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Title	Housing and tuberculosis in an Inuit village in Nunavik, Québec: a case-control study
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Reviewer 1	Tom Kovesi
Institution	Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ont.
General comments (author response in bold)	<p>This is a clear and well-written paper, about an important condition, and complements other research this group has published about this outbreak. In addition, I think it's important to add to the body of knowledge about housing conditions in the Canadian far north, with quantitative data.</p> <p>I have concerns about using CO<sub>2</sub> as a tracer gas, as CO<sub>2</sub> directly reflects ventilation. The ASHRAE guidelines cited in the paper indicate that this technique requires steady-state conditions, which are more readily-achieved in a large office building than a small house, and that the house is unoccupied or has very few occupants when the measurements are made (Persily, ASHRAE 1997).</p> <p><b>Steady state conditions were ensured through the use of two fans that were on during CO<sub>2</sub> release.</b></p> <p>Reported air changes per hour with the heating on (1.69 per hour) were more than double rates (0.67 and 0.7 per hour) measured in presumably-similar housing in Nunavut using a perfluorocarbon tracer gas technique (Kovesi, <i>Indoor Air</i> 2006, Kovesi <i>CMAJ</i> 2007, respectively). Furthermore, calculated air change rates may be high in very small houses. It seems counter-intuitive that air change rates in tightly-sealed housing in arctic Canada is higher than general patient ward rooms in a low risk hospital in Montreal, where this group reported an air change rate of 1.2 (Menzies, <i>Ann Int Med</i> 2000). In addition, extrapolating ventilation between houses is unlikely to be valid, as differences within houses (use and condition of kitchen and bathroom fans, leaks in the building envelope, etc.) may have large effects on air change rate. The air change rate per average occupancy is probably a more important measure - a high air change rate in a particularly overcrowded house may ultimately lead to worse relative ventilation than a low air change rate in a relatively un-occupied residence. Authors need to compare their ventilation findings with other studies, and discuss these potential pitfalls of measuring adequacy of ventilation using their method, versus other methods, some as indoor CO<sub>2</sub> concentration, or perfluorocarbon tracer gas.</p> <p><b>The reviewer is raising concerns about our method, in part because our reported rates were double those reported in Kovesi et al.'s paper in <i>CMAJ</i>. However, we observed high air change rates only when the forced air heating system was activated and blowing fresh heated air into the room, and our rates with the heating system off were similar to those reported by Kovesi et al. Furthermore, Kovesi et al's study did not report on the method of heating used in the houses they studied. Moreover, because their study was in Nunavut, while ours was conducted in Nunavik, and the two areas are governed separately with completely independent housing authorities, it is possible that different methods of heating were used in the houses we studied compared to those studied by Kovesi. Lastly, we would like to point out that in Kovesi's original publication, in <i>Indoor Air</i>, ACH rates of up to 2.2 were reported. In summary, our findings are consistent with those reported by Kovesi et al, and the discrepancies between the two reports could have arisen because we measured air exchange with forced air heating on or if different heating systems are used in Nunavut vs Nunavik—hence, we disagree that the ACH values we reported can reasonably cast doubt on our methods of ventilation measurement as suggested by the Reviewer.</b></p> <p><b>The reviewer states that it is "counter-intuitive" that air change rates were higher in "tightly sealed Arctic housing" than what Menzies et al reported in patient rooms—however, to us this is not counterintuitive at all— as levels of ventilation were only higher in our study when the forced air heating systems were blowing fresh heated air into the houses. Overall—we consider our methods rigorous and our estimates representative of the ventilation levels in the community we studied, and Nunavik at large, where most houses are heated with forced air systems.</b></p> <p><b>The reviewer also raises an issue about our use of CO<sub>2</sub> as a tracer gas because "CO<sub>2</sub> directly reflects ventilation". The criticism being raised here is not clear—but we assume that the reviewer is concerned that human production of CO<sub>2</sub> may have affected our estimates of ventilation. In fact, we recognized this and took a number of measures to ensure this was not the case—details have been added to the Supplemental Methods. First, we did not rely on human produced CO<sub>2</sub>—rather we released large quantities of pure CO<sub>2</sub> from a pressure tank—so that the concentration rapidly exceeded ambient levels. Additionally, we</b></p>

ensured mixing of air with fans so that steady-state conditions were met when measuring ventilation. Furthermore, we discouraged occupants from staying in the rooms while measurements were taken. Moreover, when occupants were present, we noted the number of people, and the number entering and leaving. When we calculated ACH measures using multivariable multi-level linear regression, we included the number of persons that had been in the room as one of the independent variables— this allowed us to adjust for the possible effects of human-produced CO<sub>2</sub>.

