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Housing and tuberculosis in an Inuit village in Nunavik, Québec: a case-control study

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Abstract:	Background Between November 2011 and November 2012, 7.4% (69/933) of an Inuit village's population developed active tuberculosis (TB); contact investigations involving 695 villagers demonstrated TB infection was very prevalent (435/695, 62.6%), particularly over age 14 (360/457, 78.8%). This event triggered a series of scientific investigations. Genotyping revealed multiple, independent TB outbreaks had occurred during this period. A nested case-control study found nutritional inadequacy was associated with acquisition of infection, but not with progression to disease. Here, we report a nested case-control study investigating housing

	conditions. Methods We enrolled 200 contacts. We assessed whether characteristics of the dwelling where they lived were associated with their odds of new TB infection, and/or odds of progression to disease, between November 2011 and November 2012. Results The participants lived in 79 dwellings. Mean number of persons per room (PPR) was 1.1 (standard deviation:±0.5). Mean room size and ventilation level of the common living space (kitchen and living/dining rooms) were 67.9(±9.4) m3 and 1.69(±0.26) air changes per hour, respectively. After adjusting for potential confounders, PPR was positively associated with odds of new infection, and odds of disease, but only among participants that lived with someone with smear-positive TB— the minority of participants. Other dwelling characteristics were not associated with either outcome. Interpretation Reducing household crowding may contribute to TB control. Overall, our investigations have not identified associations that explain the elevated disease risk. Given the high prevalence, treatment of latent infection is an essential intervention for long-term reduction of TB incidence in this village.

Title **Housing and tuberculosis in an Inuit village in Nunavik, Québec: a case-control study**

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ABSTRACT (249 words)

Background

Between November 2011 and November 2012, 7.4% (69/933) of an Inuit village's population developed active tuberculosis (TB); contact investigations involving 695 villagers demonstrated TB infection was very prevalent (435/695, 62.6%), particularly over age 14 (360/457, 78.8%). This event triggered a series of scientific investigations. Genotyping revealed multiple, independent TB outbreaks had occurred during this period. A nested case-control study found nutritional inadequacy was associated with acquisition of infection, but not with progression to disease. Here, we report a nested case-control study investigating housing conditions.

Methods

We enrolled 200 contacts. We assessed whether characteristics of the dwelling where they lived were associated with their odds of new TB infection, and/or odds of progression to disease, between November 2011 and November 2012.

Results

The participants lived in 79 dwellings. Mean number of persons per room (PPR) was 1.1 (standard deviation:±0.5). Mean room size and ventilation level of the common living space (kitchen and living/dining rooms) were 67.9(±9.4) m^3 and 1.69(±0.26) air changes per hour, respectively. After adjusting for potential confounders, PPR was positively associated with odds of new infection, and odds of disease, but only among participants that lived with someone with smear-positive TB— the minority of participants. Other dwelling characteristics were not associated with either outcome.

Interpretation

Reducing household crowding may contribute to TB control. Overall, our investigations have not identified associations that explain the elevated disease risk. Given the high prevalence, treatment of latent infection is an essential intervention for long-term reduction of TB incidence in this village.

INTRODUCTION (words=3316)

Between 2008 and 2012, average annual tuberculosis (TB) incidence among the Inuit in Canada was 190 per 100,000, compared to a national average of 5 per 100,000 [1-5]. The reasons for this dramatic difference are unclear, although major disparities in socioeconomic status [6], and general health [7, 8] are thought to contribute.

Housing has been a concern for Inuit communities for several years owing to the high prevalence of overcrowding and disrepair of dwellings [9, 10]. While housing is widely regarded as an important determinant of TB [11, 12], there is surprisingly little evidence supporting a causal association between housing conditions and TB infection or disease. Associations between crowded housing and TB have mostly been reported in ecologic studies [13-15], but these community-level associations could have been due to confounding by other social, environmental, or biological determinants of TB that are often co-prevalent with crowded households. An association between low ventilation—which is the exchange of indoor air with outdoor air—and the risk of TB infection has been demonstrated in healthcare settings [16], but its role in TB transmission in homes has not been established.

Between November 2011 and November 2012, an Inuit village in Nunavik (Québec) experienced a surge in the occurrence of active TB [17]. During this year, 5.4% of the village's population (50/933) were diagnosed with culture-confirmed TB and another 2.0% (19/933) with clinically probable TB disease. As part of an intensified medical and public health response, 695 villagers were evaluated for TB infection or disease during this period. Our study was motivated by two observations: 1) the elevated rate of newly diagnosed TB infection ("new TB infection")

among villagers evaluated as contacts during this period (27.1%, 188/695) ; and, 2) the very high rate of active disease – 28.2% (53/188) – among contacts with new TB infection. While similar rates of TB disease have been reported in outbreaks of multidrug-resistant strains [18] and among people living with HIV [19], neither of these were contributing factors in this village. By November 2012, TB notifications had returned to baseline; hence, we planned an intensive investigation of the association between demographic, economic, housing, dietary, and lifestyle factors and the acquisition of infection or development of disease that had occurred during the period of elevated incidence (November 2011 to November 2012). In parallel, whole-genome sequencing of all isolates from culture-positive cases demonstrated that the surge in incidence was not related to the introduction of a new strain, nor the emergence of a more transmissable or virulent organism [17]. Sequencing also revealed that the surge had resulted from the contemporaneous occurrence of at least six independent reactivation events with multiple chains of transmission rather than a single point-source outbreak [17]. A detailed evaluation of dietary and lifestyle factors identified inadequate intake of fruits and vegetables, and also of carbohydrates, as nutritional factors associated with infection [20]. These variables were not associated with disease.

This paper focuses on the relationship between TB outcomes and housing characteristics. Our two main objectives were to determine if characteristics of an individual's dwelling were associated with: (1) acquisition of new TB infection; and (2) progression to confirmed or probable disease among those with TB infection.

METHODS

Ethics

This study was approved by the Nunavik Nutrition and Health Committee, the mayor and municipal council of the village, and the Institutional Review Board of McGill University.

Consent for questionnaires

Informed consent was obtained from each participant, or their parent/guardian, prior to the administration of study questionnaires. For the housing assessment, consent was obtained from the individual identified as the head of the household.

Setting

Between November 2011 and November 2012, 695 of 933 persons residing in the village were identified as a contact of at least one person with active TB, or diagnosed with active TB. Evaluation of these individuals included a detailed clinical history, physical examination, plain chest radiograph, and tuberculin skin testing (TST) (performed among those who did not have a documented prior positive TST). All contacts with radiographic or clinical suspicion of TB disease submitted three spontaneous or induced sputum samples which were sent for acid-fast microscopy and liquid culture. As the village has little in-migration, one clinic and a single public health authority, villagers' medical records provided complete information on lifelong past investigations for TB infection or disease.

