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Predicting Airborne Infection Risk: Association Between Personal Ambient Carbon Dioxide Level Monitoring and Incidence of Tuberculosis Infection in South African Health Workers

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Background. High rates of tuberculosis (TB) transmission occur in hospitals in high-incidence countries, yet there is no validated way to evaluate the impact of hospital design and function on airborne infection risk. We hypothesized that personal ambient carbon dioxide (CO_2) monitoring could serve as a surrogate measure of rebreathed air exposure associated with TB infection risk in health workers (HWs).

Methods. We analyzed baseline and repeat (12-month) interferon-γ release assay (IGRA) results in 138 HWs in Cape Town, South Africa. A random subset of HWs with a baseline negative QuantiFERON Plus (QFT-Plus) underwent personal ambient CO_2 monitoring.

Results. Annual incidence of TB infection (IGRA conversion) was high (34%). Junior doctors were less likely to have a positive baseline IGRA than other HWs (OR, 0.26; $P = .005$) but had similar IGRA conversion risk. IGRA converters experienced higher median CO_2 levels compared to IGRA nonconverters using quantitative QFT-Plus thresholds of ≥0.35 IU/mL ($P < .02$) or ≥1 IU/mL ($P < .01$). Median CO_2 levels were predictive of IGRA conversion (odds ratio [OR], 2.04; $P = .04$, ≥1 IU/mL threshold). Ordinal logistic regression demonstrated that the odds of a higher repeat quantitative IGRA result increased by almost 2-fold (OR, 1.81; $P = .01$) per 100 ppm unit increase in median CO_2 levels, suggesting a dose-dependent response.

Conclusions. HWs face high occupational TB risk. Increasing median CO_2 levels (indicative of poor ventilation and/or high occupancy) were associated with higher likelihood of HW TB infection. Personal ambient CO_2 monitoring may help target interventions to decrease TB transmission in healthcare facilities and help HWs self-monitor occupational risk, with implications for other airborne infections including coronavirus disease 2019.

Keywords. tuberculosis; tuberculosis infection control (TB-IC); IGRA; carbon dioxide monitoring; health workers.

Globally, tuberculosis (TB) remains a leading infectious killer, causing 10 million people to become sick each year, as well as 1.5 million deaths, which have risen as a result of the impact of the coronavirus disease 2019 (COVID-19) pandemic on TB care services [1]. Within countries like South Africa, high rates of TB transmission have long been reported in health facilities [2, 3]. TB in hospitals is driven by a high, undiagnosed burden of TB in patients [4–6]. Although evidence-based guidelines on TB infection control (TB-IC) exist [7], these guidelines are poorly implemented in high-incidence countries [8]. Furthermore, TB-IC focuses on patients with known or suspected TB and is neglected when TB is unsuspected [4, 5, 9], leading to high rates of nosocomial TB transmission. Health workers (HWs) are disproportionally affected by the risk of TB transmission and have at least a 3-fold higher incidence of TB than the general population [10–13]. Since latent TB testing and treatment are currently not recommended for HWs in high-incidence settings like South Africa, data on the incidence of latent TB in HWs in such settings are limited [10, 14].

Nosocomial TB transmission represents an important public health problem that puts both HWs and patients at risk [3, 10, 11, 15]. The risk of new TB infections has been correlated with occupancy density and air change rate, which are partially a

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function of building design [16, 17]. However, although health facility building design and function are integral to TB transmission control, there is no validated way to evaluate these factors relative to their impact on airborne infection risk. The concept of shared (rebreathed) air fraction as a risk factor for TB transmission has been studied in the setting of schools [18] and public transportation, typically using carbon dioxide (CO_2) tracer gas decay measurements [19, 20]. However, this only provides data for a snapshot in time and does not answer questions about building use, including movement of personnel, which is a dynamic process. Rebreathed air fraction, based on ambient CO_2 levels, has been studied in the school setting [18] and is proposed as a more useful correlate of risk of infection than the Wells-Riley model for airborne disease transmission, which assumes steady-state conditions and an estimate of generation rate of infectious quanta (doses) [19, 21].

We evaluated whether exposure to shared air, estimated by using personal ambient CO_2 monitoring, could serve as a novel surrogate measure of airborne infection risk that may be associated with risk of TB infection, measured using interferon-gamma (IFN-γ) release assay (IGRA) conversion in HWs at a tertiary referral hospital in South Africa.

METHODS

Study Setting, Participants, and Sample Size

We conducted a prospective observational cohort study from August 2017 to June 2019 among HWs employed at Tygerberg Hospital, an 1800-bed tertiary teaching hospital in Cape Town, South Africa. HWs were sequentially recruited for IGRA testing (using QuantiFERON-Plus [QFT-Plus], Qiagen, Hilden, Germany) at baseline and 12 months later. Hypothesizing that junior staff were more likely to have a baseline negative IGRA test, we made targeted efforts to recruit junior doctors (interns) and nurses. Aside from age >18 years, the only other exclusion criteria were having a prior history of TB or prior positive IGRA test. The sample size was calculated to ensure adequate power. We did not identify studies that provided relevant CO_2 level estimates, given our unique patient population (HWs), setting (hospital), and use of personal rather than stationary monitoring. We assumed the average CO_2 exposure for IGRA converters would be 900 ppm, and nonconverters 600 ppm, with a standard deviation of 250 ppm, which would require 11 converters to achieve a power of 0.8 with $\alpha = .05$. To enroll 11 converters anticipating a baseline conversion rate of 20% [14], we needed to enroll $11/20 \times 100$ (ie, 55) participants with a negative baseline IGRA. Factoring in some loss to follow-up, we aimed to recruit at least 70 IGRA-negative HWs.

