

## **Tuberculosis transmission in public locations in Tanzania: a novel approach to studying airborne disease transmission**

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**Abbreviations:**

CI	Confidence interval
CO <sub>2</sub>	Carbon dioxide gas
HCF	Health Care Facility
Mtb	<i>Mycobacterium tuberculosis</i>
PPM	Parts per million
SD	Standard deviation
TB	Tuberculosis
WHO	World Health Organization

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## ABSTRACT

**Objectives** – For tuberculosis (TB) transmission to occur, an uninfected individual must inhale the previously infected breath. Our objective was to identify potential TB transmission hotspots in metropolitan city of Dar es Salaam, Tanzania and to model the annual risk of TB transmission in different locations of public importance.

**Methods** – We collected indoor carbon dioxide (CO<sub>2</sub>) data from markets, prisons, night clubs, public transportation, religious and social halls, and from schools. Study volunteers recorded social contacts at each of the locations. We then estimated the annual risks of TB transmission using a modified Wells-Riley equation for different locations.

**Results** – The annual risks of TB transmission were highest among prison inmates (41.6%) and drivers (20.3%) in public transport. Lower transmission risks were found in central markets (4.8% for traders, but 0.5% for their customers), passengers on public transport (2.4%), public schools (4.0%), nightclubs (1.7%), religious (0.13%), and social halls (0.12%).

**Conclusion** – For the first time in a country representative of sub-Saharan Africa, we modelled the risk of TB transmission in important public locations by using a novel approach of studying airborne transmission. This approach can guide identification of TB transmission hotspots and targeted interventions to reach WHO's ambitious End TB targets.

## BACKGROUND

One quarter of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (Mtb).<sup>1</sup> Transmission of Mtb occurs when uninfected persons inhale infectious droplet nuclei from the infected.<sup>2</sup> Droplet nuclei with diameters of 1 to 5  $\mu\text{m}$  can remain suspended in air for many minutes to hours,<sup>3</sup> thus making Mtb highly transmissible in overcrowded locations with poor ventilation. For this and other reasons, tuberculosis (TB) remains a major public health problem worldwide.

One way to estimate the risk of TB transmission begins with measuring environmental levels of carbon dioxide (CO<sub>2</sub>) levels.<sup>4,5</sup> CO<sub>2</sub> levels combined with social contact data allow calculation of the volumes of rebreathed air in order to estimate the potential for airborne disease transmission.<sup>6</sup> A modified Wells and Riley equation can be used to estimate TB transmission, taking into account the re-breathed air fraction (estimated from indoor and outdoor CO<sub>2</sub> levels), time at risk, the infectious dose (quanta of contagion), and the number of people occupying the confined space.<sup>4,6,7</sup>

Until recently, only studies from Cape Town, South Africa have used this approach. Additional studies in settings more representative of sub-Saharan African countries, which have the highest burden of TB, are needed. We therefore studied potential TB transmission hotspots in metropolitan Dar es Salaam, Tanzania using this novel, CO<sub>2</sub>-based approach to model the risk of TB transmission as the basis for planning intervention studies.

## METHODS

### Study locations and design

We used exposure assessment methods in Dar es Salaam where 22% of 62,952 new TB cases in Tanzania were notified in 2013, making the city a TB hotspot.<sup>8</sup> Adult volunteers carried CO<sub>2</sub> monitors to locations of public importance, and they also recorded the time spent and the number of people at each location. Volunteers collected data between February 2015 and August 2015. We did not include health care facilities (HCF), as waiting rooms are usually open-air in Tanzania and as a study from South Africa indicated that the contribution of HCFs to the annual risk of TB transmission was small with indoor contact accounting only 0.5% of all contacts.<sup>9</sup> We obtained written permission from the Ministry of Health and Social Welfare through the National Tuberculosis and Leprosy Program to collect the infrastructure-related CO<sub>2</sub> data at public locations. In addition, the Ministry of Home Affairs (Tanzania Prisons) issued permission to enter prisons for data collection.

