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Optimizing diagnosis and treatment of tuberculosis infection in community and primary care settings in two urban provinces of Viet Nam: a cohort study

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ABSTRACT

Objectives: To end tuberculosis (TB), the vast reservoir of 1.7-2.3 billion TB infections (TBI) must be addressed but achieving global TB preventive therapy (TPT) targets seems unlikely. This study assessed the feasibility of using interferon-gamma release assays (IGRA) at lower healthcare levels and the comparative performance of 3- and 9-month daily TPT regimens (3HR/9H).

Methods: This cohort study was implemented in six districts of Ho Chi Minh City and Hai Phong, Viet Nam, from May-2019 to Sept-2020. Participants included household contacts (HHC), vulnerable community members and healthcare workers (HCW) recruited at community-based TB screening events or HHC investigations at primary care centers, who were followed up throughout TPT. We constructed TBI care cascades describing indeterminate and positivity rates to assess feasibility, and initiation and completion rates to assess performance. We fitted mixed-effect logistic and stratified Cox models to identify factors associated with IGRA-positivity and loss to follow-up (LTFU).

Results: Among 5,837 participants, the indeterminate rate was 0.8% and 30.7% were IGRA-positive. TPT initiation and completion rates were 63.3% (3HR=61.2% vs. 9H=63.6%; p=0.147) and 80.6% (3HR=85.7% vs. 9H=80.0%; p=0.522), respectively. Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78]; p<0.001), aged 45-59 years (1.30 [1.05, 1.60]; p=0.018) and exhibiting TB-related abnormalities on X-ray (2.23 [1.38, 3.61]; p=0.001) were associated with positive IGRA results. Risk of IGRA-positivity was lower in peri-urban districts (0.55 [0.36, 0.55]; p=0.007), aged <15 years (0.18 [0.13, 0.26]; p<0.001), aged 15-29 years (0.56 [0.42, 0.75]; p<0.001), and HCWs (0.34 [0.24, 0.48]; p<0.001). The 3HR regimen (adjusted Hazard Ratio=3.83 [1.49, 9.84]; p=0.005) and HCWs (1.38 [1.25, 1.53]; p<0.001) showed higher hazards of LTFU.

Conclusion: Providing IGRA at lower healthcare levels is feasible and along with shorter regimen may expand access and uptake towards meeting TPT targets, but scale-up may require complementary advocacy and education for beneficiaries and providers.

Keywords: tuberculosis, infection, community, urban, interferon-gamma release assay, short-course, tuberculosis preventive therapy

Running head: Optimizing diagnosis and treatment of TB infection in Viet Nam

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of the study was the large sample size of persons tested by interferon-gamma release assay across two sites with varying characteristics in background tuberculosis infection as well as demographic and clinical characteristics, which enabled comparative analyses of subsegments of the sample.
- The community setting in which participants were recruited and tested using sophisticated diagnostics decentralized to lower care levels further contributes to the evidence base for scale-up of tuberculosis prevention, especially given the size of the sample.
- Embedding the study in routine tuberculosis program activities exposed it to common limitations such as heterogeneity in supply chain as well as health worker knowledge, attitudes and practices commonly experienced by the program.

INTRODUCTION

After a brief relegation due to the COVID-19 pandemic, tuberculosis (TB) is once again the world's leading infectious disease killer.[1] One of the key reasons is the estimated 1.7–2.3 billion people infected with TB without suffering from active disease, whose activation continues to fuel incidence.[2,3] An estimated 5-15% of people with TB infection (TBI) develop active TB disease in their lifetimes, serving as a vast reservoir for future TB disease, even if new TB transmission were completely eliminated today.[4,5] This was also observed by a study in London at the height of the pandemic which showed that social distancing mitigated incidence of several respiratory diseases, but not of TB.[6] Thus, research and modeling suggest that increased emphasis on TBI is needed in order to reduce worldwide TB incidence.[7] However, while efforts to find and treat people with TB who are missed by existing TB care programs have been launched in most high TB burden countries, relatively few are addressing the burden of TBI at scale.[8–11]

This muted response was historically linked to World Health Organization (WHO) guidelines recommending TB preventive therapy (TPT) in high TB burden settings only for people living with HIV (PLHIV), under-5 household contacts (HHC) of persons with bacteriologically-confirmed, pulmonary TB and persons with occupational risk factors for progression to active TB.[12] Beyond conservative guidelines, other commonly cited bottlenecks have included shortages in commodities and particularly diagnostic consumables such as tuberculin, high health system costs of diagnosis, treatment and follow-up depressing TPT uptake, and lack of patient-friendly treatment regimen negatively affecting adherence.[13,14]

In recent years, the WHO has issued updated technical and operational guidelines with expanded TPT eligibility criteria, such as HIV-negative household contacts of all ages.[15,16] However, a key recommendation for this expanded eligibility was the inclusion of an appropriate clinical and laboratory evaluation, which in select settings translated to the prerequisite of immunological confirmation of TBI by tuberculin skin test (TST) or interferon-gamma release assay (IGRA) for TPT within national guidelines.[14,17] The updated WHO guidelines also introduced new short-course TPT regimens with better tolerability and safety profiles, which high TB burden countries have eagerly integrated into national TBI guidelines and national strategic plans.[18,19]

One of these countries is Viet Nam, which ranks 11th among the 30 high TB burden countries. During the first prevalence survey, the annual rate of TB infection was measured to be 1.7% with a TBI prevalence of 16.7% in children aged 6–14 years using TST with a threshold of 10mm.[20] A subsequent study in rural Ca Mau province measured a TBI rate of 36.8% using IGRA.[21] In 2014, Viet Nam passed legislation codifying its goals to drastically reduce TB prevalence in alignment with the WHO End TB Strategy.[22] On World TB Day 2020, the Ministry of Health introduced the country's inaugural guidelines on diagnosis and treatment of TBI. Viet

Nam further demonstrated its focus on TB prevention by committing at the UN High-Level Meeting on Ending TB to scale-up provision of TPT to 291,500 people by 2022.[23]

However, the country has experienced many of the challenges related to the scale-up of TPT as described above. Specifically, Viet Nam requires TBI confirmation within the expanded eligibility criteria prior to treatment, but has experienced tuberculin supply chain shortages and batch-variance in the positivity threshold. While WHO-recommended IGRAs are commercially available, the National TB Control Programme (NTP) has consigned this assay class to tertiary care facilities due to the delicate specimen handling and sophistical laboratory requirements,[24,25] which is underscored by the lack of published evidence of the assay's deployment at the point-of-care domestically and worldwide. In addition, the prohibitively high costs per test have precluded serious consideration for routine TB program activities.