All participants completed an interviewer-administered questionnaire to gather data regarding TB-associated occupational and community risk factors and TB infection control and screening practices. All participants were offered rapid human immunodeficiency virus (HIV) testing. Patients with a positive HIV test result were referred to Occupational Health, unless they were already receiving HIV care elsewhere. Patients were invited to report their HIV status if they had undergone recent prior testing. Refusal to disclose HIV status or undergo HIV testing did not preclude inclusion in the study.

The study was approved by the human research ethics committee of the Faculty of Medicine and Health Sciences (FMHS) University and Tygerberg Hospital, Cape Town, South Africa. Additional approval was obtained from the Institutional Review Board of the Brigham and Women's Hospital in Boston, Massachusetts, USA.

IGRA Testing

QFT-Plus testing was performed according to the manufacturer's instructions. IGRA conversion was defined as a negative baseline test and a positive follow-up test [22], defined for QFT-Plus as change from a baseline IFN-γ value <0.35 IU/mL to a follow-up IFN-γ value ≥0.35 IU/mL in either the TB1 or TB2 tube. Reversion was defined as a baseline positive test with a negative test at follow-up. Based on prior studies demonstrating an increased risk of incipient TB with higher quantitative repeat QFT-Plus values [23–25], we also analyzed QFT-Plus conversion data for (1) baseline IFN-γ <0.35 IU/mL and repeat IFN-γ ≥0.7 IU/mL; (2) baseline IFN-γ <0.35 IU/mL and repeat IFN-γ ≥1 IU/mL; and (3) baseline IFN-γ <0.35 IU/mL and follow-up IFN-γ ≥4 IU/mL.

CO_2 Monitoring

A random subset of HWs with a baseline negative QFT-Plus result were selected using sequence generation from participants in the following departments: emergency room, medicine, surgery, pediatrics, and obstetrics and gynecology. Each participant was given a commercially available ambient CO_2 monitor/data logger (model SAN-0001, CO2Meter, Ormond Beach, Florida [26]) worn for 1 to 3 routine work shifts on their waists. We conducted a prerecruitment optimization phase to confirm that measurements from CO_2 monitors worn in this position were not impacted by participant respiration. The CO_2 monitors were precalibrated by the manufacturer. CO_2 levels, measured in ppm, were logged every 30 seconds, with an accuracy of ±200 ppm or 10% of the reading per the manual. We analyzed personal ambient CO_2 levels for the first 5 hours during the CO_2 level monitoring period (this duration enabled us to analyze data from all participants to avoid results being skewed by potential outlier results from the few HWs who had the monitors for longer durations than their work shifts).

Statistical Analyses

Statistical analyses were performed using Stata version 16 software (Stata Corp, College Station, Texas). The prevalence of TB-associated risk factors and test outcomes were calculated at

baseline. Annual rates of IGRA conversion at different thresholds were calculated. We conducted univariate logistic regression analysis to evaluate associations between potential risk factors for TB infection and both baseline and follow-up IGRA results. Covariates found to be independently associated with IGRA positivity were considered for inclusion in the multivariate model. Wilcoxon-Mann-Whitney nonparametric testing was conducted to evaluate differences in CO_2 levels experienced by HWs stratified by their IGRA conversion status. A hypothesized dose-response relationship between CO_2 exposure and IGRA conversion was tested using ordinal logistic regression. Comprehensive ordered results categories were defined using IGRA thresholds based on manufacturer recommendations and the literature. The odds ratio (OR) and 95% confidence interval (CI) were reported.

RESULTS

Participant Enrollment and Demographic Data

188 HWs were approached for participation. After 1 HW with a prior history of TB was excluded, all consented to participate, representing a response rate of 100% (Figure 1). At 12 months postenrollment, 74% (138/187) of HWs underwent repeat QFT-Plus testing. Reasons for HWs being lost to follow-up were leaving the facility for other employment (n = 25), refusal (n = 16), maternity leave (n = 1), and could not be recontacted (n = 7).

Participant Demographic Data

The majority of the HWs were female (154/186 [83%]; $P = .02$), reflective of the high proportion recruited from the nursing staff. Forty-two percent of HWs were aged <30 years and 8% were aged >50 years. Only 5% of HWs reported having HIV or tested positive for HIV. The duration of time employed in healthcare settings was <5 years for the majority of HWs (34%), with 11% employed for >20 years. All enrolled HWs reported working with TB patients (Table 1).

Baseline IGRA Results

Of the 187 HWs tested, 93 (50%) had a negative baseline QFT-Plus result and 94 (50%) had a positive baseline QFT-Plus result. The likelihood of having a negative baseline QFT-Plus result was higher for males ($P = .020$), those who were younger (based on median age, $P = .019$), and doctors compared to nurses and other health workers ($P < .001$; Table 1). Multivariate regression confirmed that when adjusted for age, sex, and department, being a doctor, compared to a nurse or other health worker, was associated with a lower likelihood of having a positive baseline QFT-Plus result (OR, 0.27; $P = .002$) (Table 2). More specifically, this lower risk in doctors was driven by the high proportion of interns who, compared to noninterns, had a lower likelihood of baseline QFT-Plus positivity (OR, 0.26; $P = .005$). HWs working in Accident and Emergency had a higher likelihood of baseline QFT-Plus positivity (OR, 2.93; $P = .008$). Of those HWs with a positive baseline QFT-Plus result, 83% had both TB1-nil and TB2-nil results that were ≥0.35 IU/mL, with 7% positive based only on the TB1-nil result and 10% positive based only on the TB2-nil result (Table 3). When we examined IGRA positivity based on higher quantitative values, 70% had either TB1-nil or TB2-nil values that were ≥1 IU/mL (Table 3).