To the paragraph discussing study limitations we have added (lines 281-287, page 15):

**“Another limitation is the possibility of measurement error for air change rates, which could have arisen from our use of CO<sub>2</sub> as a tracer gas—however, we adjusted our analyses to account for CO<sub>2</sub> production by persons present during the measurement (see Online Supplement). Furthermore, the ACH rates we reported with heating off were in keeping with those reported by other investigators that used perfluorocarbon methods.”**

I'm also concerned that the method of assessing occupancy level may not have been valid; authors need to justify using census data. I wonder whether questionnaire data administered at the time of this study might not have been better.

**The census data we used was a list that had been compiled during the period of the outbreak, by the public health authorities, of every dwelling in the village and its inhabitants. We used this census rather than the information gathered on the study questionnaires, because the study took place several months after the outbreak was felt to be under control. This has been specified in the Methods (Page 9, Lines 174-175)**

Presumably, housing conditions were reasonably similar within this 1 village. Study may have been more likely to detect a significant effect of ventilation if the study was extended to include other villages in Nunavik. This should be mentioned in the Discussion.

**We respectfully disagree. All villages in Nunavik are under the purview of the same regional government and housing authority. There is no reason to expect that ventilation or housing conditions in this village are not representative of the housing conditions in other villages in Nunavik.**

I agree it is possible that the intensity of exposure in a house is sufficiently high that usual levels of ventilation may not be protective. I disagree with the author's interpretation of the Inuit infants on Baffin Island study - in this study, CO<sub>2</sub> - as a proxy of poor ventilation - was associated with lower respiratory tract infections. The author's assertion (page 16, line 16) is too strong, based on the limited data available - the authors need to indicate that increasing ventilation may not reduce the incidence of TB...

**In Kovesi's Baffin Island study, the perfluorocarbon estimates of ventilation—the method that the reviewer earlier expressed confidence in—were not significantly associated with respiratory infection (univariable odds ratios for ACH was 0.98 [95%CI: 0.86–1.13], for ventilation in litres per second was 1.21 [95%0.98–1.50]). The reviewer refers to a univariable association between ambient-CO<sub>2</sub> and lower respiratory tract infection in Kovesi's report—but this may have been explained by ambient-CO<sub>2</sub> being a marker of overcrowding and hence a correlate of greater exposure intensity. As multivariable analyses were not performed in Kovesi et al's publications—one cannot exclude that their observed univariable association between human-generated ambient-CO<sub>2</sub> and lower respiratory tract infections was not due to confounding by overcrowding versus due to lower ventilation. For these reasons we maintain our interpretation of Kovesi et al's study. However, we have revised our comment about ventilation and TB incidence, as per the Reviewer's suggestion (page 14, lines 265-268):**

**“Given the lack of association in our study — and the absence of other published data on the effects of residential ventilation on TB transmission – increasing air exchange rates in houses may not reduce the incidence of TB infection in this village, or other Inuit communities.”**

I would have liked to see data on whether TB cases were associated with travel to other communities in Nunavik.

