Performance of TB Antigen-Based Skin Tests Amongst Healthcare Workers—Sevagram, India, 2023–2024

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MAJOR ARTICLE

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Background. Tuberculosis infection among healthcare workers poses a major occupational health risk in resource-limited, high-burden settings. SIILTIBCY® (CY-TB) is a novel antigen-based skin test for TBI that may offer a simpler, low-cost, field-deployable alternative to laboratory-based interferon-gamma release assays such as QuantiFERON-TB® Gold In-Tube Plus (QFT).

Objective. To estimate TBI prevalence among HCWs at Mahatma Gandhi Institute of Medical Sciences/Kasturba Hospital Sevagram (MGIMS) and evaluate the diagnostic performance of CY-TB compared to QFT.

Methods. In a prospective cohort at MGIMS, consenting HCWs without TB disease underwent both CY-TB and QFT testing during July 2023–June 2024. Diagnostic performance of CY-TB was assessed using QFT as the reference standard.

Results. Of 2071 HCWs offered screening, 1753 (84.6%) consented and 1338 (76.3%) had paired test results. The median age was 29 years (IQR: 19.5, 38.5); 63% were female. Overall prevalence of TB infection was 28.5% (95% CI 26.1–31.0). CY-TB sensitivity and specificity were 76.4% (95% CI 71.6–80.7) and 97.0% (95% CI 95.7–97.9), respectively. The positive and negative predictive values were 90.9% and 91.1%.

Conclusions. CY-TB performance was comparable to QFT, suggesting it may be a practical, low-cost tool for TB infection screening in resource-limited healthcare settings.

Keywords. CY-TB; healthcare workers; QFT; tuberculosis infection.

Prevention of tuberculosis (TB) among healthcare workers (HCWs) is a priority in high-burden settings due to ongoing exposure and risk of transmission to patients, other staff, and the community [1, 2]. Early detection and treatment of TB disease reduce TB transmission, while identification of tuberculosis infection (TBI) can additionally indicate recent exposure to a patient or staff member with undiagnosed TB disease [2, 3]. Tuberculosis preventive treatment (TPT) for those with TBI prevents future development of TB disease [3–7]. Key activities in a HCW screening program consist of regular periodic screening for TB disease and TBI; including symptom screening, evaluation, diagnosis, and treatment of TB disease and testing and treatment for TBI [1].

Diagnostic options for TBI included the tuberculin skin test (TST), which is low-cost but limited by false positives in BCG-vaccinated persons, and interferon-gamma release assays (IGRAs), such as QuantiFERON-TB® Gold In-Tube Plus (QFT; QIAGEN, Hilden, Germany) QFT, which offer higher specificity but have greater laboratory, personnel, and cost requirements [8, 9]. Uptake for TPT can be challenging, and TBI "test and treat" policies using tests that distinguish BCG-related false-positive results from TBI may increase TPT acceptance [3, 4]. The most recent global recommendations include new TB antigen-based skin tests (TBSTs) for TBI, which provide the benefits of high specificity, eliminating false-positive results as a consequence of BCG vaccine or non-tuberculous mycobacteria infection, and do not require additional laboratory infrastructure [3, 5, 6]. SIILTIBCY® (CY-TB; Serum Institute of India) is one TBST which has been approved for use in India [10]. However, data on its performance among HCW remain limited. We sought to compare its performance with QFT in a high TB prevalence setting through simultaneously collected CY-TB and QFT tests from HCWs being evaluated for TBI.

Mahatma Gandhi Institute of Medical Sciences/Kasturba Hospital (MGIMS), SHARE INDIA, and US Centers for Disease Control and Prevention worked closely on a program of interventions to detect and prevent TB and TBI in HCWs working at MGIMS. These activities were conducted to inform the development of a routine program for TB screening and prevention among HCWs at MGIMS. Routine HCW screening also provided an important opportunity for early diagnosis and prevention of other transmissible diseases such as COVID-19 and influenza, as well as

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noncommunicable diseases such as diabetes, and hypertension [11]. As newly recommended TBSTs such as CY-TB are being implemented, it is important to evaluate their performance in the field. The primary objectives of this analysis were to measure TBI prevalence in MGIMS HCWs and assess test performance of CY-TB relative to QFT amongst HCWs during baseline TBI screening.