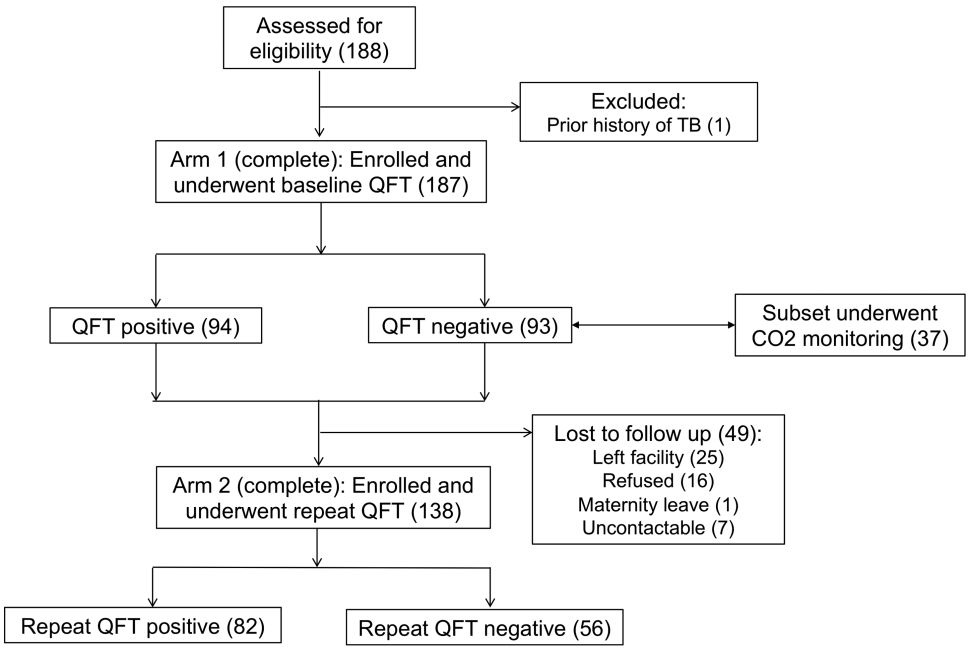

Figure 1. Study flow diagram. Abbreviations: CO_2, carbon dioxide; QFT, QuantiFERON-Plus; TB, tuberculosis.

Table 1. Characteristics of Health Workers Who Underwent Baseline Quantiferon-Plus Testing

Characteristic	HWs (n = 187)	Baseline QFT-Plus Positive (n = 94)	Baseline QFT-Plus Negative (n = 93)	*P* Value[a]
Sex				
Male	32 (17.2)	10 (11)	22 (24)	**.020**
Female	154 (82.8)	84 (89)	70 (75)	
Age, y, median (IQR)	33 (26–42)	34 (28–45)	29.5 (25–40.5)	**.019**
Age categories, y				
20–29	80 (42)	32 (34)	48 (52)	
30–39	50 (27)	29 (31)	21 (23)	
40–49	41 (22)	24 (26)	17 (18)	
≥50	16 (8.6)	9 (9.6)	7 (7.5)	
HW type				
Nurse	116 (62)	73 (78)	43 (46)	**<.001**
Doctor	53 (28)	13 (14)	40 (43)	
Other	18 (9.6)	8 (8.5)	10 (11)	
Intern				
Yes	39 (21)	8 (8.5)	31 (33.3)	**<.001**
No	148 (79)	86 (91.5)	62 (66.7)	
Department				
Medicine	38 (20)	16 (17)	22 (24)	**.004**
Surgery	50 (27)	21 (22)	29 (31)	
Pediatrics	29 (15)	15 (16)	14 (15)	
OB-GYN	16 (8.6)	10 (11)	6 (6.5)	
A&E	47 (25)	32 (34)	15 (16)	
Other	7 (3.7)	0 (0)	7 (7.5)	
Time employed in healthcare, y, median (IQR)	4.84 (0.99–10.7)	5.80 (2.87–10.8)	1.59 (0.66–10.7)	**.013**
Time category, y				
<5	80 (34)	35 (37)	45 (48)	
5–10	30 (13)	20 (21)	10 (11)	
10–15	6 (2.5)	3 (3.2)	3 (3.2)	
15–20	7 (2.9)	5 (5.3)	2 (2.1)	
>20	25 (11)	11 (12)	14 (15)	
HIV status				
Negative	172 (92)	88 (94)	84 (90)	.534
Positive	10 (5)	4 (4.3)	6 (6.4)	
Works with TB patients				
Yes	179 (96)	91 (97)	88 (95)	
No	0 (0)	0 (0)	0 (0)	

Data are presented as No. (%) unless otherwise indicated.

The values in bold indicate results for which the *P* value is <.05.

Abbreviations: A&E, accident and emergency; HIV, human immunodeficiency virus; HW, health worker; IQR, interquartile range; OB-GYN, obstetrics and gynecology; QFT-Plus, QuantiFERON-Plus; TB, tuberculosis; y, year.

[a]Based on comparison of baseline QFT-Plus positive vs negative HWs.

HW Annual Incidence of TB Infection, Based on IGRA Conversion

Of the HWs who underwent repeat testing, 41% (56/138) had a negative QFT-Plus result and 59% (82/138) had a positive QFT-Plus result. Of the HWs with a baseline negative QFT-Plus result, 25 of 74 (34% [95% CI, 23.2%–45.7%]) had a positive repeat test at 12 months. When we considered definitions of IGRA conversion with higher quantitative values (Table 3), 8 of 74 (11%) had both repeat TB1-nil and TB2-nil that were ≥1 IU/mL. Only 1 HW had both repeat TB1-nil and TB2-nil that were ≥4 IU/mL. Of the 64 HWs with a baseline positive QFT-Plus result, 7 had a negative repeat test at 12 months (11% reversion rate [95% CI, 4.5%–21.2%]). Of the 7 reversions, 5 (71%) had a baseline positive QFT-Plus result that had been <1 IU/mL for both TB1-nil and TB2-nil. Quantitative baseline and repeat results for TB1-nil and TB2-nil were significantly different for IGRA converters but not reverters when analyzed as groups (Figure 2).