In accordance with Canadian standards [21] a positive TST reaction was defined as 5mm or greater if the TST was performed as part of contact investigations during this period. *New positive TST* was defined as a positive TST performed during this period without any previously

documented TST. *TST conversion* was defined as a reaction of 5mm or greater, and a previous TST reading of less than 5mm, or an increase of 6mm or more from previous TST measuring 5 to 9mm.

By November 2012, among 695 community members investigated, 92 (13.2%) had been treated for active TB. Of these, 50 (7.2%) had culture-confirmed disease and 19 (2.7%) clinically probable disease (defined below). There were no cases of confirmed or clinically probable TB among villagers with a negative TST. As shown in **Figure 1**, 247/695 (35.5%) had been documented as TST-positive prior to November 2011, and 188/695 (27.1%) were documented to have a new positive TST or a TST conversion between November 2011 and November 2012. Prevalence of infection was 89.3% (208/233) in the age group 30 years or older, 67.9% (152/224) among those 15 to 29 years old, and 31.6% (75/237) in the age group 14 years or younger. Across all age groups, the rate of disease was highest among newly infected contacts (**Figure 2**). Persons considered to have TB disease, or latent infection, were treated according to Canadian standards.[21] By November 2012, among contacts that were not treated for active TB, treatment for latent infection had been initiated in 94.5% (121/135) of those with a new positive TST or TST conversion.

Study definitions

Based on detailed clinical information collected between November 2011 and November 2012 we grouped all investigated contacts into one of three categories: (1) New TB infection, defined as a new positive TST or TST conversion; (2) Prior positive TST, defined as a positive TST documented before November 2011; (3) Uninfected, defined as at least one negative TST

between November 2011 and November 2012, with no prior positive TST result, and no TB disease. We categorized villagers treated for active TB as having confirmed TB disease if they had at least one positive culture for *M. tuberculosis,* or probable TB disease if there were typical clinical and radiological features, including response to therapy, but without culture confirmation. This designation was made by two experienced chest physicians, who independently reviewed all clinical and radiological information.

Study design & Outcomes

We conducted a case-control study nested within the 695 persons who were identified and investigated between November 2011 and November 2012. The study was undertaken between February and July of 2013. For our first objective, we compared participants with new TB infection (regardless of their disease status) to a control group of contacts that were uninfected. For the second objective, we compared participants with confirmed or probable disease to a control group comprised of those with infection but no disease.

Participants

Community members were eligible for inclusion if, between November 2011 and November 2012, they had resided in the village and were either diagnosed with confirmed or probable TB disease, or had been investigated as contacts of someone with confirmed or probable disease with at least (a) one TST performed during this period, or (b) documented prior positive TST.

For the first objective, we aimed to recruit persons with new infection to serve as cases and an equal number of uninfected persons, to serve as controls. For the second objective, we planned

to recruit as many persons with confirmed or probable active TB as possible, and aimed to recruit twice as many persons without disease but with TB infection to serve as controls.

Data collection

The Online Supplement provides details about questionnaires, definitions of socioeconomic variables and housing characteristics, the methods for measuring and extrapolating ventilation levels, and our approach to multivariable analyses.

Trained study staff administered questionnaires assessing housing, nutrition, socioeconomic, and lifestyle factors [20]. Parents or guardians provided responses for children aged up to 12.

We used information collected during contact investigations, and from the study questionnaires, to determine whether participants could have been exposed to TB in their own home, or in other dwellings that they visited at least weekly. Community members had raised concerns that individuals were at greater risk of TB if they had visited a subset of dwellings that had been used for social activities. To address these concerns, we specifically evaluated whether visiting these dwellings, at least once weekly, was associated with each study outcome.

The dwelling of each participant was visited by study personnel to administer questionnaires, and perform a standardized walk through assessment (for enumerating rooms and assessing need for major repairs). In accordance with Statistics Canada, the kitchen, living/dining area, and bedrooms were counted as rooms [22].

Ventilation was measured in air changes per hour (ACH), in the rooms where participants slept and in the common living area (living, dining and kitchen area which were contiguous in all dwellings), using CO_2 as a tracer gas, as described elsewhere [23, 24]. In dwellings with "forced air" heating systems which blow heated outdoor air into rooms, measurements were taken with the heating both on and off. Because the design and construction of many dwellings were identical, ventilation was not directly measured in all dwellings of the same type. Instead, these were assigned the weighted average ACH measured in dwellings of the same construction model and layout; these average values were estimated using multi-level linear regression. Details are found in the Online Supplement.

To determine the occupancy level (i.e. "crowdedness") that each participant had been exposed to between November 2011 and November 2012, we used a census list created as part of the public health response to ascertain the number of persons that lived in each dwelling during that period. We divided the total number of occupants by the number of rooms in each dwelling to obtain our measure of occupancy— persons per room. Per Statistics Canada, we defined "overcrowding" as greater than 1 person per room in the dwelling [22].

Statistical Methods

The level of analysis was the individual. We used the method of generalized estimating equations for logistic regression, with clustering at the dwelling level, to identify associations between each outcome of interest and housing characteristics, potential TB exposures in dwellings, and factors recognized as important determinants of TB (e.g. smoking tobacco). To analyze ventilation as a risk factor for TB, we used the ventilation level in the common living

area of participants' dwellings— since all household occupants shared these areas, and many slept in these areas. We used interaction terms to test the hypothesis that occupancy level would be associated with TB transmission in dwellings where someone with smear-positive TB lived. Because our results supported this hypothesis, we used the same approach to analyze the impact of occupancy on disease. Additional details are found in the Online Supplement. The multivariable models in this report do not adjust for measures of nutritional inadequacy; a detailed evaluation of nutritional factors is reported elsewhere [20].

RESULTS

Study population

Details about enrollment, and comparisons between participants and non-participants have been previously reported [20]. Of 695 eligible villagers, 200 were enrolled in the study; within each TST category, age and gender distributions were similar among participants and non-participants (**Online Supplement Figure S1**, **Tables S1A & S1B**). Similarly, among villagers with confirmed or probable TB disease, participants and non-participants shared similar age and gender distributions, and also proportions in each TST category (**Online Supplement Table S1B**).

Of the 200 villagers enrolled, 67 (34%) were uninfected, 88 (44%) had new TB infection, and 45 (23%) had a prior positive TST. Of the 133 participants with TB infection, 44 (22%) had confirmed (n=33) or probable (n=11) TB disease, and 89 (44.5%) had TB infection with no disease. Among participants, the mean (± standard deviation) age was 21.5 (± 14.1) years, 107

(54%) were female, 118 (59%) were current smokers, and 118 (59%) had an annual personal income less than $20,000 (for children, this was the income of their parent or guardian).