**Market.** The largest market in Dar es Salaam, known as Kariakoo, has an underground floor, which is populated daily by 100-180 people during each hour of the day. Most retail traders elsewhere in Dar es Salaam make wholesale purchases of agricultural products from this market.

**Prisons.** The two largest facilities in the Dar es Salaam region with over 1,000 inmates were included. One prison is a short-term facility for the temporarily remanded who awaits court rulings, while the other is a long-term correctional facility. While inmates are outdoors during the day, at night they share cells that are occupied by approximately 40 inmates. Prison guards placed the monitors in different cells during the night to collect CO<sub>2</sub> data in the facilities.

**Night clubs.** We collected data from eight of the largest popular nightclubs in the city

that prohibit indoor cigarette smoking. The night clubs were sound proof and relied upon alternative ventilation mechanisms such as closed air conditioning systems.

**Public transportation.** Public transportation in Dar es Salaam largely relies upon two commuter bus designs with carrying capacities of 15 to 22 and 32 to 40 passengers.

**Religious and social halls.** Religious halls consist of mosques and churches with open ventilation complemented by fans for cooling. Social halls, in contrast, have closed ventilation systems that rely on air conditioning, and they are used for family events such as wedding receptions.

**Schools.** We collected data from colleges and schools (day and boarding schools) in Dar es Salaam. The schools typically have open windows and no other type of ventilation. The classrooms hold 40 to 50 students in each room.

## **Data collection, definitions and statistical analysis**

We collected social contact data using standardized data collection forms (number of people and time at each location) and environmental CO<sub>2</sub> data from the monitors used in previous studies elsewhere.<sup>4,5,7</sup> The workflow for data collection is presented in Supplementary Figure 1. Volumes of rebreathed air were calculated based on indoor and outdoor CO<sub>2</sub> levels at specific times, and accounted for the number of people present and assumed a respiration rate of eight breaths per minute.<sup>4,5,10</sup> All analyses were performed in Stata software version 13.1 (Stata Corp; Texas, USA).

TB transmission risk was defined as the probability of an individual acquiring a primary infection that would result in formation of a Ghon complex in the lungs. Annual risk of transmission was defined as the probability of an individual acquiring a primary tuberculous infection in one year in a given location. We defined quantum as the number of infectious droplet required to infect 63.2% (i.e.,  $1 - e^{-1}$ ) of susceptible

individuals in a indoor environment.<sup>11</sup>

The calculation of shared rebreathed air (either as liter/minute or liter/hour) was based on environmental CO<sub>2</sub> data and the number of people present at a given location.<sup>5,10</sup> We studied the time spent at different locations with poor ventilation (CO<sub>2</sub> level  $\geq 1,000$  parts per million).<sup>7,10</sup> For continuous variables, we used the unpaired Student's *t*-test (two sided).

## Modelling the annual risk of TB transmission

We used the modified Wells-Riley considering the work of Rudnick Milton on non-steady state situations to estimate the annual risk of TB transmission.<sup>4,6,7</sup> We parameterized the Equations 1 (a-c) based on previously published assumptions<sup>5,7</sup> and based on data collected in this study (Supplementary Table 1). The annual risk (*AR*) of transmission was calculated as function of the time spent per year at a given location. We used 38,000 parts per million as the CO<sub>2</sub> levels in exhaled breaths (CO<sub>2</sub> breathed out).<sup>5,7</sup> Briefly, we calculated the risk of TB transmission at each time (*P*) by using equation 1a:

$$P = 1 - e^{\left(\frac{-flqt}{n}\right)} \quad \text{Equation: 1a}$$

Where rebreathed fraction,  $f = \frac{CO2\ indoor - CO2\ outdoor}{CO2\ breathed\ out}$

*P*, probability of TB transmission; *f*, rebreathed fraction; *l*, number of infectious individuals in space; *q*, rate of generation of infectious quanta; *t*, duration of exposure; *n*, total number of contacts met by one infectious person.<sup>4,6,7</sup>

