Quantification of Shared Air: A Social and Environmental Determinant of Airborne Disease Transmission

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation
Wood, Robin, Carl Morrow, Samuel Ginsberg, Elizabeth Piccoli, Darryl Kalil, Angelina Sassi, Rochelle P. Walensky, and Jason R. Andrews. 2014. “Quantification of Shared Air: A Social and Environmental Determinant of Airborne Disease Transmission.” PLoS ONE 9 (9): e106622. doi:10.1371/journal.pone.0106622. http://dx.doi.org/10.1371/journal.pone.0106622.

Published Version
doi:10.1371/journal.pone.0106622

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:12987408

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Quantification of Shared Air: A Social and Environmental Determinant of Airborne Disease Transmission

Robin Wood1, Carl Morrow1, Samuel Ginsberg2, Elizabeth Piccoli1, Darryl Kalil1, Angelina Sassi1, Rochelle P. Walensky3, Jason R. Andrews4
1 Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine, and Department of Medicine, University of Cape Town Faculty of Health Sciences, Cape Town, South Africa, 2 Department of Electrical Engineering, Faculty of Engineering & the Built Environment, University of Cape Town, Cape Town, South Africa, 3 Center for AIDS Research, Harvard Medical School, Boston, Massachusetts, United States of America, 4 Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, California, United States of America

Abstract

Background: Tuberculosis is endemic in Cape Town, South Africa where a majority of the population become tuberculosis infected before adulthood. While social contact patterns impacting tuberculosis and other respiratory disease spread have been studied, the environmental determinants driving airborne transmission have not been quantified.

Methods: Indoor carbon dioxide levels above outdoor levels reflect the balance of exhaled breath by room occupants and ventilation. We developed a portable monitor to continuously sample carbon dioxide levels, which were combined with social contact diary records to estimate daily rebreathed litres. A pilot study established the practicality of monitor use up to 48-hours. We then estimated the daily volumes of air rebreathed by adolescents living in a crowded township.

Results: One hundred eight daily records were obtained from 63 adolescents aged between 12- and 20-years. Forty-five lived in wooden shacks and 18 in brick-built homes with a median household of 4 members (range 2–9). Mean daily volume of rebreathed air was 120.6 (standard error: 8.0) litres/day, with location contributions from household (48%), school (44%), visited households (4%), transport (0.5%) and other locations (3.4%). Independent predictors of daily rebreathed volumes included household type (p = 0.002), number of household occupants (p = 0.021), number of sleeping space occupants (p = 0.022) and winter season (p < 0.001).

Conclusions: We demonstrated the practical measurement of carbon dioxide levels to which individuals are exposed in a sequence of non-steady state indoor environments. A novel metric of rebreathed air volume reflects social and environmental factors associated with airborne infection and can identify locations with high transmission potential.
Carbon dioxide (CO₂) is a natural tracer gas produced during normal human respiration. Exhaled breath contains approximately 40 000 parts per million (ppm) of CO₂ compared with approximately 400 ppm in outdoor air [23]. Our study location in Masiphumelele, a township located 40 km from Cape Town, had an average level of 390.8 ppm of CO₂ in 2012 (IQR: 389.5–391.47) [24]. In the absence of other sources, indoor CO₂ levels reflect exhaled breath (respiration) and air exchange (ventilation) [6,25,26]. Rudnick and Milton demonstrated that measuring “excess” CO₂ in indoor air can be used to estimate the fraction of air in each inhalation that has been exhaled from other room occupants, and that the “rebreathed fraction” can estimate risk of infection with airborne particles [25]. The equation derived by Rudnick and Milton expanded upon the work of Wells and Riley and used rebreathed fraction to substitute for the more difficult analysis of room ventilation and size. We postulated that the sum of rebreathed air volumes (RAV) from others during normal indoor activities would allow quantification of the social and environmental factors impacting TB transmission. We therefore developed a portable CO₂ logging device to continuously measure the levels of CO₂ to which township adolescents were exposed and to thereby determine RAV in all visited indoor locations during a 24-hour period.

Materials and Methods

CO₂ and Global Positioning System logger

A portable logger [Figure 1] was designed to measure CO₂ concentration, temperature and humidity every 60 seconds, using the COZIR Ambient 0–1% transducer (Gas Sensing Solutions Ltd, Glasgow, United Kingdom, http://www.cozir.com/), together with location data captured from a global positioning system (GPS) receiver and time from an onboard, independently powered clock. The logger’s dimensions were 10 x 6 x 2.5 centimetres and component costs were approximately $250.