METHODS

This analysis was part of a larger prospective cohort study aimed to identify, treat, and prevent the acquisition and progression of TB amongst HCWs over time. During July 2023–June 2024, we approached HCWs stationed at MGIMS to participate in the screening activities. healthcare workers included medical and paramedical personnel, medical and nursing students, and staff from administrative and ancillary departments. For those that consented, HCWs were screened for symptoms of TB disease (eg, cough, fever, night sweats, weight loss) and tested for TBI. Those reporting symptoms on TB screening received a chest radiograph, consultation with a medical officer, and had sputa collected for further TB diagnostic testing. Both CY-TB and QFT were conducted for TBI testing on all consenting participants. Asymptomatic participants with any positive TBI test results received a chest radiograph and additional evaluations for TB.

Briefly, venous blood was collected and processed for QuantiFERON-TB® Gold In-Tube Plus tests (QIAGEN, Hilden, Germany) as per the manufacturer's manual of procedures. Interferon-gamma concentrations ≥0.35 IU/mL and ≥25% above the nil value were considered positive. Afterwards, 0.1 mL dose of CY-TB was administered intradermally using the standardized Mantoux technique. CY-TB test results were read 48–72 hours postadministration, and indurations ≥5 mm were considered positive. Serum Institute of India provided standardized training curriculum and practicums on CY-TB placement for project staff. Training and successful completion of proficiency testing were required for laboratory staff conducting QFT at MGIMS before project initiation. Site visits, including laboratory assessments, were conducted for quality assurance; CY-TB readings by different staff were conducted to measure inter-reader consistency.

Overall TBI was defined as at least one positive test result on either CY-TB or QFT, consistent with global guidance, and principles for clinical decision-making [1, 3, 12]. We evaluated CY-TB diagnostic test performance (ie, sensitivity, specificity, positive predictive value, negative predictive value, Cohen's Kappa coefficient [κ]) with accompanying confidence limits (95% CL) using QFT-based results as the reference standard [13]. Participants without paired results were excluded from diagnostic performance analyses. This study was conducted and reported according to STROBE guidelines [14].

RESULTS

Of 2071 HCWs offered screening, 1753 (84.6%) consented to participate. Among 1753 participants, 1746 (99.6%) completed QFT testing and 1345 (76.7%) completed CY-TB testing; 1338 (76.3%) participants had both tests and were included in paired analyses (Figure 1). The median age of the HCW cohort was 29 years (IQR: 19.5–38.5) and the majority were female (n = 808; 63%).

Of 1746 HCW tested by QFT, 435 (24.9%) were positive; the median quantitative value was 1.21 IU/ml (IQR: 0.60–2.98 IU/mL). Among 1345 HCW tested by CY-TB, 298 (22.1%) were positive, with a median induration of 14 mm (IQR:12–16 mm). Among the 1338 (76%) HCWs with both test results, the prevalence of TBI based on either positive test was 28.5% (95% CL: 26.1–31.0). Using QFT as the reference standard, the sensitivity and specificity of CY-TB among those with paired results were 76.4% (95% CL: 71.6–80.7) and 97.0% (95% CL: 95.7–97.9), respectively (Table 1). The positive and negative predictive values were 90.9% (95% CL: 87.5–93.5) and 91.1% (95% CL: 89.5–92.6), respectively, assuming a TBI prevalence consistent with this setting. Agreement between CY-TB and QFT was substantial ($\kappa = 0.77$; 95% CL: 0.73–0.81) (Table 1).

Healthcare workers who refused either QFT or CY-TB test were more likely to be male, aged 18–30 years old, or students (Table 2). For paired tests, there were 83 QFT-positive/CY-TB-negative and 30 QFT-negative/CY-TB-positive discordant results. More than half of the QFT-positive discordant results had quantitative values <1.0 IU/mL, and none of the CY-TB indurations were near the 5 mm cutoff value (Table 3). All administered CY-TB tests were read, no indeterminate QFT results were observed.

DISCUSSION

Historical examples and modeling studies highlight the critical role TB prevention plays in achieving TB elimination goals [15–17]. Without an effective TB vaccine, TPT is the only proven intervention to prevent progression from infection to TB disease [1, 3]. Healthcare worker are rarely prioritized for TPT due to competing program priorities and the challenges of diagnosing TBI in high-prevalence settings like India [4]. However, HCW face an elevated risk of acquiring TB due to occupational exposure to patients with delayed or missed TB diagnoses [18–22].