Then we calculated the annual exposure time (*T*) at each location using equation 1b:

$$T = \sum_a C_a t_a \quad \text{Equation: 1b}$$

Where  $C_a$  is the annual number of visits at a given location, and  $t_a$  is the time spent during each visit at a given location.<sup>7</sup>

Finally the annual risk of TB transmission was determined by including the annual time of exposure (1a) in the instantaneous risk of transmission (1b), and is summarized in the final equation:

$$AR = 1 - e^{\left(\frac{-flqT}{n}\right)} \quad \text{Equation: 1c}$$

In summary, the calculation of the risk of transmission risk took into account (i) the time of exposure, (ii) the number of people at risk, (iii) the magnitude of infectious droplet generated, (iv) and the underlying prevalence of TB among people at risk.

## RESULTS

Prisons had the highest mean CO<sub>2</sub> level 1,892 ppm, followed by night clubs (1,488 ppm) and social halls (1,262.9 ppm). The lowest mean CO<sub>2</sub> levels were recorded in schools and religious halls (655 ppm and 629 ppm, respectively). Summary statistics for CO<sub>2</sub> levels in Dar es Salaam's largest market, prisons, nightclubs, public transportation, religious settings and social halls, and schools are further detailed in Table 1.

**Risk of TB transmission in the largest market.** The mean value (standard deviation) of rebreathed air inside the market was 0.05 (0.02) L/min. At mean CO<sub>2</sub> levels of 730 ppm, the annual risk of TB transmission for a trader and customer were 4.8% and 0.5%, respectively (Figure 1). The mean annual risk of TB transmission was significantly higher for traders than for customers (4.9%, 95% confidence interval [CI]: 4.77, 5.05%, vs. 0.49%, CI: 0.48, 0.51%;  $P < 0.001$ ; Figure 2).

**Risk of TB transmission in prisons.** On average a prisoner rebreathed 0.14 (0.1) L/min of air from fellow prison inmates at night. A prison inmate rebreathed an average of 65 L (95% CI: 63.8, 67.8) of air per night from another inmate. At mean CO<sub>2</sub> level, the annual risk of TB transmission for a prisoner spending nights in a cell occupied by 40 prison inmates was 41.6% (Figure 1).

**Risk of TB transmission in nightclubs.** Poor ventilation conditions were observed in 15.8 (64.3%) hours out of 2.5 hours of observation, with a mean rebreathed air value of 0.2 L/min (Supplementary Figure 2). The mean rebreathed air was significantly higher during Friday night than Saturday night (0.5 vs 0.3 L/min,  $P < 0.001$ ). Assuming one infectious case per 100 people, the risk of TB transmission ranged from 0.02% for 2 hours to 0.03% for four hours. Assuming one spends four hours per weekend in a

nightclub and quanta of contagion rate of 1.25/hour, we estimated the annual risk of TB transmission to be 1.7% inside a nightclub at a mean CO<sub>2</sub> level of 1,488 ppm (Figure 1).

**Risk of TB transmission on public transportation.** Overall, commuters spent 62.5 (39.5%) hours of the total time under observation (158 hours) on buses in poorly ventilated conditions. The annual risk of TB transmission for a passenger making 264 bus trips could be up to 2.4% per year (Figure 1). The annual risk for a bus driver or conductor on a bus for 10 hours each day for 264 days was 20.3% (Figure 3). Overall, the mean annual TB transmission risk for a driver was significantly higher than for a passenger: 20.3 (95% CI: 20.0, 20.5%) vs. 2.36 (95% CI: 2.3, 2.4%;  $P < 0.001$ , Table 1, Figure 3).

**Risk of TB transmission at religious and social halls.** Overall, mosques and churches were well ventilated, with CO<sub>2</sub> levels not exceeding 1,000 ppm. Assuming two hours spent each week in these religious halls, the mean annual risk of TB transmission was only 0.13%. Social halls had a mean CO<sub>2</sub> level of 1,262.9 (149) ppm (Table 1). However, the mean annual risk of TB transmission was only 0.12% with visits to social halls totaling 32 hours per year (Figure 1).