![Portable logger diagram](image)

**Figure 1.** Portable logger to measure CO₂ concentration, temperature and humidity. An internal view of the portable personal CO₂ logger incorporated a COZIR Ambient 0–1% transducer (Gas Sensing Solutions Ltd., Glasgow, United Kingdom), GPS sensor, independent power supply and USB interface. Unit dimensions were length 10 cm, width 6 cm and depth 2.5 cm.

do:10.1371/journal.pone.0106622.g001

The data are delivered to the microcontroller device in serial digital format, which is then stored on flash memory. The microcontroller device can then retrieve flash memory data, on demand, for uploading to a computer via a Universal Serial Bus (USB) port. The logger is powered by Nickel Metal Hydride (NiMH) batteries and includes circuitry for recharging from external power sources. For safety purposes, the electronic circuitry is fused to prevent current in either discharge or charge mode from exceeding safe limits. In addition, a thermostat device has been incorporated to cut the battery from the circuit should battery temperature exceed 70 degrees Celsius. The accuracy of CO₂ measurements taken by the sensor is ±50 ppm or 3% of each reading (www.cozir.com).

Time-location diary

A time-location diary was provided to all participants to capture daily routine data including date, location type, time of arrival and departure, and numbers of individuals present for all locations visited. Each diary was filled out continuously, and a field worker clarified incomplete diary entries. The diaries were then entered into a database and were later rechecked by a research assistant. Twenty location types were aggregated to 5 major location categories for data analysis: school/work (daytime activity), transport, own home, other household, and other places. This instrument had been previously used for a social contact study in this community [19].

Air sampling

Participants underwent training on how to use and recharge the logger, and complete the diary. The logger was attached to a provided lanyard (~50 cm) or worn in a waist pocket during a 48-hour period. Participants were instructed not to breathe directly into the logger. Sets of more than 1 100 logged environmental data points recorded during any 24-hour period were used in subsequent analyses.

Pilot study

A pilot study established the practicality of carrying the logger for 48 hours, including position on person, battery recharging procedures and recording of location data in the diary. A heterogeneous sample (15 females and 2 males) with a median age of 39-years (range: 21–63 years) was recruited from the clinical, research and secretarial staff of the Desmond Tutu HIV Centre at the University of Cape Town. The subjects provided 29 daily records with an overall mean RAV of 58.6 [standard error (SE) 11.4] litres per day [Figure 2]. Volume contributions by location were highly variable; mean RAV in transport was 7.1 (SE 3.4) litres per day but with up to 83.5 litres per day recorded in public transport. The location contributions to daily-RAV were 12.4% for transport, 50.3% for own and visited households, 26.8% for workplace and 10.4% for various other locations. The pilot study population was a low TB risk group as no TB diagnoses had been made in the prior 10 years.

Adolescent study population

A high-TB risk study population of 63 adolescents (37 female, 26 male) with a median age of 17-years (range: 12–20 years) was recruited at the Desmond Tutu Youth Centre in Masiphumelele, Cape Town; a poor community where the annual TB notification rate exceeds 2000 cases per 100 000 [27].
Data processing and analysis

The data were downloaded as text files and entered into a customised Microsoft Access database. The diary data and times were aligned with the CO₂ values and corresponding times recorded by the CO₂ logger. The time period of interest was identified and the rebreathed values were calculated against the lowest CO₂ value measured in the 24-hour time period. Small gaps in the environmental data capturing were observed and these were filled using an automated algorithm that identified gaps in the trace of more than one minute in length, averaged the starting and ending rebreathed values, multiplied the result by the period of the gap to estimate rebreathed air during the gap. This value was distributed between the beginning and end point of the gap.

Rebreathed proportions were calculated using Rudnick and Milton's equation as shown [25]:

\[ f = \frac{C - C_o}{C_a} \]  

Where \( f \) is equivalent to the fraction of air that is exhaled breath, \( C \) is the observed concentration of CO₂ in the indoor air, \( C_o \) is the concentration of CO₂ in the outdoor air and \( C_a \) is the concentration of CO₂ in the exhaled air (estimated from literature) [23]. In other words, the proportion of air that is being rebreathed can be estimated from the excess carbon dioxide observed in the room, divided by the concentration of carbon dioxide in exhaled breath. The outdoor CO₂ values were defined by the minimum recorded value from each 24-hour record set. For persons at low levels of physical activity, \( C_a \) was estimated to be 38,000 ppm based on a CO₂ production rate of 0.31 litres/minute and respiratory minute volume of 8.0 litres/minute [23].