Nevertheless, the NTP remains committed to the scale-up of TPT through the optimal use of available and new diagnostics and regimens.[26] Given tuberculin supply and staff capacity challenges, and lack of evidence on the impact of recently introduced shorter TPT regimen on uptake and completion, this study assessed the use of the QuantiFERON-TB Gold Plus assay (QFT-Plus; Qiagen, Hilden, Germany) at the community level and the performance of shorter TPT regimen under programmatic conditions. The goal was to inform NTP of Viet Nam and other high TB burden countries in their ambitions to meet their TPT goals.

METHODS

Study design and objectives

This was a cohort study to measure the feasibility of employing IGRA at the community and primary care levels for the diagnosis of TBI. Feasibility was defined by comparing indeterminate and positivity rates with those demonstrated in facility-based studies (primary endpoints). Secondary objectives included measuring the rate of TPT initiation and completion (secondary endpoints) in cohorts provided with two different TPT regimens, and to identify participant covariates associated with IGRA-positivity and loss to follow-up. The study followed the STROBE guideline for reporting observational studies (Supplemental material 1).

Study setting

The study was conducted in six districts of Ho Chi Minh City (HCMC) and Hai Phong municipal provinces. In HCMC, study sites included Districts 6, 8, 12, Binh Chanh, Go Vap, and Tan Binh with a cumulative population of 2,387,052 and 3,598 TB notifications in 2019. In Hai Phong, the study took place in Do Son with a population of 49,029 and 52 persons with drug-susceptible TB notified in 2019.

Study population and recruitment

The study was embedded into routine contact investigations at primary care commune health posts and community-based active TB case finding (ACF) events. Details of the ACF events are provided elsewhere.[27] The study population included HHC and close contacts, and vulnerable community members at elevated risk of active TB, such as the elderly, urban poor and economic migrants.[28] The HCMC site also included a subgroup of primary- and secondary-level healthcare workers (HCW) based on the request from local authorities. Recruitment and follow-up occurred from May-2019 to Sep-2020. All individuals presenting for screening provided routine demographic and clinical information including age, sex, residency status, history of TB, comorbidities and symptomatic presentation. Following intake, persons belonging to the study population with residency in the study districts were invited to participate in the study. Persons living outside of or intending to relocate away from the study sites, or who declined to consent were excluded. Eligible, consenting participants were recruited consecutively until the quota of available QFT-Plus tests was reached (n=5,000 in HCMC and n=1,000 in Hai Phong). Parents consented on behalf of their children.

Specimen collection and processing

Provincial lung hospital (PLH) laboratory staff hosted training sessions on specimen collection and processing for the District TB Unit (DTU) and district-level laboratory staff. The District Health Center (DHC) mobilized participants to attend ACF events or to present at commune health posts. All attendants were systematically screened for TB symptoms and directed to undergo chest radiography (CXR) to rule out active TB. Persons with parenchymal abnormalities suggestive of TB on CXR or strong clinical suspicion of TB were referred for molecular sputum testing, as per contemporary national TB treatment guidelines.[29] Attendants were counseled on TBI and invited to participate. Study staff collected blood specimens from consenting, eligible individuals as per manufacturer recommended procedures. Each participant provided 4ml of venous whole blood in four separate tubes. Blood specimens were processed and analyzed per manufacturer's recommendations. Briefly, all four tubes were immediately shaken ~10 times to dissolve all antigens on the tube's wall coating. Tubes were stored inside dry ice coolers at 17–25°C, which were transported to the PLH biochemistry–hematology departments within six hours, twice a day. Samples were incubated at 37°C for 20 hours (±1 hour) and centrifuged within one hour of completing the incubation stage at 2000-3000g for 14 minutes at room temperature. The twelve-step enzyme linked immunosorbent assay was conducted within 16-24 hours. Results were analyzed by using proprietary QuantiFERON software v2.7.1.

TPT initiation and participant follow-up

QFT-Plus test results were returned to the DHC two days after receipt of the blood specimens. Individuals with negative results were informed via phone by DHC staff. Those with positive results and eligible for preventive

treatment (i.e., with confirmed TBI and active TB ruled out) were invited to present at their respective DTU for pre-treatment counseling and TPT initiation as per national guidelines.[17] TPT regimen varied by province. In HCMC, TPT consisted of nine months of daily isoniazid (9H), while in Hai Phong eligible persons received three months of daily isoniazid and rifampicin (3HR). Individuals on TPT received in-person follow-up during monthly drug pick-up at the DTU. Community TB officers conducted phone or in-person follow-up in regular intervals or as needed. Participants experiencing adverse events were asked to present at the DTU for check-up.