**Risk of TB transmission in schools.** We observed ventilation conditions at both day schools and boarding schools (Supplementary Figure 3). The annual risk of TB transmission associated with 1,280 hours spent in a class of 50 students at a mean CO<sub>2</sub> level of 655 ppm was estimated to be 4.02% (Figure 1).

## DISCUSSION

We found the highest annual risks of TB transmission from an urban setting of Dar es Salaam in prisons (41.6%), public transportation (20.3%), schools (4.02%), and nightclubs (1.7%), while risks were lowest in markets (0.5%), religious halls (0.13%) and social halls (0.12%). Generally, the annual transmission risk varies by location due to differing times spent in these venues and their (quite varied) ventilation situations. Our quantitative comparison of transmission risks has the potential to reveal why Dar es Salaam is a TB transmission hotspot in Tanzania.

Prisons unquestionably are sites with high risk of TB transmission. We found that the annual TB transmission risk (up to 90%) was similar to that seen in prisons in South Africa and Brazil.<sup>12,13</sup> These rates challenge the public health of surrounding communities. The risk of acquiring TB in the short-term correctional facility is approximately eight times higher than that of a trader at the Kariakoo market. The TB transmission risk when visiting nightclubs was comparable to that of a regular passenger in local public transportation in South Africa.<sup>7</sup> The risks faced by personnel operating these commuter buses in Tanzania are approximately nine times higher compared to passengers taking the same buses, and four times higher compared to traders in the underground market.

At the largest market in Tanzania, we found that the annual risk among traders was ten times higher than that for customers. This market is a hotspot involving a lot of trading activities at the center of metropolitan Dar es Salaam. Due to this profile, we think this market can play a vital role in the control of TB in the country.

In the schools, we observed a lower risk of TB transmission than that seen at schools in Cape Town, South Africa, which has a different environmental profile

compared to Dar es Salaam<sup>10</sup> where, due to comparatively higher humidity and temperature, schools rely on open windows and are better ventilated.

This novel approach in the under researched area provides important findings for the control of TB epidemics.<sup>5,7</sup> This is the first study to systematically estimate TB transmission risk at important public locations using a novel approach. Perhaps the main limitation of this study lies in its collection of social contact data, which was difficult as seen in other settings with low socio-economic status. Furthermore, we did not take into account the role of immunology among susceptible persons at risk of infection and the virulence of *Mtb* bacilli. Finally, we also assumed that the air was uniformly distributed in a confined space.

Resources used in the campaign against TB are limited and need to be directed where there is maximum pay off.<sup>2</sup> Our novel approach can guide targeted infection control interventions for National TB Control Programs. This novel approach demonstrates a lower risk of TB transmission are associated with settings with adequate ventilation and a short total time of exposure such as religious and social halls, but a high risk in prisons, public transport and central markets. This study lays the foundation for the next TB transmission studies employing molecular epidemiology techniques or isolation of *Mtb* from bio-aerosols<sup>14,15</sup> that will guide interventions to control TB and reach WHO's ambitious End TB targets by 2035.