CY-TB employs the same *M. tuberculosis*-specific antigens as IGRAs, offering high specificity without the need for laboratory infrastructure. It is comparable in cost to TST, while providing IGRA-like advantages [23]. However, CY-TB retains some limitations of skin tests, including cold chain requirements, the need for trained personnel for administration and interpretation, a return visit within 48–72 hours, and subjectivity in induration measurement [24, 25]. To enhance measurement reliability, we incorporated standardized training, proficiency

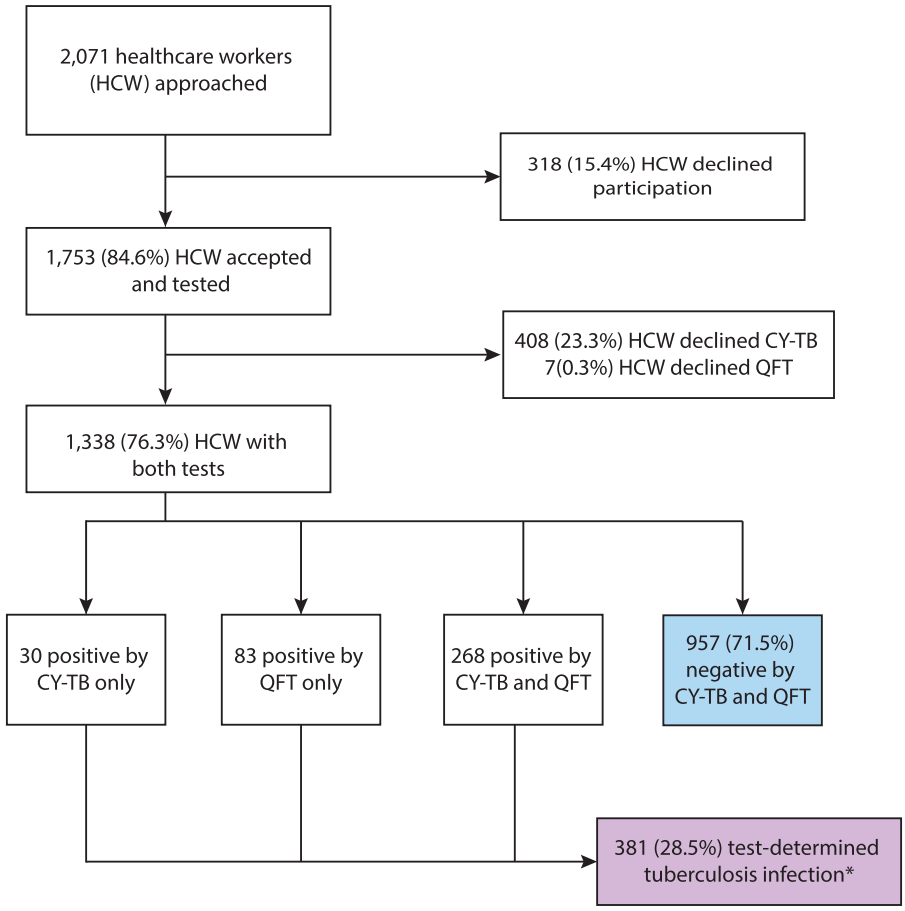

Figure 1. Study flow diagram for diagnostic testing for tuberculosis infection among healthcare workers— Kasturba Hospital, Sevagram, India, 2023-2024. *at least one positive test result on SIILTIBCY® (CY-TB) or QuantiFERON-TB® Gold In-Tube Plus (QFT).

Table 1. Diagnostic Test Performance of CY-TB Compared With QuantiFERON-TB® Gold In-Tube Plus as the Reference Standard Amongst Healthcare Workers—Kasturba Hospital, Sevagram, India, 2023–2024

	CY-TB® Result		
QuantiFERON-TB® Result	Positive	Negative	Total
Positive	268	83	351
Negative	30	957	987
Total	298	1040	1338
Performance Metrics	Value	95% CL	
Prevalence	28.5%	26.1	31
Sensitivity	76.4%	71.6	80.7
Specificity	97.0%	95.7	97.9
Positive predictive value[a]	90.9%	87.5	93.5
Negative predictive value[a]	91.1%	89.5	92.6
Kappa	0.77	0.73	0.81

[a]Values dependent on disease prevalence of 28.5% (26.1–31.0) CL = confidence limits.

