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 (CO₂) 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 CO₂ 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 CO₂ levels compared to IGRA nonconverters using quantitative QFT-Plus thresholds of ≥0.35 IU/mL (P < .02) or ≥1 IU/mL (P < .01). Median CO₂ 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 CO₂ levels, suggesting a dose-dependent response.

Conclusions. HWs face high occupational TB risk. Increasing median CO₂ levels (indicative of poor ventilation and/or high occupancy) were associated with higher likelihood of HW TB infection. Personal ambient CO₂ 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 unsuspicious [4, 5, 9], leading to high rates of nosocomial TB transmission. Health workers (HWs) are disproportionately 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
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 (CO₂) 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 CO₂ 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 CO₂ 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 CO₂ level estimates, given our unique patient population (HWs), setting (hospital), and use of personal rather than stationary monitoring. We assumed the average CO₂ 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 α = .05. To enroll 11 converters anticipating a baseline conversion rate of 20% [14], we needed to enroll 11/0.20 × 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.

CO₂ 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 CO₂ monitor/data logger (model SAN-0001, CO2Meter, Ormond Beach, Florida [26]) worn for 1 to 3 routine work shifts on their waist. We conducted a preremoval optimization phase to confirm that measurements from CO₂ monitors worn in this position were not impacted by participant respiration. The CO₂ monitors were recalibrated by the manufacturer. CO₂ 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 CO₂ levels for the first 5 hours during the CO₂ 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 CO₂ levels experienced by HWs stratified by their IGRA conversion status. A hypothesized dose-response relationship between CO₂ 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: CO₂, carbon dioxide; QFT, QuantiFERON-Plus; TB, tuberculosis.](cid202275.15oct.1299)
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).

**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* |
|-----------------------------------------|---------------|------------------------------------|-------------------------------------|----------|
| **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**                             |               |                                    |                                     | <.001    |
| Nurse                                   | 116 (62)      | 73 (78)                            | 43 (46)                             |          |
| Doctor                                   | 53 (28)       | 13 (14)                            | 40 (43)                             |          |
| Other                                    | 18 (9.6)      | 8 (8.5)                            | 10 (11)                             |          |
| **Intern**                              |               |                                    |                                     | <.001    |
| Yes                                      | 39 (21)       | 8 (8.5)                            | 31 (33.3)                           |          |
| No                                       | 148 (79)      | 86 (91.5)                          | 62 (66.7)                           |          |
| **Department**                          |               |                                    |                                     | .004     |
| Medicine                                 | 38 (20)       | 16 (17)                            | 22 (24)                             |          |
| 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**                          |               |                                    |                                     | .534     |
| Negative                                 | 172 (92)      | 88 (94)                            | 84 (90)                             |          |
| 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.

*Based on comparison of baseline QFT-Plus positive vs negative HWs.
converters had been exposed to higher median CO₂ 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 CO₂ 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 CO₂ 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.
The observed 

CO₂ 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 CO₂ 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

| 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) PValue | IGRA Nonconverters vs IGRA Converters OR (95% CI) PValue | IGRA Nonconverters vs IGRA Converters OR (95% CI) PValue |
|-----------|-----------------------------|-------------------------|---------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|
| Age, y, median (IQR) | 32 (25–42) | 37 (34–49) | 37 (34–43) | 1.05 (0.98–1.13) | 1.03 (0.96–1.11) | 1.04 (0.94–1.15) |
| Age category, <30 y, No. (%) | 11/24 (46) | 3/13 (23) | 1/5 (20) | 0.355 (0.18–1.62) | 0.181 | 0.443 (0.19–2.09) | 0.304 | 0.295 (0.13–3.05) | 0.306 |
| Male sex, No. (%) | 9/24 (38) | 2/13 (15) | 0/5 (0) | 0.303 (0.15–1.69) | 0.173 | 0.167 (0.02–1.53) | 0.113 | … | … |
| Intern, No. (%) | 8/24 (33) | 4/13 (31) | 1/5 (20) | 0.889 (0.21–3.80) | 0.874 | 1.14 (0.12–6.09) | 0.861 | 0.500 (0.05–5.24) | 0.563 |
| Department, No. (%) | 6/24 (25) | 3/13 (23) | 2/5 (40) | Reference | … | … | … |
| Medicine | 6/24 (24) | 3/13 (23) | 2/5 (40) | Reference | … | … | … |
| Surgery | 9/24 (38) | 1/13 (8) | 1/5 (20) | 0.222 (0.03–2.67) | 0.236 | 0.333 (0.04–7.10) | 1.00 | 1.00 (0.63–1.60) | 1.00 |
| A&E | 3/24 (13) | 1/13 (8) | 1/5 (20) | 0.667 (0.2–6.27) | 0.705 | 1.00 (0.63–1.60) | 1.00 | 1.00 (0.63–1.60) | 1.00 |
| Other | 6/24 (25) | 8/13 (62) | 1/5 (20) | 2.67 (0.47–8.47) | 0.270 | 3.50 (0.50–24.3) | 0.205 | 0.500 (0.04–7.10) | 0.609 |
| Time in healthcare, mo, median (IQR) | 42.5 (5–236.5) | 12 (10–107) | 12 (12–107) | 0.99 (0.99–1.00) | 0.589 | 0.99 (0.99–1.00) | 0.253 | 0.99 (0.99–1.00) | 0.679 |
| Temperature, °C, median (IQR) | 28 (27–30) | 29 (26–30) | 30 (25–30) | 1.05 (0.77–1.42) | 0.736 | 1.11 (0.79–1.55) | 0.545 | 1.06 (0.69–1.62) | 0.814 |
| CO₂, ppm/100, median (IQR) | 5.37 (4.95–6.73) | 6.60 (5.85–8.00) | 8.00 (7.85–9.00) | 1.58 (0.99–2.53) | 0.056 | 1.66 (1.02–3.16) | 0.042 | 2.04 (1.05–4.98) | 0.036 |
| Time spent at CO₂ level, min, median (IQR) | 82.5 (13.5–146) | 6.5 (0–33.5) | 0 (0–14) | 0.98 (0.97–0.99) | 0.028 | 0.98 (0.96–0.99) | 0.23 | 0.96 (0.90–1.01) | 0.138 |
| CO₂ level <500 ppm | 154 (125–230) | 209 (102–244) | 209 (102–214) | 1.00 (0.99–1.01) | 0.551 | 1.00 (0.99–1.01) | 0.410 | 1.00 (0.98–1.01) | 0.750 |
| CO₂ level <1000 ppm | 1.5 (0–13.3) | 11.5 (0–47) | 47 (29–59.5) | 1.01 (0.99–1.03) | 2.08 | 1.01 (0.99–1.03) | 1.73 | 1.02 (1.03–1.05) | 0.122 |
| CO₂ level <1500 ppm | 0 (0–0.75) | 0 (0–1.5) | 1.5 (0–1.5) | 1.02 (0.87–1.21) | 0.823 | 1.00 (1.85–1.18) | 0.904 | 1.07 (0.90–1.26) | 0.462 |

Abbreviations: A&E, accident and emergency; CI, confidence interval; CO₂, carbon dioxide; IGRA, interferon-γ release assay; IQR, interquartile range; OR, odds ratio; ppm, parts per million.
A 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
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 CO2 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 CO₂ 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 CO₂ levels increased the odds of IGRA conversion. We propose that personal ambient CO₂ 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 copyrighted 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.

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