Housing characteristics

Table 1 summarizes the characteristics of 78 of the 79 dwellings where the 200 participants resided between November 2011 and November 2012. We could not determine the characteristics for one dwelling because the participant had moved prior to the study and research staff could not gain access to their original residence. These 78 dwellings comprised 40% of all dwellings in the village. The majority of dwellings used forced air heating systems, and in these dwellings, ACH were higher when the heating was on.

Community members identified 18 dwellings that had been used for social activities. These dwellings' characteristics were similar to the other 178 dwellings in the village (**Online Supplement Table S2**).

Determinants of new TB infection

As shown in **Table 2**, in univariable analyses, participants with new TB infection were significantly more likely than uninfected participants to have visited, at least once weekly, a dwelling that was used for social activities. Newly infected participants were also more likely to have lived in a dwelling with someone who had smear-positive TB.

The method of heating, level of ventilation, and the volume of the living area, were not associated with infection, and did not meet criteria for inclusion in multivariable analyses (**Table 3**). Age greater than 14 years old, and visiting dwellings used for social activities at least

once weekly, were associated with new infection. The effect of occupancy (as measured by persons per room) on infection was dependent on living with someone with smear-positive TB. Among participants that had lived with someone who had smear-positive TB, odds of new infection increased as the number of persons per room increased; this association was not seen among those that had not lived with someone who had smear-positive TB. This interaction also meant that the association between living with someone who had smear-positive TB and infection was stronger in dwellings with more persons per room (the odds ratios for this association shown in Table 3 corresponds to living in a dwelling with 1.2 persons per room, which was the median value for this variable).

Determinants of TB disease among participants with TB infection

As shown in **Table 4**, in univariable analyses amongst participants with TB infection, active TB was not associated with visiting dwellings used for social activities, or with having lived with someone who had disease.

As seen in **Table 5**, the heating method and ventilation level were not associated with disease. Living area size was associated in univariable but not multivariable analysis. We again observed an interaction between occupancy and living with someone with smear-positive TB — the odds of disease increased with the number of persons per room only among participants that had lived with someone who had smear-positive TB. This analysis also demonstrated that risk of disease was significantly higher among participants with new compared to previous TB infection, after adjusting for potential confounders.

DISCUSSION

During a twelve month period when the incidence of TB dramatically increased in this village, the number of persons per room was the only housing characteristic associated with new TB infection — and it was only associated among participants that had lived with someone who had smear-positive disease. Similarly, the number of persons per room was the only housing characteristic associated with progression to TB disease among infected participants, and this association was also dependent on living with someone who had smear-positive TB. Other factors associated with new TB infection were: age over 14 years old, visiting one of the dwellings that was used for socializing, and having lived with someone who had smear-positive TB. Prior TB infection was the only other factor associated with disease (against which it was protective).

Our results suggest that crowding in houses negatively affects TB control 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. 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.

Very little is known about the role of ventilation on TB transmission in people's homes. While the level of ventilation in healthcare settings has been shown to affect the risk of TB infection amongst healthcare workers, in our study, air exchange rates in participants' dwellings were not associated with infection. We speculate that exposure to TB-containing droplet particles was so intense during interactions in people's homes, that air exchange rates within the range of

values measured in our study were insufficient to produce an observable reduction in the probability of transmission. It is plausible that exposure intensity is greater in people's homes compared to other settings, due to greater duration or closer physical proximity of interactions. This may apply to other airborne infections of the respiratory tract— a study of Inuit infants on Baffin Island also did not find an association between ventilation and lower respiratory tract infections [25]. 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 cannot be considered as a reliable intervention for reducing the incidence of TB infection in this village, or other Inuit communities.

This study had a number of limitations, including the timing of the study, which was initiated a few months after public health authorities considered TB incidence to have returned to baseline. This delay was unavoidable— given the need to allow the health services to complete all necessary evaluations and initiate treatment for active and latent TB plus the complexities of arranging a scientific investigation in a remote community. However, bias due to this delay is unlikely as all participants—even those that had moved— were assigned the characteristics of their original residence (except one); furthermore, characteristics of houses are unlikely to have changed substantially before the study was undertaken.

Strengths of the study included the availability of detailed medical records for all participants (usually lifelong records) that allowed accurate categorization of persons as having new or prior TB infection, and probable or confirmed disease. This permitted a unique study of risk factors for acquisition of infection, and for progression to disease among those infected, within the

same population. In addition, we conducted a very thorough evaluation of housing, which included a standardized walk-through assessment, enumeration of occupancy, and direct measurement of outdoor air exchange rates (ventilation) using a validated protocol based on tracer gas techniques [23]. To account for seasonal fluctuations in air exchange rates, we manipulated the heating system to simulate different conditions, although we were unable to acount for all other factors (outdoor temperature, indoor activities) that may influence ventilation.

Conclusions

This is the third report from a series of investigations that were undertaken to understand why an Inuit village experienced a surge in the occurrence of active TB between November 2011 and November 2012. Despite a rigorous evaluation that has included whole genome sequencing of all culture-positive isolates [17], and studying the role of nutritional [20], lifestyle [20], and housing characteristics — we have been unable to identify the factors that clearly explain the elevated disease rate. Our findings suggest that improved nutrition and less crowding in households may contribute to reducing the risk of TB infection. However, given that the impact of nutritional, lifestyle, or housing interventions on the risk of active TB remains uncertain, similar events could happen in other villages where TB infection is highly prevalent. Hence treatment of latent TB infection should be even further emphasized to achieve long-term reduction in TB incidence in this village, and other communities where TB infection is highly prevalent.

Declaration of interests

The authors declare no competing interests.