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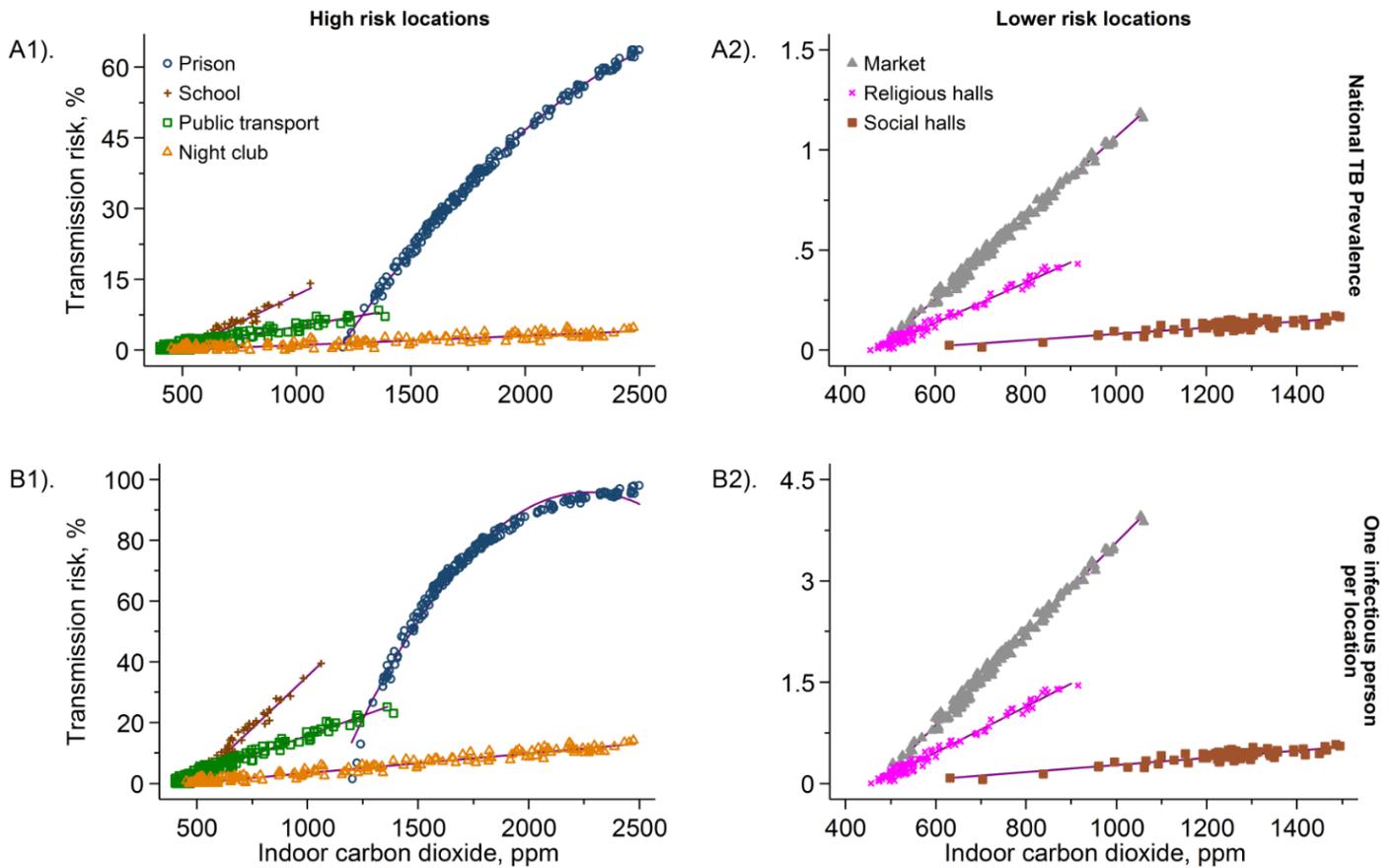