**While data on inter-village travel was not collected for our investigation, whole genome sequencing studies of Nunavik TB isolates, conducted by some of our co-authors and published elsewhere (Lee et al. *PNAS* November 3, 2015 vol. 112 no. 44 13609-13614), have demonstrated that the vast majority of TB transmission in Nunavik occurs within villages, rather than between villages.**

	<p>I would like to see more detail, if available, on housing construction (above ground, usual location of furnace if forced air, fuel used by furnace, total house volume or area, % homes in need of major repair or contaminated with mold).</p> <p><b>All houses are above ground. The furnace was always located in a room on the first floor, called the furnace room. All furnaces in Nunavik use oil for fuel. Total house volume was not measured; however, room volumes of the most relevant rooms was measured and is reported in the paper. Self-reported need for major repairs in the dwelling was noted in 21/79 (27%) of dwellings. Any mold was visible in 25/79 dwellings (32%). We note that all this information has been supplied to the community and the public health authorities, as well as representatives of the housing authority. We have omitted from the publication as these variables were not considered plausible candidates for determinants of TB outcomes—they could be proxies for other correlates such as ventilation level or socio-economic status, but we measured these directly and used these measurements in our study.</b></p> <p>MINOR ISSUES</p> <p>1st sentence of the abstract is confusing - suggest: Between November 2011 and November 2012, 7.4% (69/933) of an Inuit village's population developed active tuberculosis (TB); contact investigations involving 695 of the villagers demonstrated TB infection was very prevalent...</p> <p><b>The change has been made.</b></p> <p>Setting - define "contact." Were these household contacts, close contacts, etc.?</p> <p><b>Contacts included both household and social contacts, the latter including persons who visited the same houses that were used for social gatherings. As we are already over the word limit, we have referred readers to the 2 other publications where additional details can be found. Lines 82, Page 5.</b></p> <p>Conclusion, last sentence: rewrite as: treatment of latent TB infection should be even further emphasized to achieve a long-term reduction in TB incidence in this village, and in other communities where TB infection is highly prevalent.</p> <p><b>The suggestions have been incorporated.</b></p>
<p><b>Reviewer 2</b></p>	<p>Pam Orr</p>
<p>Institution</p>	<p>Departments of Medicine (Section of Infectious Diseases), Medical Microbiology and Community Health Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Man.</p>
<p>General comments (author response in bold)</p>	<p>This article is on a topic of importance to Canadian public health (TB rates among the Inuit), focusing on a determinant (housing) about which we have little data.</p> <p>The following comments are offered in the hope that they may strengthen what is already a good study. Please correct me if I missed some explanatory point in the text.</p> <p>1. The phrase "TB control" is no longer recommended by many leading groups, including STOP TB Partnership and the International Union Against TB and Lung Disease. I suggest you replace it in this paper with one of their recommendations- TB prevention and care, or TB management.</p> <p><b>We thank the reviewer for this thoughtful suggestion. We have made the following changes:</b></p> <p><b>- Line 24, Page 2: "Reducing household crowding may contribute to TB control prevention."</b></p> <p><b>- Line 247, Page 13: "Our results suggest that crowding in houses negatively affects efforts to eliminate TB control in from Canada's Northern communities."</b></p> <p>2. I suggest you replace the term "new infection" with "newly diagnosed infection". Some of the people in that category may have acquired their infection many years ago, but never had a skin test over the years to indicate this.</p> <p><b>We have made the changes as suggested.</b></p> <p>3. On page 6 you indicate that 92 people were treated for TB but only 50 had culture confirmation and 19 were diagnosed clinically (50 + 19 = 69). Please add a sentence to explain this- I assume you will say that some people were treated but they did not really have TB when all the facts came in, or perhaps the facts did not come in???</p> <p><b>The 23 other persons that were treated for active TB were retrospectively considered to not, in fact, have had active TB. This evaluation was done after the outbreak by two physicians who independently reviewed all clinical and radiological data (as described in Methods-Study Definitions, Line 118-119, Page 7). To further clarify we have made the following modification (Lines 96-98 Page 5):</b></p> <p><b>Of these, 50 (7.2%) had culture-confirmed disease and 19 (2.7%) clinically</b></p>

**probable disease (defined below) (23 [3.3%] persons treated during the outbreak were later considered to not have had active TB).**

4. It is common in Inuit communities for people (especially young people) to say that they live in House X (and the hamlet data indicates that they live in House X), but they actually sleep in House Y (the house of their grandmother, or their girlfriend etc.). Did you ask questions that would have ensured that this kind of information bias did not occur?