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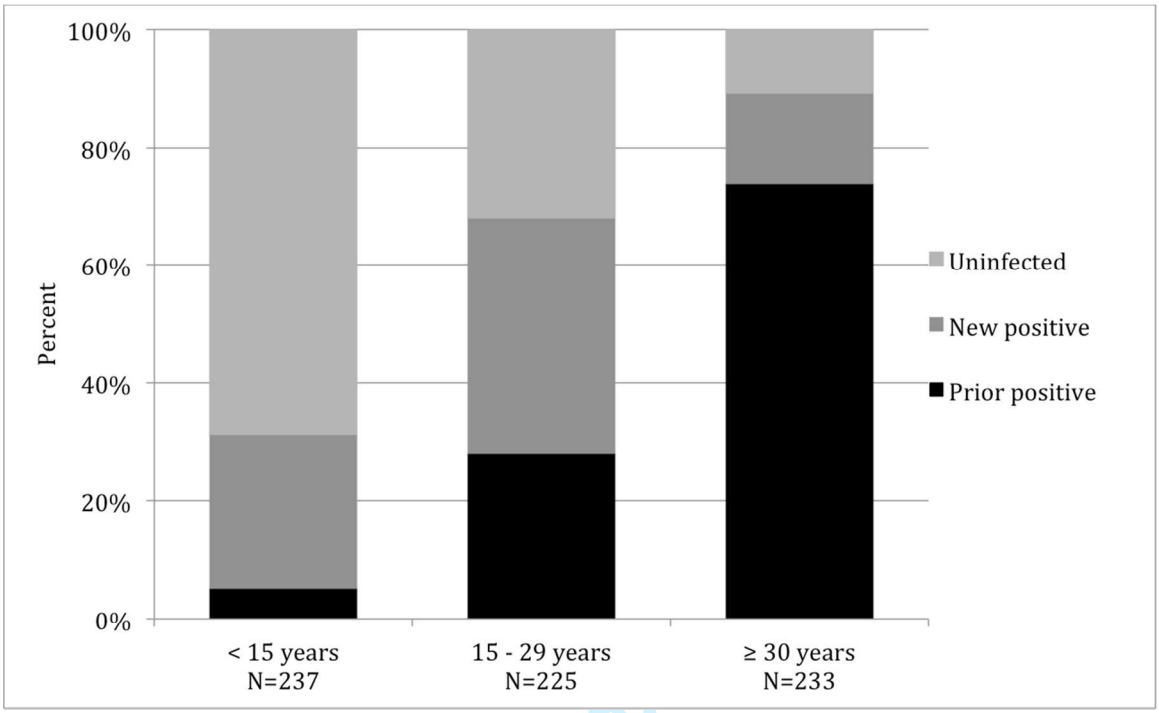
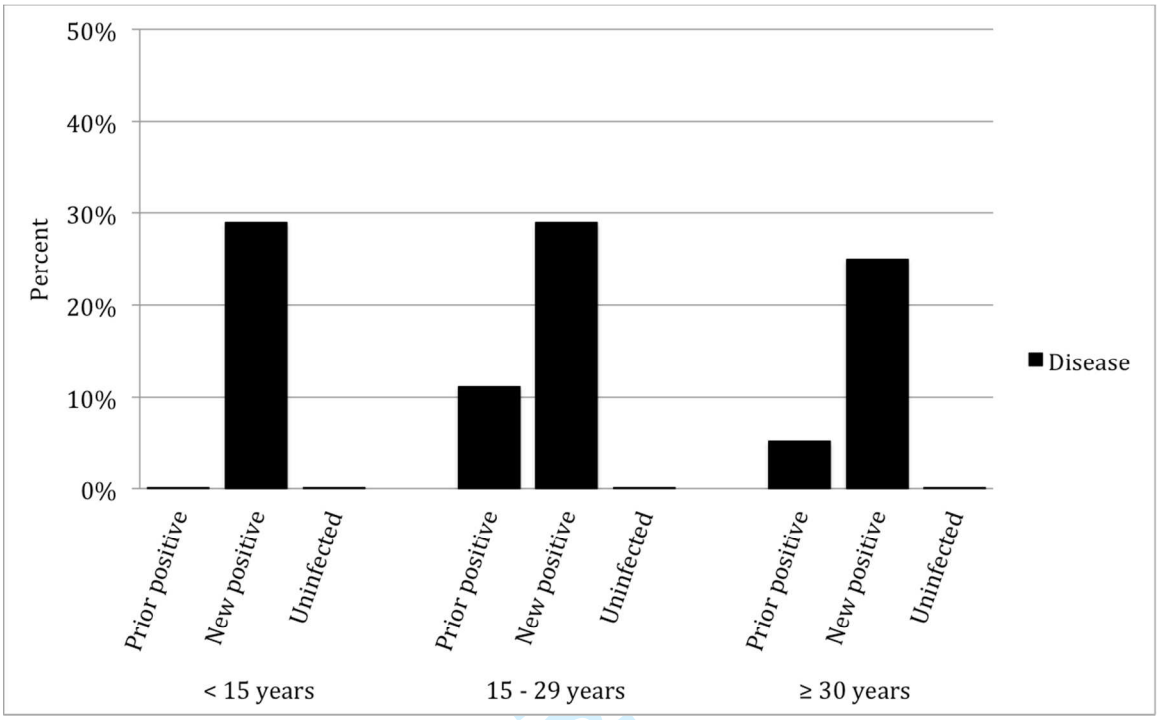
Figure 1. Percentage of contacts investigated between November 2011 and November 2012 who were uninfected, newly infected, or previously infected.[†]



[†] *New positive* and *prior positive* categories include contacts with disease and also contacts that did not develop disease between November 2011 and November 2012. No TST (tuberculin skin test) negative (uninfected) person developed confirmed or probable TB disease.

Figure 2 – Percentage of contacts who developed microbiologically confirmed or probable active TB disease, by TST status and age group



TST, tuberculin skin test

Table 1. Characteristics of 79 dwellings where study participants lived between November 2011 and November 2012[†]

Dwelling characteristic		Summary
Total number of dwellings inhabited by participants		79
Years since dwelling was built, mean ±SD		19.3 ±8.2
Heating method, N(%)		
Radiator		8 (10%)
Forced air		70 (90%)
Dwelling occupancy		
Number of occupants, mean ±SD		6.1 ±3.0
Persons per room,[††] mean ±SD		1.1 ±0.5
Overcrowded,[†††] N(%)		39 (50%)
Ventilation[*]		
Air changes per hour (ACH)	*Living area*	*Bedrooms*
ACH with heating off, mean ±SD	0.67 ±0.28	0.31 ±0.28
ACH with heating on, mean ±SD	1.69 ±0.26	1.29 ±0.29
Volume of room, m^3 , mean ±SD	67.9 ±9.4	27.7 ±4.4

[†] Data on dwelling characteristics were available for 78/79 dwellings. We could not determine the characteristics for one dwelling because one participant had moved before the study and research personnel could not access their original residence. Five dwellings were studio apartments without separate bedrooms.

[††] Calculated by dividing the number of occupants by the total number of rooms in the dwelling.

[†††] Statistics Canada's defines "overcrowded" as occupancy exceeding 1 person per room.

* Dwellings in this community are grouped into five main construction types that share the same design and layout. Ventilation was directly measured using tracer gas technique in 52 dwellings. Dwellings where ventilation was not directly measured were assigned the average ventilation level of dwellings of the same construction type. The average ventilation values for each construction type were calculated using multi-level multivariable linear regression techniques (See Online Supplement "Methods Supplement, Section 2" for details).

Table 2. Associations between acquisition of TB infection and potential exposures to villagers with active TB when visiting other dwellings, or at home.