Table 2. Characteristics of Healthcare Workers (HCWs) With Paired QFT/CY-TB Results Compared With Those Without Paired Test Results—Kasturba Hospital, Sevagram, India, 2023–2024

Characteristic	HCWs with Paired Results (n = 1338) n/(%)	HCWs Without Paired Results (n = 415) (%)	*P* Value[a]
Total	1338/1753 (76.3%)	415/1753 (23.7%)	
Sex			
Male	530/1338 (39.6%)	220/415 (53%)	*P* < .001
Female	808/1338 (60.9%)	195/415 (47%)	
Age group, years			
18–30	735/1338 (54.9%)	266/415(64.1%)	*P* < .001
31–43	342/1338 (25.6%)	85/415(20.5%)	
44–56	222/1338 (16.6%)	57/415 (13.7%)	
57–70	39/1338 (2.9%)	7/415 (1.7%)	
Healthcare worker category			
Medical/ nursing student	548/1338 (41%)	227/415 (54.7%)	*P* < .001
Hospital staff	790/1338 (59%)	188/415 (45.3%)	

[a]χ^2 test compared distributions across each category.

assessment, and quality assurance procedures, including inter-reader evaluations and blinded chart reviews.

MGIMS is located near the rural village of Sevagram, where many HCWs and students reside on or near the hospital campus. This setting facilitated follow-up for test measurements and clinical evaluation, through structured counseling

Table 3. Quantitative Values for Discordant QFT/CY-TB Results Amongst Healthcare Workers—Kasturba Hospital, Sevagram, India, 2023–2024

	Quantitative QFT Range (IU/mL)	Number of Results	CY-TB Induration (mm)	Number of Results
QFT-positive/CY-TB-negative	0.35–0.70	36	<5 mm	83
	0.71–1.0	10		
	> 1.0	37		
QFT-negative/CY-TB-positive	<0.35	30	5 mm	0
			6–7 mm	1
			8–9 mm	0
			>10 mm	29

and follow-up reminders. The absence of indeterminate QFT, while uncommon, has been reported previously in this setting [26]. This may reflect the relatively young and healthy HCW population, and near-point-of-care specimen processing. These findings suggest that CY-TB implementation may be feasible in similar settings; however, feasibility and performance may differ in settings with limited access to occupational health services, or those with restricted operational hours.

The performance of CY-TB compared to QFT among HCW from MGIMS Sevagram, India approximated those reported in other published studies [27–30]. Agreement from our study ($\kappa = 0.77$; 95% CL: 0.73, 0.81) was similar to a recent systematic review used to guide global recommendations for CY-TB among people without HIV ($\kappa = 0.80$; 95% CL: 0.76, 0.83) as compared to QFT [3], along with findings from earlier randomized controlled trials [27–28], and other studies in high and low-TB incidence settings [29, 30]. Our CY-TB results met the 2017 global target product profile targets for TBI diagnostic tests, with an acceptable target of sensitivity ≥75% and ideal target of specificity ≥90%; in line with optimal performance characteristics of currently available TBI tests [31]. The high specificity of CY-TB compared to QFT is not surprising, since they share the same *M. tb*-specific antigens. However, the sensitivity of CY-TB and TST, both skin tests, are different; CY-TB sensitivity was lower than QFT, whereas TST is comparatively higher.

The reasons are unclear and future studies may clarify whether our findings reflect the performance of CY-TB in the field. Use of CY-TB in people with immunosuppression or increased risk of progression to TB will need to be carefully considered and clinicians may choose dual testing along with an interferon-gamma release assay, such as is done sometimes for hemodialysis patients, HIV contacts, or TNF-antagonist recipients in low-TB incidence countries.

The utility of a TBST such as CY-TB in different epidemiologic settings requires careful consideration. From a programmatic perspective, CY-TB may be preferred in settings where laboratory capacity, cost, and access limit the feasibility of IGRAs, particularly for large-scale or routine HCW screening. Its high specificity and operational simplicity support its use as a primary test in resource-limited, moderate- to high-incidence settings where follow-up for test reading is feasible. In contrast, IGRAs such as QFT may remain preferable in settings where return visits are impractical or where laboratory infrastructure is readily available. Dual testing with CY-TB and QFT may be considered for individuals at higher risk of progression to TB disease—such as those with immunosuppression—or when test results are discordant and clinical decision-making is uncertain, as a combined approach may improve diagnostic confidence and better inform decisions regarding TPT. An immunocompetent person has a ∼10% lifetime risk of progression from TBI to TB; the risk rises for persons with immunocompromised conditions such as HIV [5, 6]. Because TPT carries a small but potentially serious risk of adverse events, diagnostic strategies that prioritize specificity can help minimize false positives (due to BCG vaccination) and target therapy to those most likely to benefit [3]. Additionally, all current available TBI tests rely on host immune response and may have reduced sensitivity in conditions associated with immune anergy, including advanced HIV infection, hemodialysis, immunosuppressive therapies, malnutrition, or active TB disease [32]. In such populations, providing TPT without prior TBI testing is common practice in high-burden settings [33]. Selection of TBI diagnostic approaches should therefore balance patient risk, feasibility of follow-up, availability of laboratory infrastructure, and programmatic constraints. To date, there are no published studies looking at predictive value or outcomes of TPT effectiveness on TB progression based on positive CY-TB results, although future follow-up of this and other cohorts, like those currently underway in Vietnam [34], will address this issue.