Statistical analyses

The primary measures of interest were QFT-Plus positivity and indeterminate rates. Secondary variables of interest included TPT initiation and completion rates within the study population. Missing data were retrieved through post-event follow-up of participants or excluded from individual analyses. We constructed TBI care cascades in aggregate and segmented by site ranging from persons recruited to participants with a successful TPT completion. We documented losses along the cascade and reported median and interquartile ranges of diagnostic delay, i.e., time from testing to TPT initiation. We calculated descriptive statistics for key sample characteristics by QFT-Plus result and TPT completion and fitted a saturated, mixed-effect logistic regression to assess associations between positivity and participant covariates to adjust for confounding and inherent bias. Study district was the random effect to account for intra-cluster correlation. The survival analysis designated loss to follow-up (LTFU) a failure and censored adherent participants on 3HR and 9H at three and nine months, respectively. We constructed Kaplan-Meier survival curves and conducted log-rank tests to assess the equality of survival between the two TPT regimen. We fitted a saturated Cox model and assessed validity of the proportionality assumption using log-log plots and Schoenfeld residuals. Violations were addressed via stratification or modeling of time-variance for parameters of interest. The final model passed both the global postestimation proportional hazards test and tests of individual parameters. P-values of validation tests were provided in the Supplemental material 2. Hypothesis tests were two-tailed. A threshold of $p<0.05$ was considered significant. Analyses were conducted using STATA v17 (Stata Corp.; College Station, TX, USA).

Patient and public involvement

While TB patients and their families were not involved in setting the research question, a consensus building meeting was held at the beginning of the study for government stakeholders and community members to provide feedback and recommendations and reach consensus about the study design and implementation. Patients, their families and public stakeholders were also central to dissemination of study information, which helped to motivate community involvement during and beyond the study.

RESULTS

Sample characteristics

Of the 5,837 participants in the sample, 59.3% (n=3,463) were female (Table 1). Children under 15 years constituted 19.5% (1,136/5,834) of the sample and the median participant age was 40 (IQR: 20–55). Overall, most participants were recruited at community-based ACF events (55.8%; n=3,257), lived in urban areas (65.6%; n=3,827), were permanent residents (90.5%; 3,116/3,444) and were enrolled on social health insurance (90.4%; 5,269/5,832). About 2.9% (n=167) were diabetics and 1.1% (n=62) reported a history of TB. Moreover, 39.5% (n=2,306) reported experiencing at least one of the four core TB symptoms (cough, weight loss, fever, and/or night sweats) during recruitment, while 2.3% (n=134) participants exhibited TB-related CXR abnormalities.

194 **Table 1: Participant characteristics and adjusted odds ratios associated with IGRA-positivity**

	Total (N = 5,837) N (%)¤	IGRA(+)¥ (N = 1,792) N (%)	IGRA (-)¥ (N = 4,000) N (%)	Indeterminate (N = 45) N (%)	aOR¥ (95% CI)	p-value†
Sex						
Female	3,463 (59.3)	1,048 (30.3)	2,392 (69.1)	23 (0.7)	Ref	
Male	2,374 (40.7)	744 (31.3)	1,608 (67.7)	22 (0.9)	1.51 [1.28; 1.78]	<0.001
Age¶						
<15 years	1,136 / 5,834 (19.5)	134 / 1,792 (11.8)	997 / 3,997 (87.8)	5 / 45 (0.4)	0.18 [0.13; 0.26]	<0.001
15-29 years	891 / 5,834 (15.3)	195 / 1,792 (21.9)	687 / 3,997 (77.1)	9 / 45 (1.0)	0.56 [0.42; 0.75]	<0.001
30-44 years	1,290 / 5,834 (22.1)	418 / 1,792 (32.4)	864 / 3,997 (67.0)	8 / 45 (0.6)	Ref	
45-59 years	1,679 / 5,834 (28.8)	704 / 1,792 (41.9)	957 / 3,997 (57.0)	18 / 45 (1.1)	1.30 [1.05; 1.60]	0.018
≥60 years	838 / 5,834 (14.4)	341 / 1,792 (40.7)	492 / 3,997 (58.7)	5 / 45 (0.6)	1.06 [0.80; 1.40]	0.673
Median age (IQR)	*40 (20–55)*	*49 (35–58)*	*35 (15–52)*	*45 (24–54)*		
Study site						
Ho Chi Minh City	4,840 (82.9)	1,603 (33.1)	3,200 (66.1)	37 (0.8)	Ref	
Hai Phong	997 (17.1)	189 (19.0)	800 (80.2)	8 (0.8)	0.69 [0.40; 1.20]	0.186
Screening location						
Community screening event	3,257 (55.8)	993 (30.5)	2,244 (68.9)	20 (0.6)	Ref	
Primary care center	2,580 (44.2)	799 (31.0)	1,756 (68.1)	25 (1.0)	0.88 [0.69; 1.13]	0.325
Target group						
Household and close contacts	2,431 (41.7)	897 (36.9)	1,495 (61.5)	39 (1.6)	1.11 [0.67; 1.82]	0.690
Vulnerable community members	2,995 (51.3)	821 (27.4)	2,168 (72.4)	6 (0.2)	Ref	
Healthcare workers	411 (7.0)	74 (18.0)	337 (82.0)	0 (0.0)	0.34 [0.24; 0.48]	<0.001
Urbanization						
Urban	3,827 (65.6)	1,135 (29.7)	2,669 (69.7)	23 (0.6)	Ref	
Peri-urban	2,010 (34.4)	657 (32.7)	1,331 (66.2)	22 (1.1)	0.55 [0.36; 0.85]	0.007
Residency status‡,¶						
Grade 1	3,116 / 3,444 (90.5)	799 / 907 (25.6)	2,294 / 2,511 (73.6)	23 / 26 (0.7)	Ref	
Grade 2	91 / 3,444 (2.6)	27 / 907 (29.7)	62 / 2,511 (68.1)	2 / 26 (2.2)	1.08 [0.66; 1.74]	0.765
Grade 3	202 / 3,444 (5.9)	68 / 907 (33.7)	134 / 2,511 (66.3)	0 / 26 (0.0)	1.36 [0.96; 1.92]	0.083
Grade 4	35 / 3,444 (1.0)	13 / 907 (37.1)	21 / 2,511 (60.0)	1 / 26 (2.9)	1.54 [0.73; 3.26]	0.260
Social health insurance¶						
No	563 / 5,832 (9.7)	180 / 1,790 (32.0)	376 / 3,997 (66.8)	7 / 45 (1.2)	Ref	
Yes	5,269 / 5,832 (90.4)	1,610 / 1,790 (30.6)	3,621 / 3,997 (68.7)	38 / 45 (0.7)	1.11 [0.84; 1.46]	0.473