The recorded number of people present in the indoor location was used to estimate the rebreathed proportion from other people:

\[ f_0 = f \times \frac{(n - 1)}{n} \]  

Here, \( n \) is the number of people recorded at the indoor location (including the participant). RAV for each 60-second time-period was calculated from the product of \( f_0 \) and the minute respiratory volume, \( p \) (8 liters per minute), and summed over all observations:

\[ \text{Rebreathed Air Volume} = \sum_{t=1}^{j} p f_0(t) \]  

Thus, continuously recorded ambient CO₂ values [Figure 3A] can be transformed (using equations 1 and 2) into continuous
measures of rebreathed (shared) air at different visited locations [Figure 3B]. The RAV for any time-period was the sum of the 60-second rebreathed volumes accruing in that time period equal to the area under the curve of rebreathed air for the time-period of interest [Figure 3B].

We examined determinants of RAV through linear, mixed-effects, multilevel bivariate and multivariate models, including age, sex, housing type (shack/brick), season, and the number of individuals in household and sleeping space. To account for correlation in multiple, nested observations of the same individual on different days, we used a two-level model with individuals and observations. Season was dichotomized into colder months (May-October) and warmer months (November-April).[28] Because rebreathed litres were non-normally distributed, we log-transformed rebreathed litres, which reduced the skewness and kurtosis and improved the normality of the regression residuals. We further examined residual plots for the predicted, transformed dependent variables. For multivariable analyses, we used Allen-Cady, modified backward selection procedure. In this procedure, we pre-specified forced variables for inclusion (age and sex) and then used a threshold p-value of 0.20 for removal of variables of least importance. Ultimately, all considered variables were found to be under this p-value threshold and were retained [29]. We calculated conditional goodness-of-fit for the mixed-effects model using the approach of Nakagawa and Schielzeth [30]. We also used a multilevel model as above to compare rebreathed litres between adults (pilot study) and students. Statistical analyses were performed using Stata 11.0 (StataCorp, College Station, Texas, USA).

Ethics Statement
For adults, written informed consent for participation in the study was obtained while for minors, written informed assent was obtained along with written informed consent from a parent or guardian. The Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town approved the study.

Results
Township adolescent study
Subjects were all residents of the township, and 45 (71%) lived in a wooden shack and 18 (29%) in brick-built house. The median household size was 4 individuals (range: 4–9) and the median number of individuals sharing sleeping quarters was 2 (range: 1–5). Subjects recorded a total of 108 daily records with a median

Figure 3. Figure 3 A: Ambient parts per million of CO₂ recorded at minute intervals by the logging device carried by a subject during a 24-hour period. Figure 3 B: Litres per minute of rebreathed air with additional allocation to specific locations. Litres per minute of rebreathed air were calculated for a 24-hour period (transformation from ambient CO₂ levels in Figure 2A) and additionally allocated to specific locations using diary and GPS information. The volume of rebreathed shared air is represented by the area under the curve for each location visited and the daily rebreathed volume is the sum of all volumes at all locations visited.
doi:10.1371/journal.pone.0106622.g003
volume of air rebreathed from others of 120.6 [standard error (SE) 8.0] litres per day [Figure 2] with location contributions from own household (48%), school (44%), visited households (4%), transport (0.5%) and other locations (3.5%). While all participants rebreathed air in households every day [59.5 (SE 7.3) litres per day], only 81% (67/108) of recorded days included school attendance, with a mean RAV of 63.1 (SE 5.4) litres per day. Public transport contributed only 0.3% of total RAV of study participants as only 9 adolescents used public transport (12 recorded days) with a mean of 3.8 (SE 0.7) litres in transport per day.

Calculations of mean RAV per hour for each location type were conducted to determine the relative risk in each environment. A mean RAV of 11.5 litres per hour (SE 0.07) was recorded in schools, a mean RAV of 6.3 litres per hour in transport (SE 0.25), a mean RAV of 4.4 litres per hour in households (SE 0.02) and a mean RAV of 5.0 litres in other places (SE 0.09).