The baseline TBI prevalence of 28.5% in this cohort was within the expected range—lower than that reported among household contacts with known TB exposure but higher than estimates for the general population [35]. Study staffs were trained in skin test placement and received additional instruction from the manufacturer. However, test reliability may be reduced in settings with suboptimal reagent storage, insufficient training or delayed and missed readings.

This report evaluates the performance characteristics of CY-TB, a new test, compared to the established QFT. Since no definitive reference standard exists for TB infection [3, 31–33], studies often rely on comparative designs to estimate the accuracy of TBI diagnostics. In the absence of a reference standard, researchers typically: (1) use individuals with TB disease as controls to assess sensitivity and unexposed healthy individuals as controls for specificity, (2) infer true infection in positive cases based on TB exposure levels or disease progression, or (3) compare the new test with existing methods like TST and QFT, despite their own inherent limitations and

imperfect sensitivity [31]. These limitations apply to our study, as stratification by TB exposure or progression to TB disease was not feasible. However, this study provides a direct comparison between CY-TB with an established test in a moderate- to high-incidence setting representative of India.

HIV status was not collected, as HIV testing is not part of routine employee screening at MGIMS. In India, HIV testing is primarily recommended for key populations and close contacts of persons with HIV, which generally does not include HCWs [4]. Given that the HIV epidemic in India is concentrated within key populations, the prevalence of undiagnosed HIV among HCWs is likely low. However, undiagnosed HIV, could reduce TBI test sensitivity and lead to an underestimation of TBI prevalence.

We observed higher nonparticipation for CY-TB than QFT, the reasons for which remain unclear. This may reflect limited familiarity with CY-TB at the time of study initiation, as well as the broader decline in use of skin-based tests in India following shortages of purified protein derivative [4]. Additionally, stigma related to TB may discourage participation in screening, testing, and follow-up care among HCWs [36]. Importantly, participants without paired results differed by age, sex, and occupation type potentially biasing some performance estimates. Future studies may determine if acceptance of CY-TB will improve, or if increased awareness and availability within the general public and health sector will be needed to bolster uptake.

TB antigen-based skin tests such as CY-TB offer a practical option for TBI screening, with high specificity, lower costs, and minimal laboratory requirements, making them well suited for resource-limited healthcare settings. Incorporation of CY-TB into routine screening programs may help protect HCWs, reduce nosocomial transmission, and support broader TB elimination goals. Continued follow-up of this cohort will be important to assess the predictive value of CY-TB for progression to TB disease and to inform policy and programmatic use. The optimal role of CY-TB in low-TB incidence settings remains to be defined, although cost-effective diagnostic options are relevant across all settings.

CONCLUSION

To our knowledge, this is the first study evaluating the CY-TB performance among HCWs in a high TB-burden setting under programmatic conditions. CY-TB demonstrated strong agreement with QFT, with high specificity and moderate sensitivity for detecting TBI. These findings support the feasibility of CY-TB as a practical, low-cost alternative in settings with limited laboratory infrastructure. However, lower uptake compared to QFT highlights the need to better understand and address barriers to acceptance, including the requirement for a return visit, and limited familiarity with the test.

Notes

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Author contributions. C. S. H. and P. K. M. designed the study, and R. D., S. B., A. R., and J. P. S. performed data verification and final analysis. All authors contributed to the writing of the manuscript.

Data availability. With the purpose of respecting the privacy of individual participants, data is not publicly available, but will be shared on reasonable request to the corresponding author.

Patient consent statement. Local ethical review and approval was provided by the Institutional Ethics Committee of MGIMS in Sevagram, Maharashtra and the SHARE INDIA Mediciti ethics committee. In accordance with CDC human research protection procedures, this project was reviewed and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes. Written informed consent was obtained from all participants.

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