Article details: 2022-0026
Title: Household transmission of SARS-CoV-2 from unvaccinated asymptomatic and symptomatic household members with confirmed COVID-19 infection
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Reviewer 1
General comments (author response in bold)

1. In the abstract and introduction I believe the authors mean to say symptomatic PCR testing may be an underestimate? This should be clarified since PCR testing could be positive for several months and is sensitive I believe the word "symptomatic" is important in this context.
Thank you for the opportunity to clarify. PCR testing is very sensitive, however if only done as a one-time swab, it has the potential to miss infection (and therefore underestimate transmission) depending on the timing of the swab and whether all members of the household were tested. Thus, underestimation of transmission relates to more than symptom presence. We have edited the wording in the introduction to reflect this nuance.
Meta-analyses of household transmission studies primarily using viral swabs for detection estimate a secondary attack rate of 19%, but reliance on viral swabs may underestimate transmission and experts have advocated for the addition of serologic testing to enhance studies of household transmission.

2. For methods it says "member" does this mean household member or rather individual? Would be helpful to clarify this.
Our intention was to assert that one individual in the household (i.e. "household member") had a confirmed SARS-CoV-2 infection. We have added "household" to member in the first sentence of the Methods section. We hope this additional word clarifies the meaning for the reviewer.

3. Would put into context prior studies of 2nd attack rate of household contacts which has been less than 50% but of course agree is a major risk factor due to unprotected close contact (which is even more frequent with young children in the house). This is in the body of the document at 19% for PCR studies but consider adding into the abstract/intro too if space.
Thank you for this suggestion. The fourth sentence of the first paragraph of our introduction states "Meta-analyses of household transmission studies using viral swabs for detection estimate a secondary attack rate of 19%". We have not added this statement to the abstract as we are over the word count already. If the Editor approves the additional word -count, we are happy to add this to the abstract.

4. Would be helpful to include comments about how symptom assessment was made - how thorough was this. Making a differentiation between symptoms/asymptomatic/paucisymptomatic.
A trained research assistant administered the questionnaires at each study visit in an effort to standardize and harmonize data collection to optimize accurate symptom documentation. Documentation of specific symptoms included: fever,

sore throat, runny nose, cough, shortness of breath, chills, vomiting, nausea, diarrhea, headache, rash, conjunctivitis, muscle aches, joint aches, loss of appetite, loss of smell or taste, epistaxis and fatigue. Absence of symptoms was documented. Our data methodology did not differentiate between symptomatic and pauci-symptomatic. We edited the methods section to read as follows:
Questionnaires, informed by the WHO Household transmission investigation protocol, were administered by a trained research assistant to standardize and harmonize data collection to optimize accuracy; questionnaires were completed for the index participant and each household member at the study visit.

5. Would be good to know why vaccinated individuals would be excluded. Understandably because of the spike/NC antibody testing but might be worth adding in that rationale for those not as familiar with different antibody testing platforms.
At the time of enrollment of our cohort, vaccines were only available to a minority of the population. We assumed that vaccinated individuals would have increased protection from SARS-CoV-2 infection and thus we excluded them to keep the population homogenous to allow us to draw conclusions about the true epidemiologic spread of the virus within households. To note, we are collecting data on vaccine status and we continue to collect longitudinal blood samples for analysis in sub-populations of vaccinated and unvaccinated youth within our original cohort to determine immunity duration; statistical analysis for this sub-study is in-process. While we hope to submit this study for peer review in the coming months, this is beyond the scope of this current manuscript.

6. For asymptomatic individuals how do we know they were the index case versus secondary attack rate- would be good to indicate this in the manuscript. Was there a reason why these individuals didn't have paired PCR + serology (the contacts?)
At the time the cohort was recruited, PCR testing in our region was solely permitted for people with symptoms or high-risk contacts as per regional public health rules. The asymptomatic index cases were likely tested because of a high-risk contact. These individuals would have been assigned index status if they were the first to test positive in their household. We tracked all PCR tests performed on household members, but couldn't pair PCR testing and antibodies due to limitations of provincial testing guidelines. We have amended the last limitation in the discussion to read:
Finally, the household member with the first positive RT-PCR test was defined as the index participant. This assignment could have been erroneous if there was a co-primary infection or if the first-infected member was asymptomatic or experienced a delay in showing signs of infection (as provincial guidelines at the time only allowed PCR testing for symptomatic individuals). This assignment could underestimate the prevalence of asymptomatic spread.