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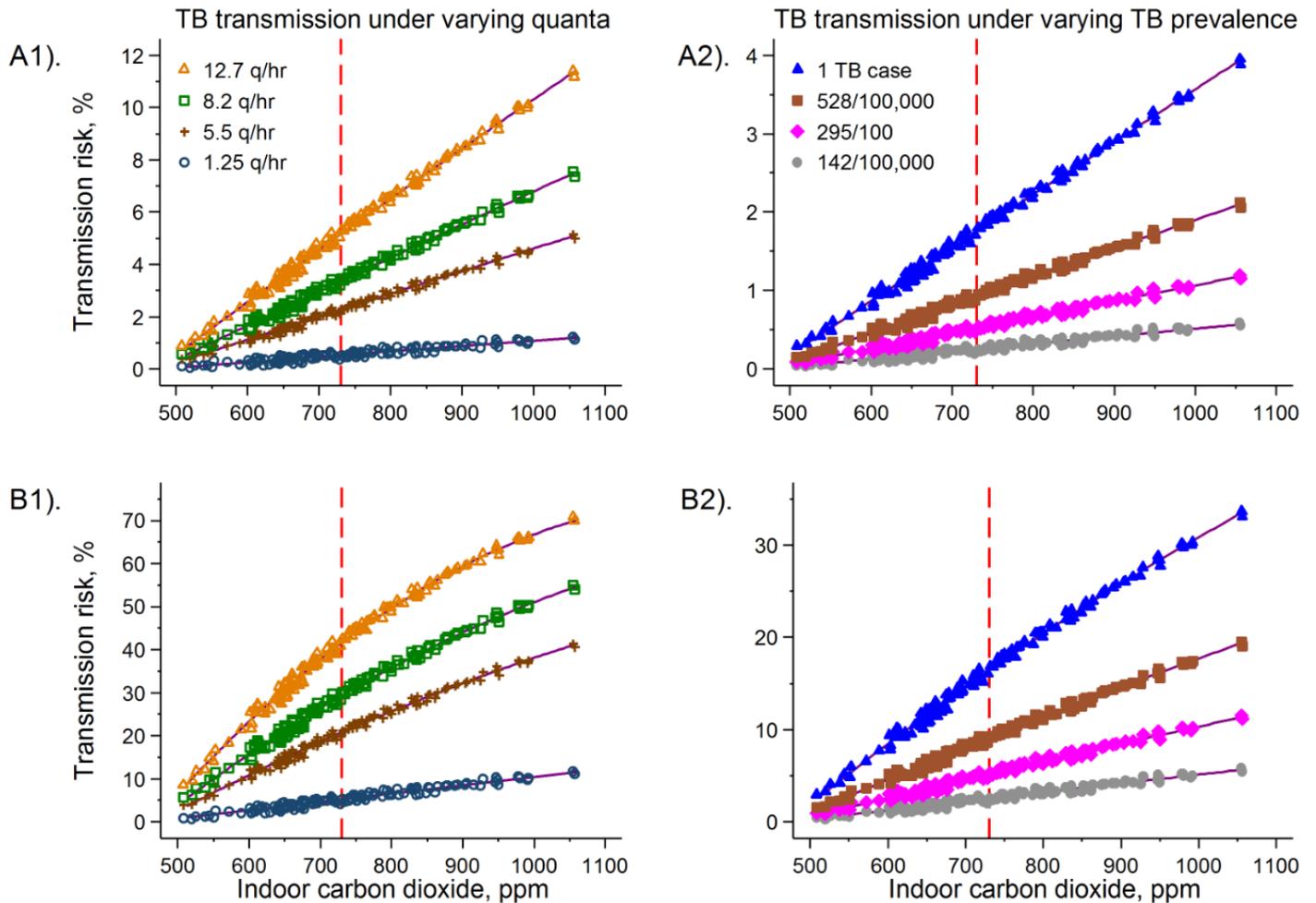