Relationship Between CO_2 Levels and IGRA Conversion

We randomly selected 37 of 74 (50%) of the baseline IGRA negative HWs to undergo CO_2 monitoring and 13 of them (35%) subsequently had IGRA conversion, in excess of the 11 we calculated would be needed. When we assessed the average CO_2 levels experienced at each timepoint, IGRA

Table 2. Logistic Regression Analyses of Demographic and Occupational Variables Comparing Participants With Baseline Negative Versus Positive QuantiFERON-Plus Results

Characteristic	Univariate Regression				Multivariate Regression	
	Negative QFT-Plus (n = 93)	Positive QFT-Plus (n = 94)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Demographic variables						
Age, y, median (IQR)	30 (25–41)	34 (28–45)	1.03 (1.00–1.0)	.026	1.00 (.97–1.04)	.888
Age <30 y	48/93 (52)	32/94 (34)	0.484 (.27–.87)	.016	1.01 (.49–2.09)	.971
Male sex	22/92 (24)	10/94 (11)	0.379 (.17–.85)	.019	0.698 (.28–1.75)	.443
Occupational variables						
Health worker type						
Intern	31/93 (33)	8/94 (9)	Reference		…	
Registrar	5/93 (5)	2/94 (2)	1.55 (.25–9.52)	.636	1.52 (.21–10.9)	.678
Medical officer	4/93 (4)	3/94 (3)	2.91 (.54–15.7)	.215	3.13 (.56–17.5)	.194
Community nurse	8/93 (9)	12/94 (13)	5.81 (1.78–19)	.004	4.96 (1.47–16.7)	.010
Auxillary nurse	14/93 (15)	29/94 (31)	8.03 (2.94–22)	<.001	5.56 (1.65–18.7)	.006
Staff nurse	5/93 (5)	14/94 (15)	10.9 (3.01–39)	<.001	7.99 (1.83–34.9)	.006
Professional nurse	16/93 (17)	18/94 (19)	4.36 (1.56–12)	.005	3.04 (.83–11.1)	.094
Other[a]	10/93 (11)	8/94 (9)	3.10 (.92–10.4)	.067	2.48 (.69–8.85)	.162
Doctors versus nurses or other HW types						
Nurses	43/93 (46)	73/94 (78)	Reference		…	
Doctors	40/93 (43)	13/94 (14)	0.19 (.09–.40)	<.001	0.27 (.11–.62)	.002
Others	10/93 (11)	8/94 (8)	0.47 (.17–1.28)	.142	0.52 (.18–1.49)	.224
Interns versus non-Interns	31/93 (33)	8/94 (9)	0.19 (.08–.43)	<.001	0.26 (.10–.67)	.005
Department						
Medicine	22/93 (24)	16/94 (17)	Reference		…	
Surgery	29/93 (31)	21/94 (22)	0.99 (.42–2.33)	.992	…	
Pediatrics	14/93 (15)	15/94 (16)	1.47 (.56–3.90)	.435	…	
OB-GYN	6/93 (7)	10/94 11)	2.29 (.69–7.61)	.175	…	
A&E	15/93 (16)	32/94 (34)	2.93 (1.21–7.14)	.018	…	
Other[b]	7/93 (8)	0/94 (0)	…		…	
A&E HWs versus non-A&E HWs	15/93 (16)	32/94 (34)	3.32 (1.58–6.98)	.002	2.93 (1.33–6.44)	.008
Time in healthcare, mo, median (IQR)	19.1 (7.9–128)	70 (34–130)	1.00 (.99–1.004)	.438	…	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: A&E, accident and emergency; CI, confidence interval; IQR, interquartile range; OB-GYN, obstetrics and gynecology; OR, odds ratio; QFT-Plus, QuantiFERON-Plus.

[a]Includes carer and clinical technologist.

[b]Includes anesthesiology and the burn unit.

Table 3. Results of QuantiFERON-Plus Testing at Baseline and Follow-up Including Annualized Rates of Conversion and Reversion

QuantiFERON-Plus Results	No. (%)
Total No. tested at baseline	187
No. tested positive	94 (50)
No. tested negative	93 (50)
TB1-nil & TB2-nil both positive	78 (83)
Only positive on TB1-nil	7 (7)
Only positive on TB2-nil	9 (10)
Either TB1-nil or TB2-nil ≥1	66 (70)
Total No. tested at follow-up	138
No. of IGRA conversions	25/74 (34)
Annual rate of conversion, % (95% CI)	34 (23.2–45.7)
When conversion is defined as: baseline IFN-γ <.35 IU/mL and follow-up IFN-γ ≥.7 IU/mL in both TB1 and TB2	9/74 (12)
When conversion is defined as: baseline IFN-γ <.35 IU/mL and follow-up IFN-γ ≥1 IU/mL in both TB1 and TB2	8/74 (11)
No. of IGRA reversions	7/64 (11)
Annual rate of reversion, % (95% CI)	11 (4.5–21.2)
No. of reversions if: baseline IFN-γ ≥.35 IU/mL and follow-up IFN-γ <.35 IU/mL AND baseline IFN-γ in either TB1 or TB2 <1 IU/mL	5/64 (8)

Abbreviations: CI, confidence interval; IFN-γ, interferon gamma; IGRA, interferon-γ release assay; TB, tuberculosis.

converters had been exposed to higher median CO_2 levels compared to IGRA nonconverters (median 660 ppm compared to 537 ppm, $P < .02$; Table 4). Furthermore, HWs who had IGRA conversion with cutoff values for TB1-nil and TB2-nil that were greater than (1) 0.7 IU/mL or (2) 1 IU/mL had been exposed to higher CO_2 levels compared to IGRA nonconverters (median 660 ppm and 800 ppm compared to 537 ppm, respectively, $P = .01$; Table 4).