Diabetes mellitus						
No/Unknown	5,670 (97.1)	1,721 (30.4)	3,906 (68.9)	43 (0.8)	Ref	
Yes	167 (2.9)	71 (42.5)	94 (56.3)	2 (1.2)	1.15 [0.75; 1.76]	0.516
Previous history of TB						
No/Unknown	5,775 (98.9)	1,764 (30.6)	3,967 (68.7)	44 (0.8)	Ref	
Yes	62 (1.1)	28 (45.2)	33 (53.2)	1 (1.6)	1.93 [0.96; 3.86]	0.063
Any TB symptoms§,¶						
No	3,531 (60.5)	1,012 (28.7)	2,499 (70.8)	20 (0.6)	Ref	
Yes	2,306 (39.5)	780 (33.8)	1,501 (65.1)	25 (1.1)	0.96 [0.80; 1.15]	0.635
Chest X-ray result						
Normal	5,502 (94.3)	1,693 (30.8)	3,768 (68.5)	41 (0.8)	Ref	
Abnormal	134 (2.3)	78 (58.2)	56 (41.8)	0 (0.0)	2.23 [1.38; 3.61]	0.001
No Chest X-ray	201 (3.4)	21 (10.5)	176 (87.6)	4 (2.0)	0.28 [0.15; 0.51]	<0.001

Notes:
¶ N sizes listed due to missing values;
§ Includes cough, fever, night sweats and weight loss of any duration;
┼ Residency grade definitions: 1=Permanent resident; 2=Long-term intra-province temporary resident; 3=Short-term, intra-province temporary resident; 4=Short-term, inter-province temporary resident
¤ Percent of total
ǂ Percent of row total
¥ IGRA=Interferon-Gamma Release Assay; aOR=adjusted Odds Ratio
† Wald test

TB infection care cascade

Of the 16,652 individuals verbally screened in both provinces, 35.1% (n=5,837) agreed to be tested by QFT-Plus for the study (Figure 1). The overall indeterminate rate was 0.8% (n=45) and 30.7% (n=1,792) of participants were QFT-Plus-positive, of whom 97.5% (n=1,748) were eligible for TPT. About 63.3% (1,107/1,748) of eligible participants initiated TPT and 80.6% (892/1,107) completed therapy. The sample included 4,840 participants in HCMC and 997 in Hai Phong (Table 2). The indeterminate rate was 0.8% in both sites, while positivity rates were 33.1% (1,603/4,840) in HCMC and 19.0% (189/997) in Hai Phong. The respective TPT initiation and completion rates in the 9H cohort in HCMC were 63.6% (995/1,565) and 80.0% (796/995) compared to 61.2% (112/183) and 85.7% (96/112) in the 3HR cohort in Hai Phong. Neither initiation nor completion rates were significantly different between the two regimens (p=0.522 & p=0.147, respectively).

Table 2: TB infection care cascade by TPT cohort

	Total (N = 5,837) N (%)	HCMC (N = 4,840) N (%)	Hai Phong (N = 997) N (%)
IGRA result & TPT¥			
Indeterminate	45 (0.8)	37 (0.8)	8 (0.8)
Negative	4,000 (68.5)	3,200 (66.1)	800 (80.2)
Positive	1,791 (30.7)	1,603 (33.1)	189 (19.0)
--Ineligible for TPT (% of positive)	**44 (0.8)**	**38 (0.8)**	**6 (0.6)**
No CXR	21 (0.4)	16 (0.3)	5 (0.5)
CXR(+), No MTB test	6 (0.1)	5 (0.1)	1 (0.1)
MTB(+)	17 (0.3)	17 (0.4)	0 (0.0)
--Eligible for TPT (% of positive)	**1,748 (97.6)**	**1,565 (97.6)**	**183 (97.3)**
CXR(-)	1,702 (95.0)	1,524 (95.1)	178 (94.7)
CXR(+), MTB(-)	46 (2.6)	41 (2.6)	5 (2.7)
--Initiated on TPT¶ (% of eligible)	**1,107 (63.3)**	**995 (63.6)**	**112 (61.2)**
--Completed TPT¶ (% of initiated)	**892 (80.6)**	**796 (80.0)**	**96 (85.7)**

Notes:
¥ IGRA=Interferon-Gamma Release Assay; CXR=Chest X-Ray; TPT=TB Preventive Therapy; MTB=*M. tuberculosis*; HCMC=Ho Chi Minh City
¶ TPT consisted of 9H in HCMC and of 3HR in Hai Phong

The sample included 46.6% (n=2,256) HHCs, 44.9% (n=2,173) vulnerable community members and 8.5% (n=411) HCWs in HCMC (Figure 2). In Hai Phong, the sample consisted of 17.6% (n=175) HHCs and 82.5% (n=822) community members. IGRA-positivity among HHCs was similar in both cities, but lower in community members in Hai Phong (123/822=15.0%) compared to HCMC (698/2173=32.1%). Similarly, positivity in HCWs was also comparatively lower (74/411=18.0%). TPT initiation rates in HHCs and community members were similar across sites ranging from 59.0% to 66.6%, and higher among HCWs (52/72=72.2%). Diagnostic delays in HCMC were shorter than in Hai Phong for both HHCs (17 vs. 59 days) and community members (15

vs. 58 days), except among HCWs (40.5). Similarly, TPT completion rates were high among HHCs and community members in both sites ranging from 77.3% to 90.5%, but only half of HCWs completed TPT.