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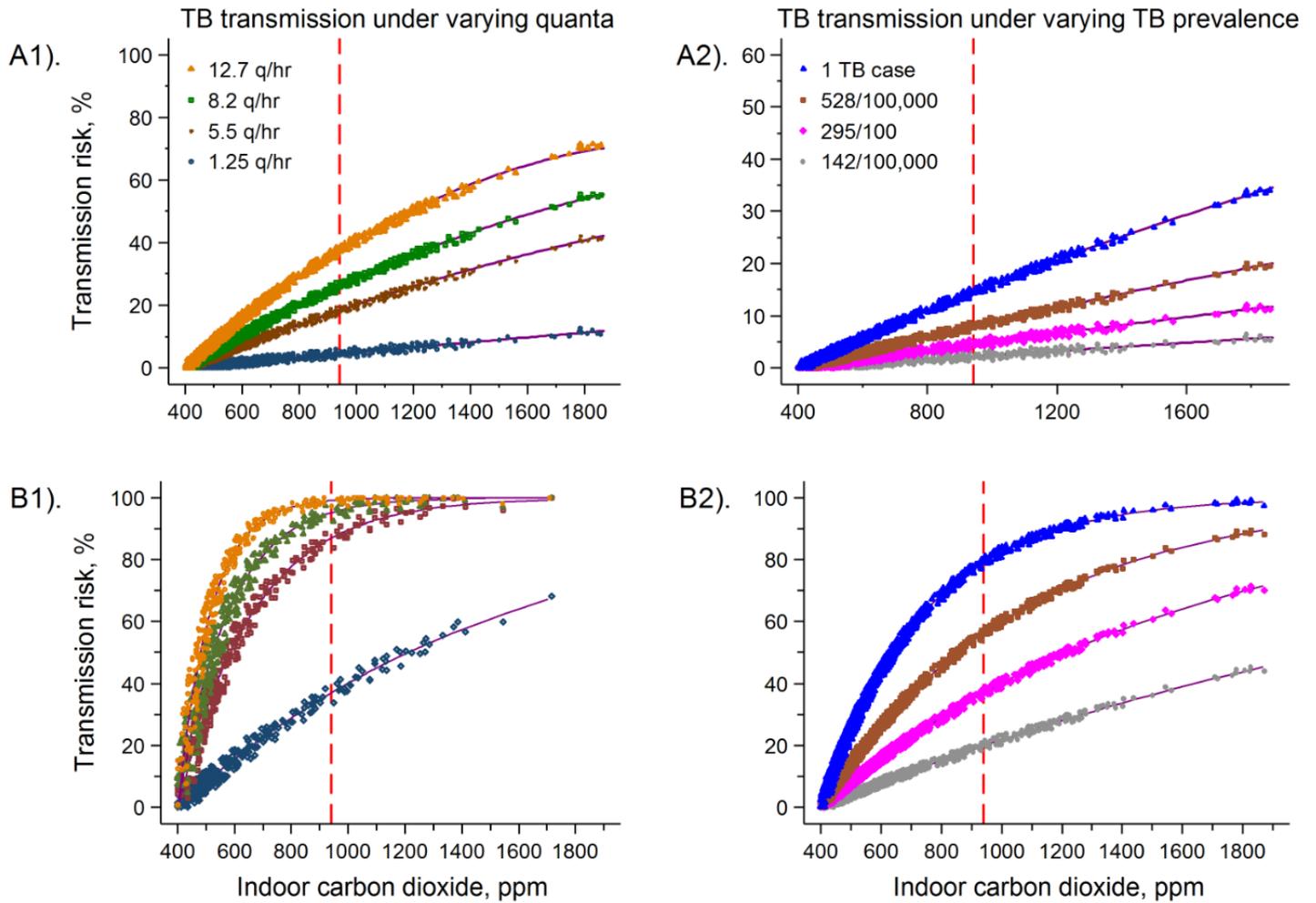
## FIGURES