Variable	Newly infected† N = 88	Uninfected N = 67	
	N (%)	N (%)	*p*
Number of participants who reported visiting at least one dwelling, at least once weekly	84 (96%)	64 (96%)	1.0
Number of participants who visited a dwelling that was NOT used for social activities, at least once weekly (178 dwellings)			
Any of these dwellings	77 (88%)	63(94%)	0.17
A dwelling where villager with TB disease lived or visited	53 (60%)	49 (73%)	0.09
Number of participants who visited a dwelling used for social activities, at least once weekly (18 dwellings)			
Any of these dwellings	47 (53%)	16 (24%)	<0.01
A dwelling where villager with TB disease lived or visited	34 (39%)	11 (16%)	<0.01
Number of participants who lived with someone who had TB			
Lived with someone who had TB disease	42 (48%)	26 (39%)	0.34
Lived with someone who had smear-positive TB	20 (23%)	2 (3%)	<0.01
Lived with someone who had smear-negative TB	36 (40%)	25 (37%)	0.77

All p-values calculated using the Pearson's Chi-squared or Fisher's exact tests.
† This newly infected group includes 53 individuals without disease and 35 individuals with disease.

Table 3. Factors associated with acquisition of TB infection between November 2011 and November 2012.

Variable	Newly infected, N=88[†] N (%) or Mean (± SD)	Uninfected, N=67 N (%) or Mean (± SD)	Univariable analysis Crude OR (95% CI)	Multivariable analysis Adjusted OR (95% CI)
Age				
Under 15 years	30 (34%)	45 (67%)	**ref**	**ref**
15-29 years	44 (50%)	17 (25%)	**3.9 (2.1-7.1)**	**5.5 (2.8-10.7)**
≥ 30 years	14 (16%)	5 (8%)	**4.2 (1.5-12.0)**	**5.2 (1.5–18.0)**
Gender				
Male	40 (45%)	31 (46%)	ref	ref
Female	48 (55%)	36 (54%)	1.0 (0.6-1.9)	0.8 (0.4-1.8)
Tobacco smoking				
Not currently smoking	30 (34%)	40 (60%)	**ref**	Not in model
Current smoker	58 (66%)	27 (40%)	**2.9 (1.5-5.4)**	
Annual personal income				
< $20,000	55 (66%)	36 (56%)	ref	Not in model
≥ $20,000	28 (34%)	28 (44%)	0.7 (0.3-1.5)	
Heating/dwelling type				
Forced air (houses)	81 (92%)	64 (97%)	ref	Not in model
Radiator heating (apartments)	7 (8%)	2 (3%)	2.8 (0.8-10.2)	
Number of persons per room[††]				
Among participants living with a smear-positive person	1.7 ±0.6	1.1 ±0.7	1.5 (0.9-2.3)	**1.8 (1.1-2.9)**
Among participants not living with a smear-positive person	1.2 ±0.5	1.3 ±0.4	0.9 (0.7-1.1)	0.9 (0.7-1.1)
*Ventilation with heating on relative to the median (*1.66 ACH*)* [†††]				
< the median	68 (77%)	51 (76%)	ref	Not in model
≥ the median	20 (23%)	15 (22%)	1.0 (0.4-2.6)	
*Volume of living area relative to the median (*65.5 m^3*)*				
< the median	32 (36%)	31 (46%)	ref	Not in model
≥ the median	56 (64%)	35 (52%)	1.6 (0.7-3.6)	
Visited a dwelling used for social activities	47 (53%)	16 (24%)	**3.7 (1.7-7.9)**	**4.2 (1.8-10.1)**
Lived with smear-positive person[*]	20 (23%)	2 (3%)	**9.6 (2.4-38.0)**	4.7 (0.95- 23.2)

OR, odds ratio; CI, confidence interval, ACH, air changes per hour

Confidence intervals where odds ratio excludes 1.0 are in **bold**.

Indicators of nutritional inadequacy were not included in the multivariable analyses reported above; for results of multivariable models assessing nutritional inadequacy see Fox *et al*. [20]

The final multivariable model includes all listed variables, except where indicated, plus an interaction term between occupancy and living with a smear-positive case that was statistically significant (p = 0.006).

Data missing on income (N=8), heating type, ventilation and volume (N=1).

One participant who had moved since the outbreak and whose original dwelling could not be accessed was excluded from multivariable analysis.

† This Newly Infected group includes 53 without disease and 35 with disease.

†† Interaction term between occupancy and living with a smear-positive person was significant in univariable analysis (p=0.049). The crude and adjusted ORs are per 0.2-unit increment in the number of persons per room. This scale was chosen because it corresponds to an increment of one occupant in a dwelling with 5 rooms (the median number of rooms). As an example of interpretation: Among those living with a smear-positive person in a dwelling with 5 rooms, if we were to compare two participants who did not live together, and whose dwellings differed in occupancy by 1 person, the unadjusted odds of new infection would be 50% higher (as the odds ratio is 1.5) for the participant living in the home with the greater number of occupants.

††† In the living area. Lowest ventilation measured in the living area also was not associated with infection (data not shown).

* Adjusted OR shows association between living with someone who had smear-positive TB and new infection if living in a dwelling with 1.2 persons per room (chosen because it was the median number of persons per room).

Table 4. Association between active TB disease, among participants with TB infection, and potential exposures to villagers with active TB when visiting other dwellings, or at home.

Variable	Disease N = 44	No Disease N = 89	
	N (%)	N (%)	*p*
Number of participants who reported visiting at least one dwelling, at least once weekly	41 (93%)	83 (97%)	0.37
Number of participants who visited a dwelling that was NOT used for social activities, at least once weekly (178 dwellings)			
Any of these dwellings	37 (84%)	80 (90%)	0.33
A dwelling where villager with TB disease lived or visited	27 (61%)	55 (62%)	0.96
Number of participants who visited dwellings used for social activities, at least once weekly (18 dwellings)			
Any of these dwellings	21 (48%)	50 (56%)	0.46
A dwelling where villager with TB disease lived or visited	14 (32%)	33 (37%)	0.57
Number of participants who lived with someone who had TB			
Lived with someone who had TB disease	21 (48%)	44 (49%)	1.00
Lived with someone who had smear-positive TB	13 (30%)	16 (18%)	0.20
Lived with someone who had smear-negative TB	17 (39%)	42 (47%)	0.45

All p-values calculated using the Pearson's Chi-squared or Fisher's exact tests.
[†] This newly infected group includes 53 individuals without disease and 35 individuals with disease.

Table 5. Factors associated with progression to TB disease from infection between November 2011 and November 2012.