7. Would a further study be planned with delta VOC ? Is it correct that by March 2021 there was not much delta in Ottawa? This is different than other parts of Canada but I agree most of your study would capture wt or B.117.
It would have been wonderful to continue to recruit new cohorts of infected individuals with each variant, unfortunately, it was impossible to predict how this pandemic would unfold and as such, the original study we planned - and were funded for – was to recruit a baseline cohort of households. We were not able to re-recruit a cohort of newly infected individuals. We have studied this cohort's

longitudinal antibody response and will be analyzing this in the months to come. To answer the reviewer's question about the prevalence of the delta variant, it became prevalent in Ottawa during summer 2021.

Reviewer 2: Lorine Pelly
Institution: University of Manitoba
General comments (author response in bold)

MAJOR POINTS

1. "Meta-analyses of household transmission studies using viral swabs for detection estimate a secondary attack rate of 19%, but reliance on viral swabs may underestimate transmission, and experts have advocated serologic testing for household studies. " (From page 7, lines 12-19). It would be helpful to clarify that antigen and nucleic acid methods specifically under-report pediatric infections and that the addition of serologic testing can help enhance studies of household transmission.
Please see our response to *CMAJ* Reviewer #1, point #1.

2. Page 7, line 41 alludes to current control strategies but these don't really reflect the present strategies in most jurisdictions.
We agree with the reviewer. At the time of our original manuscript submission, schools and most recreational activities were open. Due to fluctuating policies (which also vary by jurisdiction), the situation has again evolved in which most recreational activities (gyms, sports) remain closed/restricted whereas schools have re-opened. We have changed our wording to reflecte the nuance of the changing nature of restrictions while maintaining the understanding that children have been affected by various control strategies.
Addressing this gap in the literature would allow a more evidence-based approach to public health initiatives given that control strategies have often impacted the lives of children and youth (e.g., closing schools, suspending recreational activities) and these strategies can negatively affect their overall well-being.

3. There is no mention of the time frame for data collection for this study in the study setting section. This makes it difficult to assess of context of prior and current community spread of SARS-CoV-2 at the time of the study.
The first sentence of the Methods section contains the information of the reviewer's query: "We conducted a prospective, case-ascertained study of households where at least one household member had SARS-CoV-2 infection in Ottawa, Canada, from Sept/20 to Mar/21 when community cases ranged from 6-12 per 100,000 population".

4. The primary outcome is household secondary attack rate (page 10, line 21) but the measure that is given does not line up with the epidemiological definitions given in the cited WHO document on page 22 which defines either secondary clinical attack rate and secondary infection rate. The measure used in this study is closest to secondary infection rate as defined in the WHO document. The term secondary attack rate is commonly used in other papers though in most articles, including the meta-analysis by Madewell et al, it appears that almost all used symptom, antigen or nucleic acid methods to identify infection. Another study similar to this one (Lewis et al CID 2021 – attached) used secondary infection rate. It would be good to clarify this.
Thank you for the excellent point. The reviewer is correct that the WHO Household transmission investigation protocol uses the term "secondary infection rate" to

define what we term the "secondary attack rate". We feel that readers will be more familiar with the term secondary attack rate, which is defined by the CDC and other epidemiologists as the proportion of the new cases [among contacts] among by the total number of contacts. (https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section2.html). This is consistent with how we define the secondary attack rate on page 6 (Outcomes). We have removed the WHO reference and have added the CDC reference.

5. The total number of household contacts approached for the study are alluded to in the results but are not shown in Figure 1 (Page 31, Line 24).
Thank you for this comment. We have edited Figure 1 to include the number of eligible household contacts.

6. In Table 1, there is no data on children's exposures outside the home (school, daycare). Is this because the data is unknown or is this part of the context at the time of the study (schools and daycares closed).
We have this data (below), however, given the reviewer's comment (Minor comment #2 below) regarding trimming Table 1, we have elected to delete the section on "Working outside the home" and have not added school exposure for this same reason. Please advise if you would like these sections added back in to Table 1 or alternatively as a supplementary table.