We conducted univariate regression analyses to evaluate factors that could predict IGRA conversion and IGRA conversion at increasing quantitative thresholds (Table 5). The previously evaluated variables including HW type, which were associated with a lower risk of having a baseline positive IGRA result, were not significantly associated with the risk of IGRA conversion. Median CO_2 levels were predictive of IGRA conversion with a quantitative value ≥1 IU/mL relative to nonconverters (OR, 2.04; $P = .04$), also demonstrated visually in the logistic regression probability plots (Figure 3). IGRA nonconverters were more likely to have spent a longer period during their shift exposed to lower

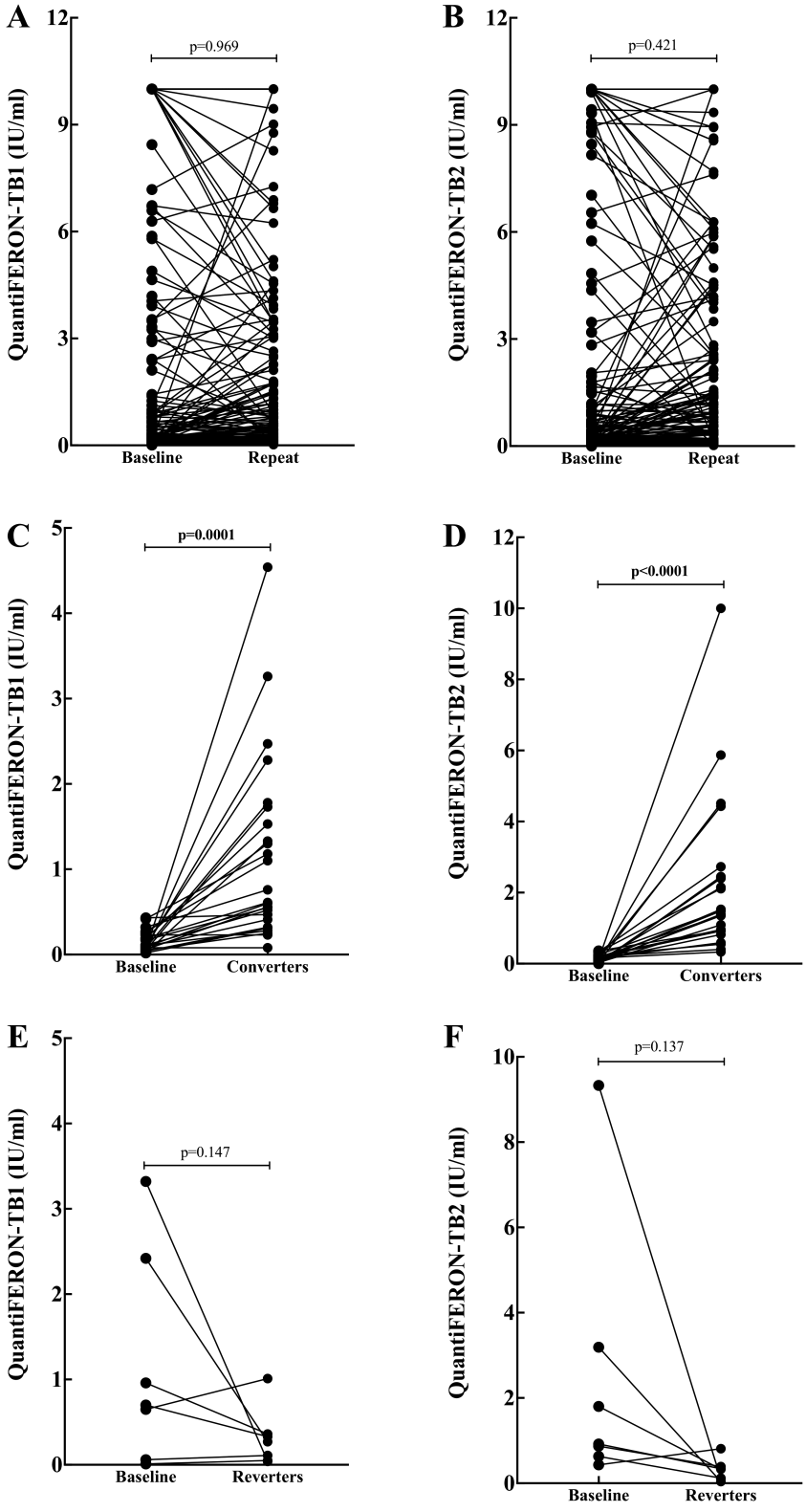

Figure 2. Comparison of quantitative baseline and repeat QuantiFERON-Plus TB1-nil and TB2-nil values. *A* and *B*, Results for all participants. *C* and *D*, Results for all interferon-γ release assay (IGRA) converters demonstrating significant differences in both TB1-nil and TB2-nil values. *E* and *F*, Results for all IGRA reverters.

Table 4. Differences Between Average Carbon Dioxide Levels Over the Period of Monitoring, Stratified by Interferon-γ Release Assay Conversion Status, Using Mann-Whitney-Wilcoxon Rank-Sum Test

	Nonconverters Average ± SD (ppm)	Converters Average ± SD (ppm)	*P* Value[a]	Converters ≥0.7 IU/mL Average ± SD (ppm)	*P* Value[b]	Converters ≥1 IU/mL Average ± SD (ppm)	*P* Value[c]
No. of HWs	24	13		11		5	
Median CO_2 level per HW	537 ± 147	660 ± 230	**.02**	660 ± 239	**.011**	800 ± 301	**.013**

The values in bold indicate results for which the *P* value is <.05.