Twenty-four adolescents recorded 20 summer weekday records with a mean RAV of 79.2 (SE 9.2) litres per day and 39 adolescents recorded 65 winter weekday records with a mean RAV of 147.1 (SE 10.5) litres per day [Figure 4] (p = 0.008). The mean number of daily contacts in summer (16.9) and winter (14.34) did not differ (p = 0.76). However, the mean time spent indoors was higher in the winter (22.2 hours) than in the summer (19.4 hours) (p < 0.001).

In order to establish if alternative locations visited during weekends might contribute to total rebreathed litres, 8 of the subjects completed 15 weekend daily records. Mean weekend litres per day (82.6; SE 20.7) were considerably lower than on weekdays (147.12; SE 10.55), with own (82%) and visited households (10%) the major contributing locations.

In multivariable analysis of the 108 adolescent daily records (Table 1), log RAV per day increased 8% per year of age, increased 14% per added household occupant, increased 17% per additional occupant of sleep space, was 77% higher in winter months and 43% lower in shacks compared with brick dwellings. The median and distribution of RAV at each indoor location are shown in Figure 4, demonstrating increased rebreathing of air in all locations during winter months with greatest impact on household and school. School was the major location of RAV contributing a mean of 77.6 litres per day in winter months.

**Discussion**

The transmission of communicable diseases is understood to be a function of social contact rates and the probability of transmission per contact. Recent studies have illuminated some of the structure and heterogeneity of social contacts [19–22], however, there have been few data on the role of the indoor environment for airborne infections which, as Wells and Riley demonstrated, is a key determinant of transmission [12,13].

Virtually all studies examining environmental risk for tuberculosis focus on households or outbreaks in single environments (e.g. commercial airliners, hospitals). However, studies from Cape Town and Lima have demonstrated that a minority of tuberculosis transmission occurs within households [7,8]. It has remained unclear where most transmission occurs in endemic settings. In this paper, we demonstrated the measurement of a simple metric—RAV—that integrates social contact and environmental data pertinent to transmission of small particle airborne infections.

We have demonstrated that it is practical to continuously measure ambient CO2 concentrations surrounding an individual and thereby estimate the RAV rebreathed from others during normal daily activities. Our approach extends the work of Wells [12], Riley [13], and Rudnick [25] by enabling quantitation of exposure to infected air in multiple non-steady state environments. The sum of the contributions from all visited indoor locations allowed estimation of total daily RAV from others. Adolescents living in a high TB-burdened community recorded very large daily volumes of rebreathed air, such that calculated annual RAV would reach between [IQR] 20 000 to 65 000 litres. Township adolescents had higher RAV compared with our pilot study adults (p<0.0001).

We were able to allocate 93% of rebreathed air to 4 locations: own home, visited homes, transport and work or school. These results corroborate findings of an earlier social mixing study performed in this community in 2010, which reported that 97% of indoor time was spent in these locations. [22] Public transportation use was minimal in this largely local school-attending adolescent population for whom school and household locations contributed the majority of RAV. The daily RAVs were nearly twice as high in the colder winter months than during summer months. The contact rates were comparable between seasons and time spent indoors in winter was only 14% higher, together indicating that increased RAVs were predominantly a result of reduced ventilation, presumably because of need for heat conservation (i.e. closed windows) in cold weather. While there is presently no data on the seasonality of TB infection, our findings may be compatible to the observed seasonality of TB disease in South Africa [31].

While earlier work has examined the role of socio-demographic contact structure in tuberculosis transmission, the role of the indoor environment has not been factored into models of endemic transmission [32].

We propose that the daily RAV may be a useful surrogate marker for the social and environmental components of TB transmission that have been so long recognised but not quantified [9–11,14]. Both the number of individuals within indoor locations and the prevailing environmental ventilation conditions impacts RAV. For an airborne disease such as TB, it is biologically plausible that the total volume exchanged with others would be a major determinant for transmission and acquisition of TB infection [33], which is also consistent with the approaches of Wells [13], Riley [14], Rudnick [25], and others [15–20]. The number of secondary active cases generated by an average person with TB in a susceptible population (the basic reproductive number, R_0) is a fundamental epidemiologic driver of TB epidemics [33]. High-RAV may therefore be a major component maintaining high levels of TB transmission in endemic township populations in Southern Africa [34].

There are several limitations to our study. The major assumption underlying the use of concentrations of inspired CO2 as a surrogate for expired air and infection risk is that the
rather than CO2 absorption or other forms of removal, is the
dominant driver of CO2 removal from indoor settings [23]. The
development of a CO2-based approach to quantify shared
occupant air has great potential as a tool to inform
counts and other respiratory infection risk, which will require larger
studies. Continuous monitoring of CO2 and subsequent quanti-
fication of rebreathed air has great potential as a tool to inform
public health interventions targeted at reducing the transmission of
airborne respiratory diseases.