	Participants with new or prior TB infection			
	Disease, N=44	No Disease, N=89	Univariable analysis	Multivariable analysis
Variable	**N (%) or Mean (± SD)**	**N (%) or Mean (± SD)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Age				
Under 15 years	12 (27%)	19 (21%)	ref	ref
15-29 years	22 (50%)	39 (44%)	0.9 (0.4-2.3)	1.0 (0.3-2.8)
≥ 30 years	10 (23%)	31 (35%)	0.5 (0.2-1.3)	1.0 (0.3-3.0)
Gender				
Male	22 (50%)	40 (45%)	ref	ref
Female	22 (50%)	49 (55%)	0.8 (0.4-1.5)	0.8 (0.4-1.7)
Tobacco smoking				
Not currently smoking	15 (34%)	26 (30%)	ref	Not in model
Current smoker	29 (66%)	62 (70%)	0.8 (0.4-1.8)	
Annual personal income				
< $20,000	31 (77%)	51 (60%)	ref	ref
≥ $20,000	9 (23%)	34 (40%)	0.4 (0.2-1.05)	0.4 (0.2-1.1)
Prior TB infection				
No documented TST-positive prior to Nov 2011	35 (79%)	53 (60%)	ref	ref
Documented TST-positive prior to Nov 2011	9 (21%)	36 (40%)	**0.4 (0.2-0.8)**	**0.4 (0.2-0.9)**
Heating/dwelling type				
Forced air (houses)	41 (93%)	83 (93%)	ref	Not in model
Radiator heating (apartments)	3 (7%)	6 (7%)	1.0 (0.3-3.4)	
Number of persons per room[†]				
Among participants living with a smear-positive person	1.9 ±0.4	1.6 ±0.6	**1.3 (1.1-1.6)**	**1.3 (1.2-1.5)**
Among participants not living with a smear-positive person	1.2 ±0.5	1.1 ±0.5	1.1 (0.9-1.2)	1.1 (0.9-1.3)
Ventilation with heating on relative to the median (1.66 ACH)[††]				
< the median	36 (82%)	67 (75%)	ref	Not in model
≥ the median	8 (18%)	22 (25%)	0.7 (0.3-1.5)	
Volume of living area relative to the median (65.5 m^3)				
< the median	13 (30%)	44 (49%)	ref	Not in model
≥ the median	27 (61%)	59 (66%)	**2.3 (1.1-5.0)**	
Visited any dwelling used for social activities	21 (48%)	50 (56%)	0.7 (0.3-1.6)	Not in model
Lived with smear-positive person[*]	13 (30%)	16 (18%)	1.9 (0.9-4.1)	0.8 (0.3-1.8)

OR, odds ratio; CI, confidence interval; ACH, air changes per hour
Confidence intervals where odds ratio excludes 1.0 are in **bold**.
Indicators of nutritional inadequacy were not included in the multivariable analyses reported above; for results of multivariable models assessing nutritional inadequacy see Fox *et al*. [20]

Adjusted OR from model that includes all variables, except where indicated, plus an interaction term between occupancy and living with a smear-positive case that was statistically significant (p=0.042). Eight participants with missing data on income status were excluded from the final model.

† Interaction term between occupancy and living with a smear-positive person was not statistically significant in univariable analysis (p=0.12), and was significant in the multivariable model (p=0.04). The crude and adjusted ORs are per 0.2-unit increment in the number of persons per room. This scale was chosen because it corresponds to an increment of one person in a dwelling with 5 rooms (the median number of rooms). As an example of interpretation: If we were to compare two participants who did not live together, and whose dwellings differed in occupancy by 1 person per room, the unadjusted odds of disease would be 30% higher (as the crude OR is 1.3) for the participant living in the home with the greater number of persons per room.

†† In the living area. Lowest ventilation measured in the living area also was not associated with disease (data not shown).

* Adjusted OR shows association between living with someone who had smear-positive TB and disease if living in a dwelling with 1.2 persons per room (chosen because it was the median number of persons per room).

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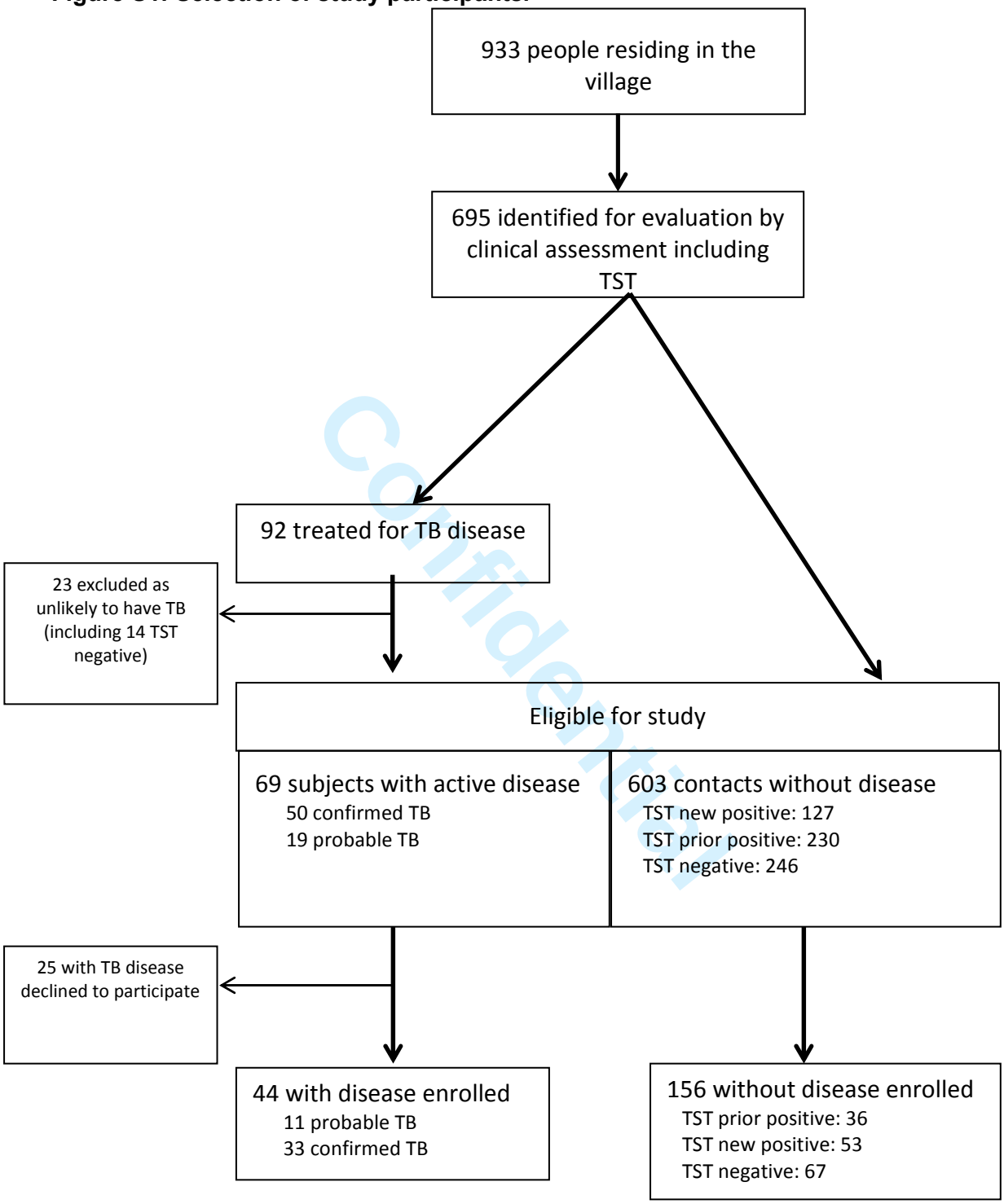
ONLINE SUPPLEMENT