Risk factors of IGRA-positivity

Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78]; p<0.001), aged 45-59 years (1.30 [1.05, 1.60]; p=0.018), and exhibiting CXR abnormalities suggestive of TB (2.23 [1.38, 3.61]; p=0.001) were associated with higher QFT-Plus positivity (Table 2). Conversely, compared to the reference group (30-44 years), the risk of QFT-Plus-positivity was significantly lower among children under 15 years (0.18 [0.13, 0.26]; p<0.001) and persons aged 15-29 years (0.56 [0.42, 0.75]; p<0.001), as well as among HCWs (0.34 [0.24, 0.48]; p<0.001) and individuals living in peri-urban areas (0.55 [0.36, 0.55]; p=0.007).

Survival analysis and risk factors of TPT completion

A total of 1,107 participants were followed for a total of 8,211 person-months with 215 recorded LTFUs (Table 3). There were 7,904 and 307 person-months of observations with mean follow-up times of 7.9 [7.8, 8.1] months and 2.7 [2.6, 2.9] months, and 199 and 16 LTFUs in the 9H and 3HR cohorts, respectively. The respective LTFU incidence rates were 25.2 and 52.1 per 1,000 person-months. Most LTFUs occurred after the first month of TPT in both the 9H (79/199=39.7%) and 3HR (13/16=81.2%) cohorts (Figures 3a and 3b). The survival analysis showed that the 3HR regimen (adjusted Hazard Ratio=3.83 [1.49, 9.84]; p=0.005) and HCWs (1.38 [1.25, 1.53]; p<0.001) were strongly associated with higher risk of LTFU.

Table 3: Participant characteristics and adjusted risk factors associated with TPT loss to follow-up¶

	Total (N = 1,107) N (%)¤	TPT completed¥ (N = 892) N (%)ǂ	LTFU¥ (N = 215) N (%)ǂ	aHR of LTFU¥ (95% CI)	p-value†
TPT regimen					
9H	995 (89.9)	796 (80.0)	199 (20.0)	Ref	
3HR	112 (10.1)	96 (85.7)	16 (14.3)	3.83 [1.49; 9.84]	0.005
Sex					
Female	645 (58.3)	512 (79.4)	133 (20.6)	Ref	
Male	462 (41.7)	380 (82.3)	082 (17.8)	1.02 [0.94; 1.11]	0.608
Age					
<15 years	86 (7.8)	72 (83.7)	14 (16.3)	0.63 [0.22; 1.79]	0.390
15-29 years	116 (10.5)	90 (77.6)	26 (22.4)	1.71 [0.88; 3.35]	0.116
30-44 years	249 (22.5)	195 (78.3)	54 (21.7)	Ref	
45-59 years	426 (38.5)	354 (83.1)	72 (16.9)	0.97 [0.56; 1.69]	0.911
≥60 years	230 (20.8)	181 (78.7)	49 (21.3)	1.14 [0.56; 2.32]	0.723
Median age (IQR)	*50 (35–58)*	*50 (35–58)*	*49 (35–59)*		
Screening location					
Community screening event	627 (56.6)	523 (83.4)	104 (16.6)	Ref	

Primary care center	480 (43.4)	369 (76.9)	111 (23.1)	1.19 [0.62; 2.30]	0.593
Target group					
Household and close contacts	585 (52.9)	458 (78.3)	127 (21.7)	1.03 [0.75; 1.39]	0.874
Vulnerable community members	470 (42.5)	408 (86.8)	62 (13.2)	Ref	
Healthcare workers	52 (4.7)	26 (50.0)	26 (50.0)	1.38 [1.25; 1.53]	<0.001
Urbanization					
Urban	729 (65.9)	598 (82.0)	131 (18.0)	Ref	
Peri-urban	378 (34.2)	294 (77.8)	84 (22.2)	1.00 [0.58; 1.73]	0.990
Diabetes mellitus					
No/Unknown	1,065 (96.2)	859 (80.7)	206 (19.3)	Ref	
Yes	42 (3.8)	33 (78.6)	9 (21.4)	0.74 [0.18; 3.11]	0.679
Previous history of TB					
No/Unknown	1,096 (99.0)	883 (80.6)	213 (19.4)	Ref	
Yes	11 (1.0)	9 (81.8)	2 (18.2)	1.03 [0.14; 7.63]	0.980

Notes:
¶ Model stratified by health insurance and residency status, so these parameters were excluded; parameters of sex and target group fitted as time-varying covariates; includes a total of 8,211 person-months
¤ Percent of total
ǂ Percent of row total
¥ LTFU=Loss to follow-up; aOR=adjusted Hazard Ratio
† Wald test

DISCUSSION

In the array of obstacles to scaling up TPT in Viet Nam, TBI diagnosis remains a critical step in the country's targeted approach. To date, however, it has also represented an insuperable bottleneck. This stems from an overreliance on TST from a single product (PPD-Bulbio), for which there is documented performance deviation compared to other TSTs and IGRA [30]. These issues are in addition to the well-understood range of confounders affecting clinical performance of TSTs in comparison to IGRAs.[31] Despite its shortcomings, TST remains the programmatic standard of care partly due to the perceived operational challenges in deploying IGRAs outside of hospital settings.

This evaluation builds on the evidence base that it is possible to deploy IGRAs at lower healthcare levels.[21] As shown previously, fidelity to manufacturer recommended procedures in terms of handling, timing and temperature-control throughout collection, transport and processing of specimens from the community to the laboratory resulted in positivity[32] and indeterminate rates[33,34] that were comparable to those of facility-based studies. Our measured positivity was also aligned with previously published IGRA-positivity measured in the community in Viet Nam (pooled positivity: 37.7%; n=2,706).[21,35] We also observed the expected dose-response pattern of rising positivity and risk of TBI in older individuals as well as the higher risk of QFT-Plus positivity in males.[20,21] Concordant with these results, our study highlighted that IGRA can be used at the community level as another option for TBI diagnosis and accelerating scale-up of TPT.