Abbreviations: CO_2, carbon dioxide; HW, health worker; ppm, parts per million; SD, standard deviation.

[a]Comparing interferon-γ release assay (IGRA) nonconverters with IGRA converters.

[b]Comparing IGRA nonconverters with IGRA converters whose TB1-nil or TB2-nil had a quantitative value ≥0.7 IU/mL.

[c]Comparing IGRA nonconverters with IGRA converters whose TB1-nil and TB2-nil had a quantitative value ≥1 IU/mL.

CO_2 levels <500 ppm than IGRA converters (OR, 0.98; $P = .028$). Correlation analyses using delta IGRA values did not reveal a significant correlation with median CO_2 levels ($r = 0.266$, Supplementary Figure 1). We considered that the comprehensive ordered results categories with thresholds derived from both TB1-nil and TB2-nil values, based on the manufacturer recommendations and the literature, would be most relevant clinically (Figure 4). The observed

Table 5. Univariate Logistic Regression to Evaluate Association Between Demographic, Clinical, and Carbon Dioxide Level Monitoring Variables and Likelihood of Interferon-γ Release Assay Conversion

Variables	IGRA Nonconverters (n = 24)	IGRA Converters (n = 13)	IGRA Converters ≥1 IU/mL (n = 5, Subset of the 13 IGRA Converters)	IGRA Nonconverters vs IGRA Converters, OR (95% CI) *P* Value	IGRA Nonconverters vs IGRA Converters ≥0.7 IU/mL, OR (95% CI) *P* Value	IGRA Nonconverters vs IGRA Converters ≥1 IU/mL, OR (95% CI) *P* Value
Age, y, median (IQR)	32 (25–42)	37 (34–49)	37 (34–43)	1.05 (.98–1.13) .147	1.03 (.96–1.11) .420	1.04 (.94–1.15) .423
Age category, <30 y, No. (%)	11/24 (46)	3/13 (23)	1/5 (20)	.355 (.08–1.62) .181	.443 (.09–2.09) .304	.295 (.03–3.05) .306
Male sex, No. (%)	9/24 (38)	2/13 (15)	0/5 (0)	.303 (.05–1.69) .173	.167 (.02–1.53) .113	…
Intern, No. (%)	8/24 (33)	4/13 (31)	1/5 (20)	.889 (.21–3.80) .874	1.14 (.26–5.09) .861	.500 (.05–5.24) .563
Department, No. (%)						
Medicine	6/24 (24)	3/13 (23)	2/5 (40)	Reference	…	…
Surgery	9/24 (38)	1/13 (8)	1/5 (20)	.222 (.02–2.67) .236	.333 (.02–4.55) .410	.333 (.02–4.55) .410
A&E	3/24 (13)	1/13 (8)	1/5 (20)	.667 (.02–2.67) .765	1.00 (.63–16.0) 1.00	1.00 (.63–16.0) 1.00
Other	6/24 (25)	8/13 (62)	1/5 (20)	2.67 (.47–9.47) .270	3.50 (.50–24.3) .205	.500 (.04–7.10) .609
Time in healthcare, mo, median (IQR)	42.5 (5–236.5)	12 (10–107)	12 (12–107)	.99 (.99–1.00) .589	.99 (.99–1.00) .253	.998 (.99–1.01) .679
Temperature, °C, median (IQR)	28 (27–30)	29 (26–30)	30 (25–30)	1.05 (.77–1.42) .763	1.11 (.79–1.55) .545	1.05 (.69–1.62) .814
CO_2, ppm/100, median (IQR)	5.37 (4.95–6.73)	6.60 (5.85–8.00)	8.00 (7.85–9.00)	1.58 (.99–2.53) .056	1.68 (1.02–2.78) .042	2.04 (1.05–3.98) .036
Time spent at CO_2 level, min, median (IQR)						
CO_2 level <500 ppm	82.5 (13.5–146)	6.5 (0–33.5)	0 (0–14)	.98 (.97–.99) .028	.98 (.96–.99) .023	.96 (.90–1.01) .138
CO_2 level >500 ppm	154 (125–230)	209 (102–244)	209 (102–214)	1.00 (.99–1.01) .551	1.00 (.99–1.01) .410	1.00 (.98–1.01) .750
CO_2 level >1000 ppm	1.5 (0–13.3)	11.5 (0–47)	47 (29–59.5)	1.01 (.99–1.03) .208	1.01 (.99–1.03) .173	1.02 (.99–1.05) .122
CO_2 level >1500 ppm	0 (0–0.75)	0 (0–1.5)	1.5 (0–1.5)	1.02 (.87–1.18) .823	1.00 (.85–1.18) .994	1.07 (.90–1.26) .462

Abbreviations: A&E, accident and emergency; CI, confidence interval; CO_2, carbon dioxide; IGRA, interferon-γ release assay; IQR, interquartile range; OR, odds ratio; ppm, parts per million.