**Figure 1. Annual tuberculosis transmission risk at locations of public importance in Dar es Salaam, Tanzania.** Annual tuberculosis transmission risk estimates based on varying environmental CO<sub>2</sub> levels (in parts per million, ppm) at higher risk (**Panels A1 and B1**) and lower risk locations (**Panels A2 and B2**, different scales), and under the assumption of the national TB prevalence (295 infectious cases/100,000 population, **Panels A**) and one infectious person at the location (**Panels B**). Lines indicate fitted risk of transmission. The model is based on quanta generation rate of 1.25/hour from infectious TB patient<sup>7</sup>. The mean outdoor CO<sub>2</sub> level at the locations was 431.1 ppm.



**Figure 2. Comparison of TB transmission risks at the largest market in Dar es Salaam.** Comparisons of TB transmission risks at a market in Dar es Salaam. Briefly, Panels A1 and A2 show estimates of annual risks of TB transmission at different quanta generation rates and TB prevalence for a customer who visits the market for one hour per week for one year. Panel B1 and B2 show the annual risks of TB transmission for a trader under different quanta generation rates and TB prevalence assuming a trader works 48 hours during each week over a period of 11 months in a year. The red dashed line show the mean CO<sub>2</sub> level in the market.



**Figure 3. Comparison of TB transmission risks on public transportation in Dar es Salaam.** A plot of annual TB transmission risks estimated from the public transport (commuter buses) in Dar es Salaam. Briefly, Panels A1 and A2 show estimates of annual risks of TB transmission under different quanta generation rates and TB prevalence for a passenger commuting on public transport for one year. Panels B1 and B2 show the annual risks of TB transmission for bus drivers and conductors working under different quanta generation rates and TB prevalence. Red dashed line show the mean CO<sub>2</sub> levels in the commuter buses.

**Table 1.** Carbon dioxide gas (CO<sub>2</sub>) levels recorded at locations of public importance in Dar es Salaam, Tanzania, and the annual tuberculosis (TB) transmission risk estimates based on varying assumptions of type and number of individuals, quanta generation rate, time of exposure and TB prevalence.

Infrastructure	Type of individuals at risk	Mean CO <sub>2</sub> (SD), ppm	Number of people	Quanta, q/hour	Time of exposure in hours	TB prevalence per 100,000 population	Annual transmission risk (%)			
							Mean	95% CI		
Market	Customers	730 (109)	100	1.25	208	295	0.49	0.48, 0.51		
				1.25	208	528	0.89	0.86, 0.91		
				12.70	208	295	4.90	4.80, 5.10		
				12.70	208	528	8.60	8.40, 8.80		
	Traders			1.25	1,112	295	4.91	4.77, 5.05		
				1.25	1,112	528	8.59	8.35, 8.83		
				12.70	1,112	295	38.61	37.73, 39.50		
				12.70	1,112	528	56.80	55.70, 57.85		
Prisons	Prisoners	1,892 (469)	40	1.25	3,200	295	38.40	37.60, 39.20		
				1.25	3,200	528	55.50	54.60, 56.40		
				12.70	3,200	295	95.20	94.80, 95.60		
				12.70	3,200	528	98.60	98.40, 98.90		
Night clubs	Club attendees			1,488 (787)	100	1.25	208	295	1.95	1.87, 2.03
						1.25	208	528	3.45	3.31, 3.60
						12.70	208	295	17.20	16.50, 17.90
						12.70	208	528	27.43	26.40, 28.40
Public transportation	Passengers	941 (246)	30			1.25	264	295	2.36	2.33, 2.39
						1.25	264	528	4.16	4.11, 4.22
						12.70	264	295	20.56	20.30, 20.8
						12.70	264	528	32.65	32.31, 32.99
	Drivers			30	1.25	2,640	295	20.29	20.04, 20.53	
					1.25	2,640	528	32.27	31.93, 32.61	
					12.70	2,640	295	80.63	80.25, 81.01	
					12.70	2,640	528	91.24	90.96, 91.51	
Religious halls	Attendees	629.31 (105)	100		1.25	104	295	0.13	0.12, 0.14	

				1.25	104	528	0.23	0.21, 0.25
				12.70	104	295	1.30	1.20, 1.40
				12.70	104	528	2.30	2.12, 2.48
				1.25	32	295	0.12	0.118, 0.125
Social halls	Attendees	1,262.9 (149)	200	1.25	32	528	0.22	0.21, 0.223
				12.70	32	295	1.23	1.20, 1.26
				12.70	32	528	2.19	2.13, 2.24
				1.25	1,280	295	4.02	3.95, 4.09
Schools	Students	655 (230)	50	1.25	1,280	528	7.03	6.91, 7.14
				12.70	1,280	295	32.30	31.95, 32.66
				12.70	1,280	528	48.78	48.34, 49.23

Abbreviations: CO<sub>2</sub>, carbon dioxide gas; 95% CI, 95% confidence interval; SD, standard deviation; ppm, parts per million; TB, tuberculosis