**Yes- we asked participants to name the house where they slept on most nights of the week, and this was used as their address.**

5. Re: the choosing of the control group: Can you indicate how the control group was chosen? Could there be a bias in the method used? Some sentences are in order on this issue. There were 695 contacts. 188 were newly diagnosed TST positives, 247 were old TST positives, leaving 260 TST negative contacts. Of that group of 260, 200 became the control group.

**For our first objective, we aimed to recruit an equal number of uninfected persons to serve as controls. For the second objective, we planned to recruit twice as many persons that had TB infection but without disease to serve as controls. Recruitment was done by radio announcements, and local Inuit study personnel contacting persons from lists. Due to the challenges in recruitment and the short time line to complete the study—we did not meet the exact number of controls we initially sought to recruit.**

**We have added the following in our Discussion as one of the study limitations (lines 281-285 page 15):**

**"An additional limitation, is the possibility of selection bias—it is possible that the distribution of risk factors amongst contacts that declined to participate was different than the distribution amongst participants. However, we think housing characteristics are unlikely to have been associated with selection probability, and hence those associations less affected by selection bias."**

6. The income analysis rests on "the income of their parent or guardian". What if there were 2 parents and they both earned money? The relevant income - the one that most accurately reflects the SE status of the people living in the house- is the total household income. I suggest you redo the stats using this indicator, or drop this analysis, because I think the income from one person in the house may well be misleading.

**We appreciate the point the reviewer is making here, about possible measurement bias in the assessment of income status. We do not have the data on total household income to redo the analysis. As per the reviewer's alternative suggestion—we ran our multivariable model again excluding the income indicator, and the remaining associations were not affected either in magnitude or statistical significance. However, the AIC of the model is lower when the income variable is included—suggesting that the income variable adds statistically important information to the model. Ultimately, we decided to leave this variable in the model to be consistent with our *a priori* decisions about variable selection.**

7. On page 14 I suggest re-wording your sentence "...increasing air exchange rates in houses cannot reliably be considered...". As you point out in your paper, we still do not have evidence to prove or disprove the reliability or effectiveness of increasing air exchange in TB programs. Change your wording to reflect that the question is still open. **Please see response to the first comment of Reviewer 1—the sentence has been changed.**

8. Can you add some sentences on possible classification bias based on the use of TST?

**We appreciate the reviewers concern about this issue in light of the widespread use of BCG in Nunavik. However, BCG is given at birth, and it is well known that fewer than 1% of persons who were BCG vaccinated in infancy remain BCG positive after the age of 10. In our study, only 43 participants were under the age of 10, and among them, 58% were TST-negative. That age group was associated with risk of newly diagnosed TB infection in our study—even in multivariable analyses, suggests that bias arising from misclassification due to BCG was minimal (as this bias would have resulted in deviating our estimates towards the null). We have not added sentences to address this, as we do not think the bias is important—and we are simply running quite low on space!**

9. Can you enlarge your analysis of potential limitations- for instance, the difficulty of finding associations when the numbers are not large, other sources of information bias, situations in which risk factors are relatively homogeneous across groups etc.