**Conclusions**

In summary, we have demonstrated the practical measurement
of CO2 over time in a sequence of non-steady state indoor
environments, which, combined with data on number of room
occupants, enabled the estimation of daily RAV from others. This
approach enables comparison of composite social and environ-
mental risk between individuals, settings, and exploration of the
determinants of risk (e.g., season). In adolescents residing in a high
burden community, this revealed marked variability in RAV
between individuals and locations. Future work will be needed to
validate this metric by assessing its ability to predict tuberculosis
and other respiratory infection risk, which will require larger
studies. Continuous monitoring of CO2 and subsequent quanti-
fication of rebreathed air has great potential as a tool to inform
public health interventions targeted at reducing the transmission of
airborne respiratory diseases.

**Supporting Information**

**Data file S1**  Rebreathed air volume data.

**Author Contributions**

Conceived and designed the experiments: RW CM SG. Performed the
experiments: CM SG EP DK AS. Analyzed the data: CM EP DK AS JRA.
Contributed to the writing of the manuscript: RW CM SG DK AS RPW
JRA.
References

1. World Health Organization (2012) Global Tuberculosis Report 2012. Geneva, Switzerland: WHO; available at http://www.who.int/tb/publications/global_report/gtr12_main.pdf (15 October 2013, date last accessed).

2. Wood R, Lawn SD, Caldwell J, Kaplan R, Middelkoop K, et al. (2011) Burden of new and recurrent tuberculosis in a major South African city stratified by age and HIV status. PLoS ONE 6(10):e25098.

3. Kritzinger FE, den Boon S, Verver S, Evanson DA, Lombard CJ, et al. (2009) No decrease in annual risk of tuberculosis infection in endemic areas in Cape Town, South Africa. Trop Med Int Health 14(2):136–42.

4. Middelkoop K, Bekker LG, Myer L, Dawson R, Wood R (2008) Rates of tuberculosis transmission to children and adolescents in a community with a high prevalence of HIV infection among adults. Clin Infect Dis 47(3):349–55.

5. Wood R, Liang H, Wu H, Middelkoop K, Oui T, et al. (2010) Changing prevalence of TB infection with increasing age in high-TB burden towns in South Africa. Int J Tuberc Lung Dis 14(4):406–12.

6. Middelkoop K, Bekker LG, Liang H, Aquino LD, Sebastian E, et al. (2011) Force of tuberculosis infection among adolescents in a high HIV and TB prevalence community: a cross-sectional observation study. BMC Infect Dis 11: 136.

7. Verver S, Warren RM, Munch Z, Richardson M, van der Spuy GD, et al. (2004) Proportion of tuberculosis transmission that takes place in households in a high-incidence area. Lancet 363(9404):212–14.

8. Brooks-Pollock E, Becerra MC, Goldstein E, Cohen T, Murray MB (2011) Tuberculosis transmission to young children in a South African commercial airliner. Risk Anal 24(2):379–88.

9. Riley RL, Wells WF, Mills CC, Nyka W, McLean RL (1957) Air hygiene in patient care areas in hospitals. Description of a new protocol. Am J Respir Crit Care Med 14(2):420–31.

10. Reider HL (1999) Socialization patterns are key to the transmission dynamics of tuberculosis. Int J Tuberc Lung Dis 3(3):177–78.

11. Chapman JS, Dyerly MD (1964) Social and other factors in intrafamilial transmission of tuberculosis. Am Rev Respir Dis 90: 48–60.

12. Reynolds SA, Schlesinger WH (1992) The global carbon dioxide flux in soil ecosystems. Cambridge (MA): Harvard University Press.

13. Riley RL, Wells WF, Mills CC, Nyka W, McLean RL (1957) Air hygiene in tuberculosis: quantitative studies of infectivity and control in a pilot ward. Am Rev Tuberc 75(3):201–17.

14. Chapman JS, Dyerly MD (1964) Social and other factors in intrafamilial transmission of tuberculosis. Am Rev Respir Dis 90: 48–60.

15. Cantarafo A (1982) Nosocomial tuberculosis. Am Rev Respir Dis 125(3):599–62.

16. Ko G, Thompson KM, Nardell EA (2004) Estimations of tuberculosis risk on a commercial airliner. Risk Anal 24(2):379–88.