However, there were patterns in the TBI care cascade indicating that scale-up of available TBI diagnostic tools and regimens requires more than simply decentralization. Fewer than half of the individuals mobilized during these ACF campaigns agreed to or were eligible for an IGRA test and only six out of ten eligible persons initiated TPT, which was concordant with prior studies in Viet Nam.[32] One potential reason for the drop-off may be process related, since we embedded the study in a programmatic setting, which meant that in general over two weeks elapsed from when participants were tested until eligible persons initiated TPT. Nevertheless, slow turnaround time may only partially explain the pre-treatment LTFU, as TPT initiation rate was consistent across both settings despite the difference in turnaround time.

By fielding the study in two separate sites with different TPT regimen and TBI rates in the community, we recorded several noteworthy observations. Specifically, while initiation rates in both sites were similar, there was a slightly higher completion rate in the 3HR cohort. Thus, even though we did not observe a greater uptake of TPT as seen on prior studies, the shorter treatment duration of 3HR may have contributed to higher TPT completion rates.[36–38] However, the survival analysis showed that more persons were lost to follow-up than expected over the shorter period of treatment. Based on informal qualitative feedback from field staff, reasons for the large drop-offs in the cascade included a lack of understanding of the implications of TBI and the benefits of TPT, and the de-prioritization of TPT among providers. Since the 3HR regimen was only used in one province which may have faced site-specific challenges, we cannot generalize these results to other areas of the country. However, they highlight the need for more education and advocacy for providers and participants to improve the acceptance and prioritization of TPT.[39,40]

Moreover, advocacy and awareness building may need to be tailored to individual subgroups. Even though positivity, initiation and completion rates did not vary substantially across sites, gender or age category, there were, however, notable differences across study populations. In our study, HCWs exhibited a lower proportion and risk of positivity, higher TPT initiation and significantly higher risk of LTFU compared to HHCs and community members in either site. The low positivity rate was particularly noteworthy for its discordance with published, albeit dated, evidence from Viet Nam[41] and WHO guidelines warranting intervention in this group due to higher occupational risk of TB infection.[42] A potential explanation for the discordance is that a sizeable proportion of HCWs were generalist primary care workers. The more recent EnTIC study (NCT02073240) measured lower TBI rates among Vietnamese HCWs in general hospitals compared to HCWs in TB hospitals (27.9% [22.8%, 33.6%] vs. 41.7% [26.2%, 58.9%]).[43] However, this TBI rate in general hospital HCWs is still higher than the rate among HCWs on this study; a future comparative analyses of TBI in HCWs in tertiary/quaternary general hospitals versus primary care workers may offer further insight.

The diagnostic delay was unacceptably long among HCWs and across all groups in Hai Phong. In Hai Phong, the lower burden and more limited TB care capacity as well as greater reliance on the lung hospital in TB care

and prevention activities may have contributed to the long delay in treatment initiation. Meanwhile, upon investigation, HCWs indicated a preference to wait for the new 12-dose regimen of isoniazid and rifapentine (3HP), but then agreed to initiate TPT on 9H as concerns over nitrosamine impurities delayed scale-up of 3HP in Viet Nam.[44,45] Nevertheless, despite a delay of almost six weeks, the TPT initiation rate among HCWs was highest across all groups and also above rates measured on prior studies (39.0%-49.6%).[46,47] Conversely, the low completion rate measured on this study was on par with other studies on HCWs receiving 9H for TPT. However, this low rate may have been avoided with shorter regimen as adherence in this study at month 3 was 100% and month 8 was still at 80.0%. These results were in line with previous studies that indicated health workers were significantly more likely to complete TPT on 3HR compared to 9H (91.4% *vs.* 76.7%, p=0.02).[48–50]

The use of the 9H regimen in the majority of participants also highlights a key limitation of this study. By conducting it under routine program conditions, the study was exposed to external bias and confounding, such as the variability in the available TPT regimen. HCMC historically has had a substantially larger burden of TB and TBI, as evinced on this study. Thus, 9H was the local regimen of choice due to its greater availability and lower costs. Similarly, we relied on routine diagnostics to rule out active TB rather than more sensitive tools such as culture due to cost implications. With respect to costs, another limitation of our study was the lack of a formal assessment of the cost barrier of IGRAs in our low-resource setting. Operationally, WHO recommends to integrate TPT into routine HHC investigations and ACF.[16] It stands to reason that such integration may also improve value for money as has been well-established for highly vulnerable people living with HIV.[51] There is ample evidence that HHC investigations and community-based ACF campaigns can reach those most vulnerable to active TB and thus most in need of TPT.[52–54] Nevertheless, given the lack of an accompanying health economic evaluation, future research should conduct impact evaluations and cost-effectiveness analyses of integrated TB and TBI testing and treatment on ACF campaigns and differences in incidence and disability-adjusted life years compared to a control cohort. Another limitation is that our cohort design did not include a post-treatment follow-up to assess incidence of TB in those with and without TPT, in part due to the social distancing measures launched in response to the pandemic. The study's convenience sampling and selection of HCMC and Hai Phong as study sites likely introduced bias towards densely populated urban settings, which consequently limits the generalizability of this study. Nevertheless, the study benefitted from its large sample size and integration into routine program operations that may help to translate the findings to recommendations for densely populated, high TB burden settings in general.