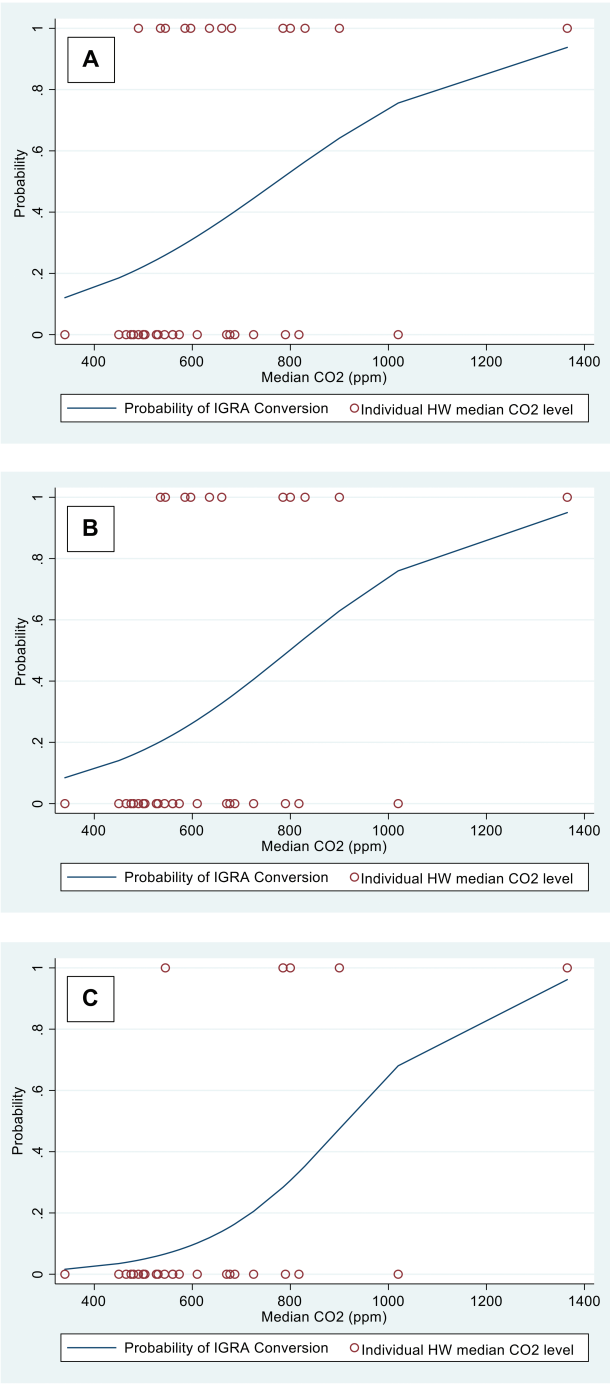

Figure 3. Logistic regression probability plots. Probability of interferon-γ release assay (IGRA) conversion using median health worker (HW) carbon dioxide (CO_2) levels comparing IGRA nonconverters to IGRA converters (*A*), IGRA nonconverters to IGRA converters whose TB1-nil or TB2-nil quantitative values are ≥0.7 IU/mL (*B*), and IGRA nonconverters to IGRA converters whose TB1-nil and TB2-nil quantitative values are ≥1 IU/mL (*C*).

dose-dependent response was supported by the ordinal logistic regression. Per 100 ppm median CO_2 increase, the OR for IGRA conversion at each successively higher threshold used to define quantitative IGRA conversion (ie, ≥0.35, ≥0.7, ≥1) relative to lower thresholds (ie, <0.35, <0.7, <1, respectively) was 1.81 (95% CI, 1.13–2.91; P = .01). This means the odds of HWs having a higher repeat quantitative IGRA response relative to lower threshold levels nearly doubled as their median CO_2 levels increased by 100 ppm.

DISCUSSION

This is the first study, to the best of our knowledge, to assess the use of personal ambient CO_2 monitoring as a surrogate measure of airborne infection risk by evaluating its correlation with transmission in HWs, measured directly based on the annual incidence of TB infection. Our results suggest that HWs who demonstrate IGRA conversion are more likely to experience higher average (median) CO_2 levels and that the magnitude of IGRA response (both TB1-nil and TB2-nil quantitative values) was positively associated with higher average CO_2 levels experienced by HWs during monitored work shifts. Other data have also suggested that intensity and proximity of exposures (which would be exacerbated by poor ventilation) are associated with TB infection acquisition and disease progression [27]. Our study demonstrates that personal monitoring of CO_2 levels is a feasible and potentially useful tool to identify poorly ventilated areas and individuals who, due to their movement or prolonged durations in these areas, have higher TB transmission risk. Our approach would be easier to scale compared to other approaches such as air sampling to detect *Mycobacterium tuberculosis*.

Prior data examining CO_2 levels in South African schools have identified a CO_2 level of 1000 ppm as a threshold to determine a higher risk of TB transmission [18]. Yet our logistic regression probability plots indicate a high probability of IGRA conversion (>50%) below this threshold, which likely reflects the higher TB transmission risk in healthcare settings and other unmeasured factors such as individual patient infectiousness (source strength) that impact the likelihood of transmission. Personal ambient CO_2 monitoring can inform the design and targeting of recommended administrative and environmental interventions such as triage to decrease crowding, improved ventilation, and/or adjunctive use of germicidal ultraviolet air disinfection to reduce nosocomial TB transmission, by illustrating where in a facility HWs or patients may be at highest risk and providing real-time, actionable data to assess the effectiveness of these interventions. While interventions at the health system and/or policy level are likely to be superior to interventions targeting individual behavior change, personal ambient CO_2 monitoring can also raise awareness among HWs and potentially serve as a nudge for this population to implement recommended TB-IC approaches to protect themselves and others. These data now have additional relevance in the context of the ongoing COVID-19 pandemic.