Title Housing and tuberculosis in an Inuit village in Nunavik, Quebec: a case-control study

Authors Faiz Ahmad Khan, Greg J. Fox, Robyn S. Lee, Mylène Riva, Andrea Benedetti, Jean-Francois Proulx, Shelley Jung, Karen Hornby, Marcel A. Behr, Dick Menzies

Figure S1: Selection of study participants.



TST = Tuberculin skin test. TB = tuberculosis. Screening comprised a chest radiograph, clinical assessment and TST to determine disease and infection status. Adapted from Fox *et al* [1].

Table S1. Comparison of participants and non-participants.

(A) By TST category: new infection, prior infection, no infection [1].

TST category*		Age group (years)			Gender
	Total	0-14	15-29	≥ 30	Male
New infection¶					
Participants	88	30 (34.1%)	44 (50%)	14 (15.9%)	40 (45.5%)
Non-participants	100	32 (32.0%)	46 (46.0%)	22 (22.0%)	45 (60.8%)
Prior infection¶					
Participants	45	2 (4.4%)	16 (35.6%)	27 (60%)	22 (48.9%)
Non-participants	202	11 (5.4%)	46 (22.8%)	145 (71.8%)	98 (48.8%)
No infection					
Participants	67	45 (67.2%)	17 (25.4%)	5 (7.5%)	31 (46.3%)
Non-participants	193	117 (60.9%)	55 (28.6%)	20 (10.4%)	104 (54.2%)

(B) Amongst villagers with confirmed or probable TB disease

Disease group*		Age group (years)			Gender	TST category	
	Total	0-14	15-29	≥ 30	Male	New infection	Prior infection
TB disease							
Participants	44	12 (27%)	22 (50%)	10 (23%)	22 (50%)	35 (80%)	9 (20%)
Non-participants	25	6 (24%)	11 (44%)	8 (32%)	12 (48%)	18 (72%)	7 (28%)

TST, tuberculin skin test; TB, tuberculosis. Gender of 2 non-participants was missing, and age of 1 non-participant in the "No infection" category. *No significant differences were found between the characteristics of participants and non-participants in any sub-group ($p>0.05$ for all comparisons, using Fisher's exact test). ¶Includes individuals with or without disease. All individuals with disease had a positive tuberculin skin test.

Table S2. Comparison of dwellings used for social activities to other dwellings in the village.

Variable	Dwellings used for social activities	Dwellings that were not used for social activities
Number of dwellings of this type in the village	18	178
Dwelling where at least one study participant lived from Nov 2011-Nov 2012, N(%)	10 (55.6%)	69 (38.8%)
Dwelling where ventilation was measured and at least one study participant lived from Nov 2011-Nov 2012, N(%)	4 (22.2%)	47 (26.4%)
Number of dwellings of this type visited weekly by at least one participant	18 (100%)	128 (71.9%)
Years since dwelling built (as of 2012), mean (±SD) †	16.4 (± 9.7)	17.4 (± 9.4)
Pulsed air heating, N(%)†	18 (100%)	137 (80.1%)
Number of rooms per dwelling, mean (±SD) †	6 (± 1)	5 (± 1)
ACH in bedrooms with heating off, mean (±SD) †	0.28 (± 0.11)	0.29 (± 0.19)
ACH in bedrooms with heating on, mean (±SD) †	1.16 (± 0.11)	1.29 (± 0.27)
ACH in living areas with heating off, mean (±SD) †	0.73 (± 0.18)	0.64 (± 0.22)
ACH in living areas with heating on, mean (±SD) †	1.60 (± 0.12)	1.68 (± 0.30)
Volume of bedrooms m^3, mean (±SD) †	29.9 (± 4.8)	28.2 (± 4.0)
Volume of living areas m^3, mean (±SD) †	70.9 (± 9.8)	66.1 (± 7.9)
Information on occupancy and TB Status of occupants-determined from cohort of 695 villagers ††		
Number of persons per dwelling, mean (±SD)	5.3(± 3.0)	5.0 (± 2.8)
Occupants per room, mean (±SD)	0.9(± 0.5)	1.0 (± 0.5)
Dwelling where at least 1 occupant had TB disease, N(%)	6 (33.3%)	41 (23.0%)
at least 1 occupant with smear-positive TB, N(%)	1 (5.6%)	10 (5.9%)

ACH, air changes per hour; SD, standard deviation

Occupant defined as person residing in the dwelling; Visitor defined as someone who visits the dwelling at least once weekly but does not reside there.

† Denominators exclude 7 dwellings that were not used for social activities for which information on housing characteristics could not be determined.

†† Data on number of persons per dwelling missing for 2 dwellings used for social activities. Data on number of rooms in the dwelling missing for 19 dwellings that were not used for social activities.

Methods Supplement

Section 1. Questionnaire data

Administered questionnaires assessed nutrition, housing, socio-economic and lifestyle factors.[1] Parents provided responses for children under the age of 12.

- *Smoking status*: was assigned based on responses on a self-administered questionnaire completed only by adult participants, and serum cotinine [2,3] which was measured in all (children and adults).

- *Annual personal income*: participants were asked to classify their annual personal income into one of three categories: less than $20,000; $20,000-40,000; or greater than $40,000. For participants under the age of 18, the annual personal income of the parent or guardian was used.

- *Identification of dwellings used for social activities:* The addresses of these houses were provided to the research team by community members and clinic staff. All other dwellings were classified as “not used for social activities”.

- *Visiting of dwelling:* In one section, participants were asked to list three dwellings they visited at least once weekly; this information was used to determine if they had visited one of the dwellings used for social activities, at least one weekly.