CONCLUSIONS

WHO's End TB Strategy highlights the need for increased testing and treatment of TB infection as a core intervention to reduce transmission and thus achieve incidence targets. While many high TB burden countries have incorporated this emphasis into their national strategic plans, operationalization of these plans is often hindered by the suboptimal application of available tools. IGRAs are the current gold standard for TBI testing, but are often underutilized, particularly at the lower healthcare levels. Shorter TPT regimen are recommended, but require further studies to assess their potential to support broad-scale TPT. This study elucidated the potential to decentralize and leverage these tools for wider and more cost-effective deployment towards meeting TPT targets, but also highlighted that scale-up of these tools, as well as overall TPT access and uptake, will likely require complementary, tailored advocacy and education for both beneficiaries and providers.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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AUTHORS' CONTRIBUTIONS

- Conceptualization: LNQV, NN, VVT, HMD, THM
- Methodology: LNQV, NTTN, TTTD, THM, HMD, VVT
- Formal analysis: LNQV, PTL
- Investigation: VVT, NTTN, TTTD, PTL
- Resources: LHN, HMD, HTT, HBN, NVN
- Data curation: LNQV, AJC, PTL, KTT
- Writing – original draft: LNQV, NTTN, TTTD
- Writing – review and editing: LNQV, AJC, JC, NN, HTT, MC
- Visualization: LNQV
- Supervision: JC, MC, LNQV, LHN, THM, HTT, HBN, NVN
- Project administration: RJF, AJC, VVT, NTTN, TTTD
- Funding acquisition: LNQV, RJF, AJC
- Final approval: all authors have read and approved the manuscript

DATA AVAILABILITY

The data that support the findings of this study are available from the Viet Nam National TB Control Program, Hai Phong Provincial Lung Hospital and Pham Ngoc Thach Provincial TB Hospital, but restrictions apply to their availability. Data are can be made available from the authors upon reasonable request and with permission of the Viet Nam National TB Control Program, Hai Phong Provincial Lung Hospital and Pham Ngoc Thach Provincial TB Hospital.

ETHICAL CONSIDERATIONS

This study was approved by the Pham Ngoc Thach Hospital ethics committee for biomedical research (897/HDDD-PNT). In addition, QFT-Plus testing is part of national guidelines and activities were approved by the NTP (1069/BVPTW-DAPCL). Participation was voluntary and did not affect the provision or standard of care. All personal identifying information was removed from the dataset prior to analysis.

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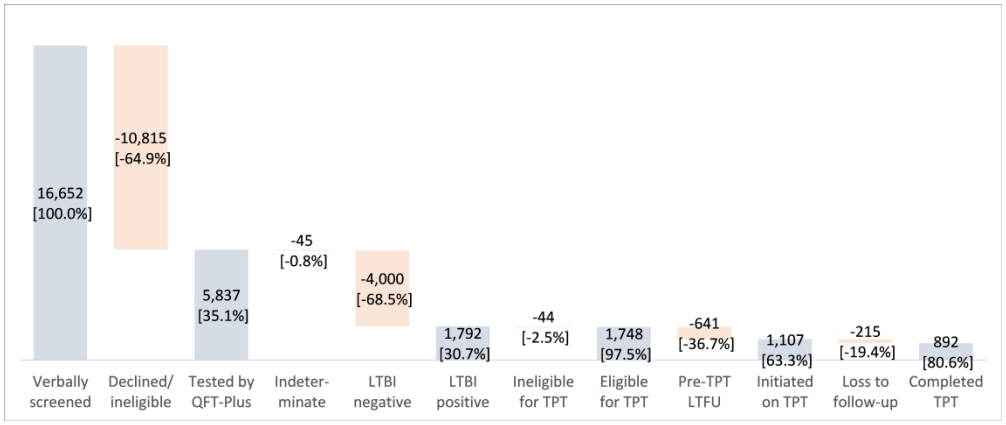

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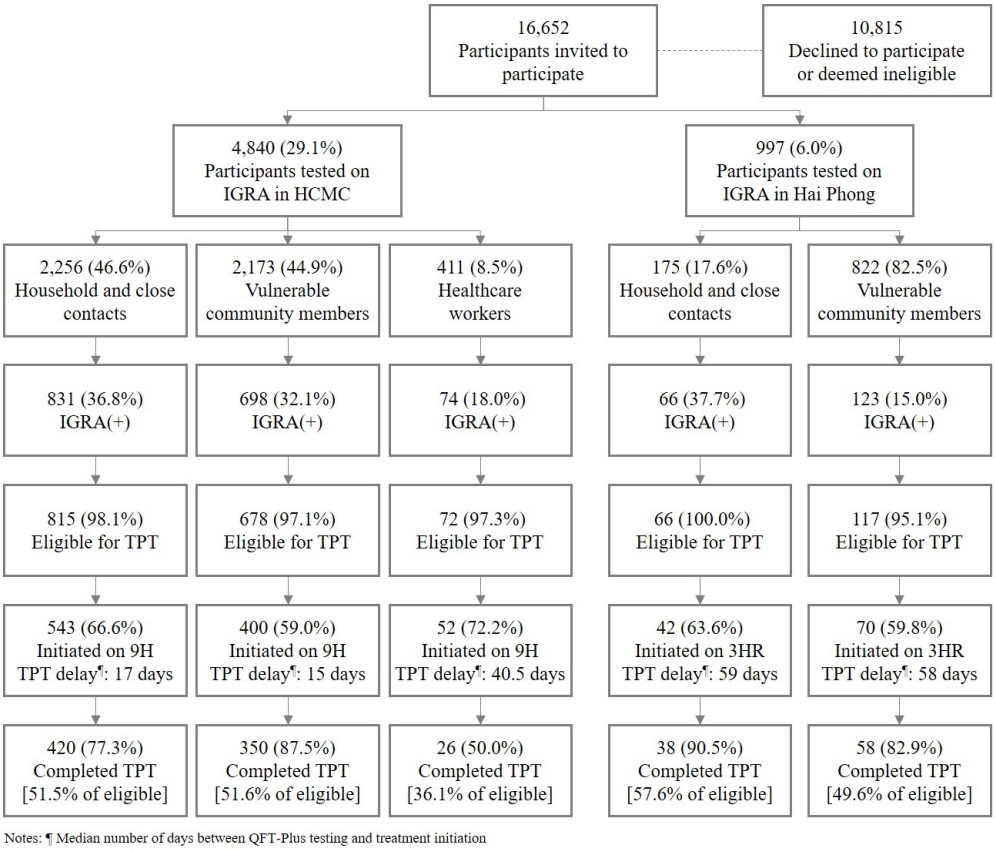

