates per population, and then, assuming the highest testing rate found in young women aged 20 – 29, they applied this to the remaining population. They also access the percent positivity, and then calculate an adjustment to the number of positives found so as to revise the incidence rate upwards, to reflect under testing.

First, this is an innovative way to demonstrate the extent to which chlamydia is under reported; second it is admirable that it is being reviewed in the Canadian Medical Journal, as it closely concerns medical practice. Usually it is relegated to a public health journal where readers are fully aware of the underdiagnosis; under reporting and consequent high and increasing rates of chlamydia in women. Last, it again draws attention to the increase in rates of STI in Canada, despite valiant efforts by relatively few applied researchers and public health staff with little funding.

The paper is of high quality and provides new information on an important topic which affects sexually active individuals and should be published after the following points are addressed.

Major points;

1) The authors should mention the likely proportions both diagnostic and screening tests are included in totals which they present. This will add to the interpretation later on. For example, if clients are more likely to present and be tested at sexual health clinics in Peel due to symptoms, then the percent positivity is likely higher than those presenting to family physicians who complete routine screening. This may reflect a higher incidence than if family physician testing rates and percentage positive, where testing comprises mostly screening tests.

The authors somewhat address this issue in the discussion, but a clear description of the testing processes (or lack thereof) for both routine screening and diagnostic testing would be better presented in the introduction as it is an essential part of the context. The testing process should include the proportion of tests for which gonorrhea was also ordered. Testing for gonorrhea affects the epidemiology of chlamydia in that gonorrhoea is more likely to be symptomatic; and coinfection with chlamydia is very common. Therefore, symptomatic clients who may be at more at risk of STI and be symptomatic may be over represented.

Related to this is also the fact that a high proportion of tests in the under 25 year olds are likely to be screened as recommended by Canadian guidelines, whereas those women 25 and older are more likely to be tested to obtain a diagnosis. In fact, describing the rates and percent positives may be elucidate some of the possible “high” and “low” incidence and test positivity rates.
Thank you for this valuable insight. We have added more context to diagnostic and screening testing in the introduction (lines 55-58). We unfortunately do not have any way to know what the breakdown of diagnostic vs screening testing performed is and it is important to note that. Additionally, we do not have information required to address the questions regarding gonorrhea co-infection. This would be an interesting topic for future work.
“Screening is a tool used to reduce disease burden, particularly in high-risk groups, and is largely important for STIs where infections can often be asymptomatic. Screening differs from diagnostic testing, in which individuals are tested due to presenting with symptoms consistent with an STI. Screening is a tool used to reduce disease burden, particularly in high-risk groups, and is largely important for STIs where infections can often be asymptomatic. Screening differs from diagnostic testing, in which individuals are tested due to presenting with symptoms consistent with an STI.”

2) The second important point to mention is what proportion of all tests are done in PHOL, of all tests done. The total number of tests available may be available from ICES, or if unavailable the authors should mention this.
Thank you for this comment, while we do not have information regarding number of tests completed at PHOL compared to private labs, we can extract the proportion of cases detected by PHOL compared to other laboratories and have included that in the methods and interpretation to give the reader more context.
Lines 226-227: "This accounted for 32% of all chlamydia cases identified in Peel region within this the study period."
Lines 444-445: "In Peel region, approximately 1/3 of cases were identified through a PHO laboratory during the study period."

Minor points

1.) STI reporting is done by 5 year age groups up until age 30 then 10 year age groups, see CDC STI surveillance report 2019. Using these age groups will facilitate comparisons with provincial and other data.
Due to data privacy, we were only able to obtain testing data in 10-year age groups and therefore had to aggregate to this level.

2.) Line 117, add an "s" into "the model follow(s) the form.."
This line has been moved to the appendix and has been updated as stated.

3.) Line 158. Insert a period after "…both sexes." "However" starts a sentence. And throughout.
Thank you for the suggestions, this line has been updated.

4.) Beautiful Figure 1!!
Thank you!

5.) Line 194. Great to mention the lack of an expected effect, not only the presence of one!

6.) Could you check the calculations for the confidence limits of 20-29 year old women in Fig 4, they seem very high.
The excess variance in the confidence interval for the females 20-29 is coming from weighting the standard error estimates. Due to the large number of tests being done in this group, there becomes a large variance.

7.) Line 257, if the client has symptom of an STI, the tests are diagnostic and not screening tests, by definition.
Thank you for this comment, we agree in this distinction between diagnostic and screening tests. We are unsure how this applies to the statement on line 257 (in the original copy) as it does not reference symptoms. It states: "In specialized public health clinics, individuals are often seeking STI testing as the reason for their visit and may also have longer consults with care providers."

8.) Italicize genus and species in references. Line 391, that should be BMJ or British Med J, not Bmj
Thank you for this comment, we have updated references to italicize genus and species and the BMJ reference has been updated (line 566).