Our data highlight the imperative to protect HWs from TB infection in high-burden settings. A prior study demonstrated annual IGRA conversion rates of 13%–22% in South African HWs [14]. Using the newer QFT-Plus assay, our study

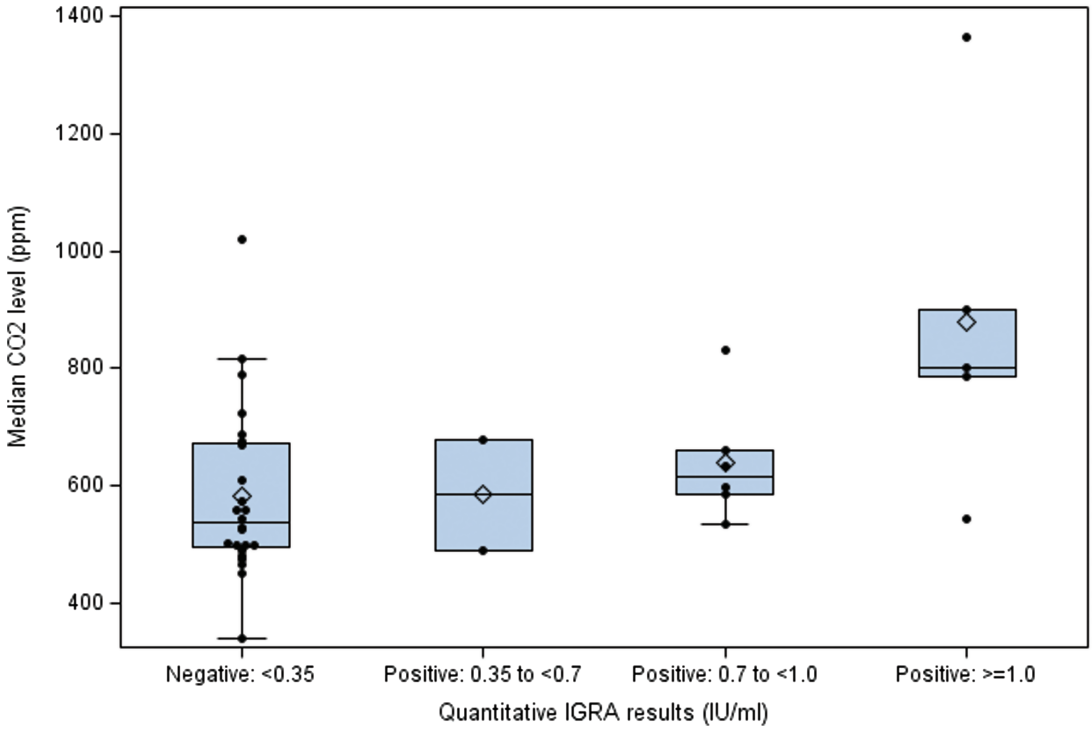

Figure 4. Box plot illustrating median carbon dioxide (CO_2) levels summarized according to interferon-γ release assay conversion group, based on repeat quantitative IGRA values. Line connects conversion level group medians; diamonds are group means. Negative: both TB1-nil and TB2-nil <0.35 IU/mL. Positive: both TB1-nil and TB2-nil ≥0.35 to 0.7 IU/mL; either TB1-nil or TB2-nil ≥0.7 IU/mL to 1 IU/mL; or both TB1-nil and TB2-nil ≥1.0 IU/mL.

demonstrates a higher HW IGRA conversion rate of 34%. The univariate regression analysis using follow-up IGRA results did not detect an association between HW type and IGRA conversion. This contrasts with the multivariate regression analysis that showed being a doctor and, more specifically, a junior doctor (intern) was associated with a lower likelihood of having a baseline positive IGRA. Our data thus suggest that once junior or lower-risk HWs are exposed to an environment with high risks of TB transmission such as a health facility, their risks of conversion become similar to those of other HWs despite differences in duration of time working in healthcare and socioeconomic status that drive differential nonoccupational TB risk (and likely explain their lower baseline risk). These data emphasize the magnitude of risk faced by HWs in TB endemic settings where there are high rates of patients with undiagnosed TB and TB-IC measures are poorly implemented [8].

In addition to prioritizing refocused TB-IC [4], there is an urgent need for occupational health system strengthening to enable HW TB screening [28, 29], at minimum for active TB but also to address latent TB infection, particularly given the potential for effective shorter TB preventive therapy regimens. We note that one-third of IGRA conversions in our study had quantitative TB1-nil and TB2-nil values of <1, and that the majority of IGRA reversions occurred when the initial positive result occurred in this potential borderline range. Understanding the potential implications of these nuanced interpretations to quantitative IGRA analysis will be important for national TB programs to address latent TB infection in high-risk populations such as HWs.

We acknowledge the limitations of drawing conclusions based on this small dataset. Unmeasured factors such as the location and infectiousness of patients with undiagnosed TB, or other factors related to host susceptibility such as differential use of personal protective equipment, may have a higher impact on the likelihood of incident TB in HWs. We also note that the feasibility of personal ambient CO_2 monitoring was impacted by technical challenges related to ensuring reliable device calibration and data logging, since the devices used were not designed for this analytical purpose. Nonetheless we were able to troubleshoot these challenges during our study period to ensure the reliability of the data. While IGRA testing remains an imperfect tool to measure TB infection, analysis of the quantitative IGRA data strengthens the rigor of our findings.

In conclusion, the higher than expected annual incidence of TB infection in a cohort of South African HWs emphasizes the urgent need for interventions to decrease TB transmission and occupational TB risk in healthcare settings. HWs who

experienced higher average personal ambient CO_2 levels (ie, exposed to a higher shared or rebreathed air fraction) were more likely to develop IGRA conversion, with evidence to support a dose-dependent response whereby increasing median CO_2 levels increased the odds of IGRA conversion. We propose that personal ambient CO_2 monitoring is a feasible and useful tool to identify poorly ventilated indoor areas to target TB transmission prevention interventions. This has important implications for other airborne infections including COVID-19, as part of a wider call-to-action to improve ventilation as an infection prevention mitigation strategy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. R. R. N. and G. T. report collaboration on an NIH U01 grant evaluating TB diagnostics, outside the scope of this work, and R. R. N. is chair of the board for TB Proof, a TB advocacy organization based in South Africa. All other authors report no other conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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