17. Neales CJ, Sleigh PA (2009) Mathematical models for assessing the role of airflow on the risk of airborne infection in hospital wards. J R Soc Interface 6: 791–800.

18. Furuya H, Naganine M, Watanabe T (2009) Use of a mathematical model to estimate tuberculosis transmission risk in an Internet café. Environ Health Prev Med 14(2):96–102.

19. Wood R, Johnstone-Robertson S, Uys P, Hargrove J, Middelkoop K, et al. (2010) Tuberculosis transmission to young children in a South African community: modeling household and community infection risks. Clin Infect Dis 51(4):401–8.

20. Johnstone-Robertson S, Lawn SD, Welte A, Bekker L-G, Wood R (2011) Tuberculosis in a South African prison - a transmission modeling analysis. S Afr Med J 101(11):899–103.

21. Johnstone-Robertson S, Mark D, Morrow C, Middelkoop K, Bekker L-G, et al. (2011) Social mixing patterns within a South African township community: implications for respiratory disease transmission and control. Ann J Epidemiol 174(11):1246–55.

22. Wood R, Racow K, Bekker L-G, Morrow C, Middelkoop K, et al. (2012) Indoor social networks in a South African township: potential contribution of location to tuberculosis transmission. PLoS One 7(6):e39266.

23. Emmerich SJ, Persily AK (2003) State-of-the-art review of CO2 demand controlled ventilation technology and application. National Institute of Standards and Technology; available at http://fire.nist.gov/bfrlpubs/build01/PDF/b011117.pdf (19 December 2013, date last accessed).

24. South African Weather Service (2012) CO2 Cape Point – SAWS. Stellenbosch, South Africa: World Data Centre for Greenhouse Gases; available at http://ds.data.jma.go.jp/gmd/wdgg/cgi-bin/wdgg/accessdata.cgi?index=CIPT134S00-SAWS&param=200612120113&select=parameter&parac=observation (19 December 2013, date last accessed).

25. Rudnick SN, Milton DK (2003) Risk of indoor airborne infection transmission estimated from carbon dioxide concentration. Indoor Air 13(3):237–45.

26. Chaumont F (1874) On the theory of ventilation: an attempt to establish a positive basis for the calculation of the amount of fresh air required for an inhabited airspace. Proc R Soc Lond; 23: 187–201.

27. Middelkoop K, Bekker L-G, Myer L, Johnson LF, Kloos M, et al. (2013) Antiretroviral therapy and TB notification rates in a high HIV prevalence South African community. J Acquir Immune Defic Syndr 63(3):263–69.

28. Average maximum and minimum monthly temperature for Cape Town. World weather on line; available at http://www.worldweatheronline.com/Cape-Town-town/weather-Western-Cape/ZA.aspx (16 October 2013, date last accessed).

29. Vittinghoff E, Glidden D, Shiboski S, McCulloch C (2004) Regression Methods in Biostatistics. New York: Springer.

30. Nakagawa S, Schielzeth H (2013) A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods Ecol Evol 4: 133–142.

31. Martineau AR, Nhamoyebonde S, Oni T, Rangaka MX, Marais S, et al. (2011) Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa. Proc Natl Acad Sci U S A 108(47):19013–17.

32. Guzzetta G, Ajelli M, Yang Z, Merler S, Furlanello C, et al. (2011) Modeling socio-demography to capture tuberculosis transmission dynamics in a low burden setting. J Theor Bio 289: 197–205.

33. Reider HL (1999) Epidemiological basis of tuberculosis control. Paris: International Union Against Tuberculosis and Lung Disease.

34. Wood R, Lawn SD, Johnstone-Robertson S, Bekker L-G (2011) Tuberculosis control has failed in South Africa - time to reappraise strategy. S Afr Med J 101(2):111–14.

35. American Society for Testing and Materials (1990) Standard Guide for Using Indoor Carbon Dioxide Concentrations to Evaluate Indoor Air Quality and Ventilation. West Conshohoken, PA: American Society for Testing and Materials. D6245–98.

36. Menzies R, Schwartzman K, Loo V, Pasztor J (2005) Measuring ventilation of residential buildings. West Conshohoken, PA: American Society for Testing and Materials. D6245–98.

37. Raich JW, Schlesinger WH (1992) The global carbon dioxide flux in soil respiration and its relationship to vegetation and climate. Tellus 44(2):81–99.