**We thank the reviewer for this suggestion. The paragraph on limitations has been expanded.**

	<p>10. All houses in Inuit villages, are basically, the site of "social events". You need to explain better what you mean about certain houses. i realize you are trying to be discreet and respectful of the people and the village, but the current wording is too obscure and raises questions in the readers mind that need a better answer. perhaps you can use some wording that is both respectful but also helps the reader understand why some particular houses were important in transmission.</p> <p><b>We appreciate the reviewers understanding of why we have not gone into detail about the houses used for social events—as there was much stigma surrounding visiting of these houses around the time of the outbreak. Our wording was carefully chosen, with input from the department of public health, and after discussions with community members—hence we do not think we can change the current wording. We note that additional details have already been reported in a prior publication focused on nutritional and lifestyle factors. We further note that molecular epidemiology data, and the aforementioned study on risk factors related to lifestyle—have both rebutted the stereotype, held by many during the outbreak, that it was the use of drugs at these houses that made them focal points of transmission.</b></p>
<b>Reviewer 3</b>	Richard Long
Institution	Department of Medicine, Pulmonary Research Group, University of Alberta, Edmonton, Alta.
General comments (author response in bold)	<p>The authors have undertaken a comprehensive study of a large tuberculosis outbreak in Nunavik, Quebec. They used a nested case-control study design among contacts of identified cases to compare those who were newly infected to those who were not infected and to compare those with disease to those with infection and no disease. The focus is on the relationship between TB outcomes and housing characteristics. The findings, both positive and negative, are important to understanding the biosocial factors responsible for the persistence of TB in Canadian Indigenous peoples, especially those living in the north. The paper is well written. A number of relatively straight forward questions are raised and several points of clarification suggested.</p> <p>1. In the second paragraph on page 9 the authors report using a census list, created as part of the public health response to the outbreak, to determine individual housing density. Since this is such an important measurement to the study outcome can they provide more detail about how this was done?  <b>Additional details have been added, as per the suggestion of Reviewer 1.</b></p> <p>2. The authors refer to contacts as having or not having lived with someone with smear-positive TB. This too is an important measurement but no detail is provided about when the contact lived with the smear-positive case - presumably before they were diagnosed - or for how long.  <b>The reviewer is correct—persons were classified as living with a smear-positive case if they had lived with them during and up to the time of diagnosis. This has been specified (Line 146-148, Page 8).</b></p> <p>3. At the bottom of page 6, 'uninfected' contacts are defined as having at least one negative TST between November 2011 and November 2012, with no prior TST result and no TB disease. Such contacts would not normally be considered uninfected unless the single TST was performed at least 8 weeks after contact with the source case was broken. Can the authors clarify?  <b>This is correct. The Canadian TB Standards were followed for all TST testing and clinical evaluation—hence, all contacts that were initially negative would have had a second TST performed 6 to 8 weeks after their last contact. We have added the following to Line 105-106, Page 6 in the Methods: "All TST testing, and treatment for TB disease or latent infection was performed according to Canadian standards."</b></p> <p>4. That all cases of active TB had a positive TST is somewhat surprising, given that those with symptoms usually undergo investigation for active disease before getting a TST and those with disease, especially if malnourished, may be TST negative. Was the performance of a TST in all contacts with the exception of those with a past positive TST, part of the study protocol?  <b>This was part of the clinical/public health protocol put in place during the outbreak—hence it was not part of the study protocol, as the study was performed after the outbreak investigations had been completed. All clinical investigations were undertaken during the outbreak, for the purposes of the outbreak. Study questionnaires and housing assessments were done after the outbreak.</b></p> <p>5. Given that overcrowding was not only positively associated with odds of new infection but also odds of disease among participants that lived with someone with smear-positive TB, might the authors want to consider adding to the discussion the possibility that reinfection was occurring? Reinfection in someone whose initial infection occurred relatively recently, is understood to increase the probability of</p>

disease.

**We thank the reviewer for their suggestion. We have added this to the paragraph in the Discussion that deals with crowding (Lines 247-254, page 13, 14):**

**“Our results suggest that crowding in houses negatively affects TB epidemiology in Canada’s Northern communities. Our findings also suggest that crowding affects TB risk amongst individuals living in a household where someone has developed smear-positive TB. Interestingly, we observed crowding was associated both with risk of infection and risk of progression from infection to disease—the latter association may have arisen if people living in crowded conditions were more likely to experience repeated infection. However, as the majority of participants with active TB did not live in such households, crowding alone does not explain the very elevated risk of disease in this village.”**

6. Can the authors indicate the BCG vaccination policy in the community? If BCG was offered can the authors provide some indication of its uptake?

**Up to 2007/2008, all infants in this community were BCG-vaccinated at birth. BCG-vaccination of newborns was re-instated in this community in 2012. Comments related to possible bias from BCG vaccination can be found in our response to question 8 by Reviewer 2.**

7. Should not the last sentence on page 5 read: "New positive TST was defined as a positive TST performed during this period without any previously documented positive TST"?

**Participants who had previously had a TST documented as negative, and subsequently found to be positive were categorized as having TST conversion. In contrast, “New positive TST” is used to identify those were newly found to be TST positive without prior documentation of any TST. Hence—the current wording is accurate.**