	No. (%)					
	Index participants			Household contacts		
	Overall n=180	Children n=74	Adults n=106	Overall n=515	Children n=266	Adults n=249
Student	76 (42.2)	69 (93)	7 (6.6)	261 (51.0)	245 (92.8)	16 (6.5)
Missing	0 (0.0)	2 (2.6)	0 (0.0)	3 (0.6)	2 (0.7)	1 (0.4)
School setting						
Daycare/Nursery	11 (6.1)	11 (14.9)	n/a	47 (9.1)	47 (17.7)	n/a
Elementary	43 (23.9)	43 (58.1)	n/a	142 (27.6)	142 (53.4)	n/a
High school	20 (11.1)	20 (27.0)	n/a	77 (15.0)	77 (28.9)	n/a
University/college	9 (5.0)	n/a	9 (8.5)	17 (3.3)	n/a	17 (6.8)

7. In the sections "transmission by age", "transmission by symptoms" and "risk factors for transmission" (page 13-14), sometimes the results are presented in more neutral language such as "in households with adult index participants, 57% of member had antibodies" (page 13 lines 21-23) and sometimes that language is much more directional such as "the youngest children transmitted to a lower proportion of household contacts" (page 13 lines 14-17). I think that the neutral language is more accurate.
We appreciate the reviewer's comment. However, it is challenging to convey findings using the language suggested by the reviewer where the outcome reported is not dichotomous (e.g., has more than 2 options). For example, the reviewer liked the presentation of "in households with adult index participants, 57% of members had antibodies"; the outcome in this instance is dichotomous so it is easier to say "present" or "not present" without adding directionality. However, in the example of "the youngest children transmitted to a lower

proportion of household contacts", this conveys the observation that index children 0-3 years old transmitted to 18.8% of household contacts, which was lower than transmission from older child index cases 4-11 years (41.6%) and 12-17 years (38.8) *and* lower than transmission from all categories of adult index cases (18-29 years 53.1%; 30-49 years 56.5%; 50+ years 64.5%). We feel the fact that the youngest children transmitted to a lower proportion of household contacts is a statement of fact; we made efforts to keep this as neutral as possible by avoiding words such as "lowest", which would imply significance.

8. "Compared with households where the index participant was the only infected individual, odds of transmission increased with every additional infected member" (Page 13 lines 48-50). Clarify what is meant by this. If you have two cases, you are more likely to have a 3rd?
Yes, this is an accurate interpretation. The more infected people you have in the home, the odds of transmission to other members within the household is increased.

9. It would be interesting to know how many households had no household contacts with positive antibodies (or how many had all the contacts with positive antibodies).
We find this interesting information as well; it is included in the last sentence of the results section titled Incidence of household infection and transmission.

10. Discussion
a) The discussion does not seem to have a clear thesis which makes it challenging to read.
We have completely re-worked the discussion to improve clarity and readability which we hope addresses the reviewer's concerns outlined in b) and c)

b) Some of the content (e.g. page 14 lines 37 to 44) and similar material may be better in the introduction.

c) Potential limitations not fully addressed:
How does that background rate of 35% positive RT-PCR in household contacts compare to other studies?

d) Could this high RT-PCR rate been a result of selection bias? Were families with a lot of transmission in their household more likely to be interested in being recruited for the study?
Thank you for the excellent questions. We have added this limitation to the discussion. The added sentence follows:
Third, a variety of strategies were used to identify eligible households, including self-identification. It is possible that characteristics of families who self-identified were different than those who were approached for participation by study team members.

e) It is stated that community transmission was low but what was the rate prior and during the study? Is there anything known about the background seroprevalence rate in Ottawa or similar areas?
In the methods section, the prevalence of COVID-19 infection during the study period is provided. We have added to this information within the first limitation in

the discussion. To our knowledge, there is no seroprevalence data available from the general population in Ottawa.

f) What are the potential impact of how the index case was identified (much more likely to be symptomatic than the household contacts) on interpretation of the data?
We have added a sentence to the last sentence of the discussion:
This assignment could underestimate the prevalence of asymptomatic spread

g) What are the potential implications of the study including policy directions or future research?
We have reworked the discussion and have dedicated a paragraph to policy implications. We hope this addresses the reviewer's concern.

MINOR COMMENTS

1. Page 9, lines 37 to Page 10, line 15. Consider reducing detail in this section by either using more citations of the method has been detailed elsewhere or moving some of the details to supplementary material
Thank you for the comment. We would be happy to move details of the serology testing to supplemental material. We will wait for advice from the Editor on how to proceed.

2. Can some of the information be edited out of Table 1 or moved to supplementary material?
Thank you for the suggestion. We have removed work exposure from this table.

3. The preprint that was cited in reference 16 (Page 20, line 41) was published as Kuwelker et al. Attack rates amongst household members of outpatients with confirmed COVID-19 in Bergen, Norway: A case-ascertained study. The Lancet Regional Health – Europe 3 (2021) 100014.
Thank you. We have updated this correction to the reference.