- *Identification of dwellings where visitors could have been exposed to someone with active TB*: We used two methods to identify dwellings where study participants could have been exposed to someone with active TB. From the questionnaires completed by

participants with confirmed or probable active TB, we determined which dwellings they visited at least weekly. From data collected as part of medical and public health investigations, we identified the addresses of where all persons diagnosed with confirmed or probable TB had lived between November 2011 and November 2012.

Section 2. Housing & ventilation assessment

Data on the year of construction, heating method, dwelling type, and layout were provided by the two municipal/regional institutions which owned these dwellings. Room dimensions were measured by study personnel and verified using floor plans provided by the housing bureau.

"Ventilation" is defined as the exchange of indoor air for outdoor air per unit of time. In the community where the study was undertaken, nearly all dwellings are heated using "forced air" (also called "pulsed air") heating systems — when the heating system is on and the temperature is lower than the thermostat setting, outdoor air is heated and delivered indoors; as a result, ventilation is higher compared to when the heating is off. (The exceptions to use of forced air systems are apartments, which are heated using radiators.) Because of this, we measured ventilation with heating off and with heating on. Measurements were taken in at least one bedroom (where the participant slept) and in the common living area (this was the living room and the kitchen in all houses visited).

To measure ventilation, all windows and doors were closed – including doors leading to all indoor rooms and doors leading to the outside. Pure CO_2 was used as a tracer gas [5,6] and released at a high rate to achieve a peak of 1500ppm above baseline (corresponding, on

average, to a release time of 6 seconds/m^2 in bedrooms, and 9 seconds/m^2 in living areas). Two motorized fans were used throughout the release and measurement to ensure mixing of CO_2 throughout the entire room. CO_2 was measured continuously with a portable device with electro-chemical detectors (Q-Trak Plus, TSI) which logged the concentration every minute. Recordings were taken for a total of 20 minutes. During the recording, study staff noted if any doors or windows were opened, the number of people present, and the number of people entering or leaving.

Because CO_2 concentration falls at an exponential rate, the following equation is used to calculate ventilation based on the changes in CO_2 concentration over time ("Standard Test Method for Determining Air Change in a Single Zone by Means of a Tracer Gas Dilution," ASTM E741-11):

$$\ln[CO_2]_i(t) = [CO_2]_0 - \beta * t_i$$

where $[CO_2]_i(t)$ is the concentration at time i, $[CO_2]_0$ is the CO_2 concentration at time zero, and β is air changes per hour (ACH), which is the number of times in one hour that the total volume of air in a room is replaced by air from outside the room.

The above relationship is applicable if CO_2 concentration has reached equilibrium throughout the room. We took several precautions to ensure that CO_2 measurements were at equilibrium when calculating ventilation. First, as mentioned earlier, two fans were running during CO_2 release and measurement to ensure mixing of air. Second, CO_2 recordings during the first three minutes of measurement were discarded. Third, we also discarded CO_2 measurements that

were outliers and unduly influencing the ACH; this was done using simple linear regression (with ln[CO_2] as the dependent variable, and time as the independent variable) to identify observations with Cook's distance greater than 4/n (where n is the number of CO_2 measurements) [7].

Dwellings in this community are grouped into five main types, each of which has between one and 3 sub-types. Dwellings of the same type share similar construction characteristics and layouts; sub-types differ in size and room number. We prioritized taking ventilation measurements in dwellings where persons with active TB had lived and dwellings of the same type as the gathering houses. When ten measurements had been performed in the most common sub-types, we performed an interim analysis of ventilation data to decide whether we had enough measurements for each sub-type. This was based on an analysis of the variance between and within buildings- when the variance of ventilation measurements between different buildings of the same sub-type was less than the variance of repeated measurements within the same building, we concluded we did not need further measures in buildings of that type. For all subsequent participants who lived in buildings of that type, they were assigned model-specific average ventilation measures (average values of all ventilation measurements from all buildings of that type). If ventilation was measured in the dwelling of a participant, these directly measured values were assigned to that participant.

Air change rates were estimated by analyzing the CO_2 recordings using multi-level multivariable regression, with ln[CO_2] as the dependent variable and time as the independent variable whose estimated slope is the ACH. These models included interaction terms to account for the effects

on ventilation of the room (living area vs bedrooms) and heating condition (on vs off), as well as a random-effect for the ACH between dwellings. This approach had several advantages. First, it ensured that dwelling-specific ACH estimates accounted for the variance of the ACH measurement in each dwelling. Second, all recordings from dwellings of the same type were used to estimate a weighted average ACH for each type. Third, multi-level regression allowed us to adjust for the number of persons who were present during the recording- this was important because people are sources of CO_2, and the presence of a continuous source of CO_2 release during the recording would slow the rate of decline in CO_2 concentration, and if not controlled for, would lead to underestimation of ventilation.

Four ACH estimates were calculated for each dwelling: with heating off in living areas, with heating on in living areas, with heating off in bedrooms, and with heating on in bedrooms. These ACHs were calculated as the sum of: the weighted average ACH of dwellings of the same type and the applicable interaction terms for the effects of the room and heating status (also for dwellings of the same type). For dwellings where ACH was directly measured, we also added the dwelling's random effect estimate.

Section 3. Details on statistical methods

a. Analysis of ventilation as a risk factor for TB infection and disease: We analyzed the ventilation level in the common living area of participants' dwellings — since all household occupants shared these areas, and many occupants slept in these areas. The maximal ventilation (with heating on) and the minimal ventilation (with heating off) were analyzed separately.

b. Multivariable modeling: For adjusted analyses we used the method of generalized estimating equations for logistic regression, with clustering at the dwelling level. For each objective, we first calculated univariable odds ratios (OR) for: (1) characteristics of the participant's dwelling (method of heating, occupancy, ACH, and room volume of the living area); (2) variables related to potential exposures to persons with TB (at least weekly visiting a dwelling that was used for social activities [yes vs. no], and having lived with someone who had smear-positive TB [yes vs. no]); and, (3) characteristics we considered well-established determinants of TB (age, gender, cigarette smoking, and socioeconomic status). In our preliminary multivariable model, we included all variables associated in univariable analysis with a p-value <0.5. Using a step-wise approach we excluded variables if their removal improved the multivariable model's fit as indicated by a lower quasi-likelihood information criterion (QICu) [8]. This approach was taken in order to minimize over-specification given our limited sample size. For the first objective, we hypothesized that occupancy would only be associated with risk of infection in dwellings inhabited by smear-positive persons, and assessed this in univariable analysis using stratification, and in multivariable analysis by including an interaction term. Interactions were considered significant if their associated p-values were <0.05. For disease, the interaction term was kept in our final model despite an increase QICu because it was statistically significant, and for consistency with our model for infection. We considered associations to be significant if the 95% confidence interval (95% CI) of the odds ratios excluded 1.0.

References Methods Supplement

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