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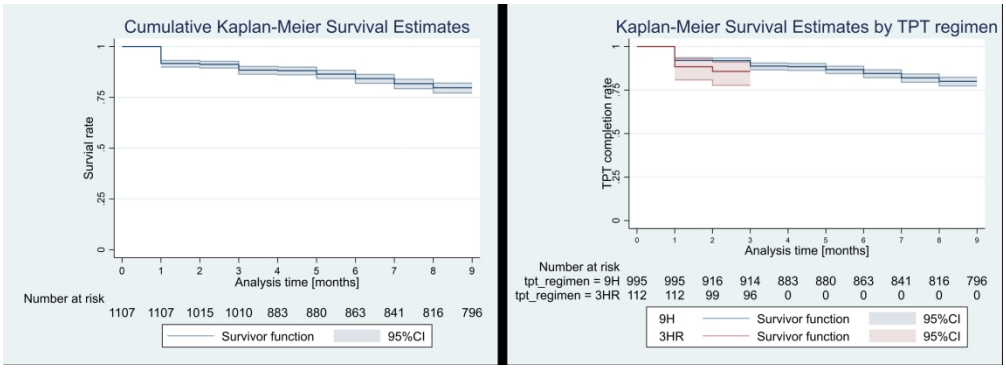

Figure 3a & 3b - Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen

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STROBE Statement

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	8-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-12
		(b) Indicate number of participants with missing data for each variable of interest	10-12
Outcome data	15*	Report numbers of outcome events or summary measures	8-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12

		(*b*) Report category boundaries when continuous variables were categorized	10, 12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

SUPPLEMENTAL MATERIAL

Model specification validation results

Figure S1: Kaplan-Meier observed survival curve of TPT regimen

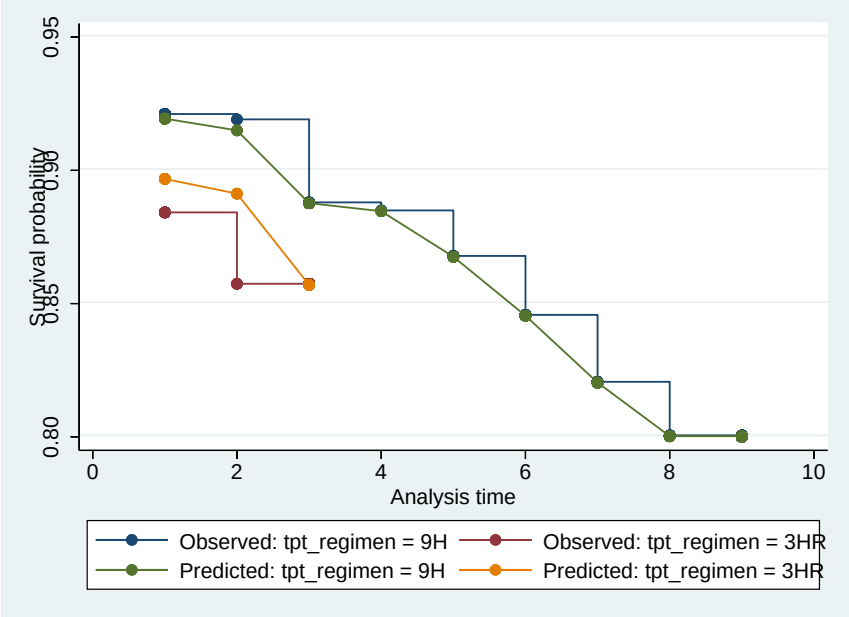
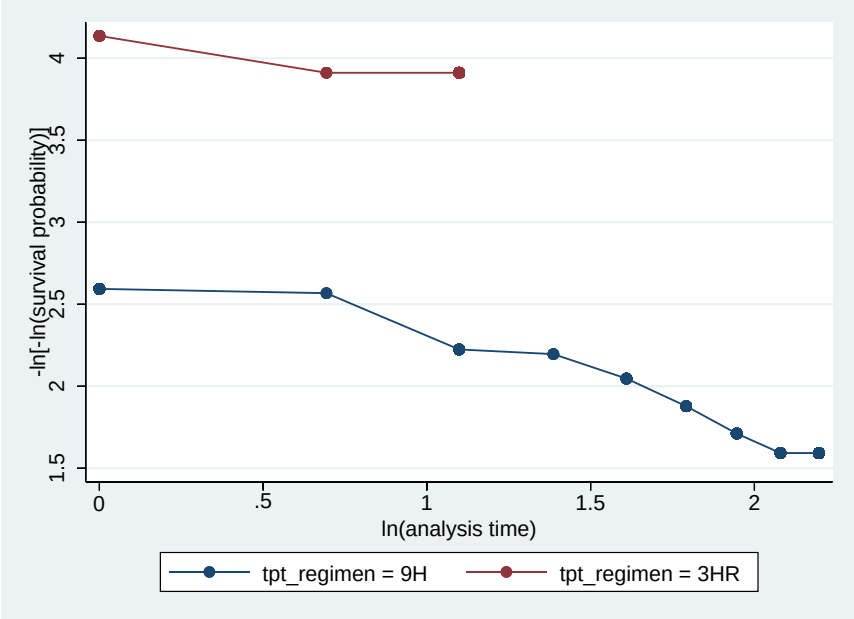


Figure S2: Log-log plot of the final Cox model



The log-rank test result to assess the equality of survival between the two TPT regimen was p=0.319.

The p-value of the global postestimation proportional hazards test 0.644 and tests of individual parameters produced p-values of 0.112<p<0.955.

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Optimizing diagnosis and treatment of tuberculosis infection in community and primary care settings in two urban provinces of Viet Nam: a cohort study

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ABSTRACT

Objectives: To end tuberculosis (TB), the vast reservoir of 1.7-2.3 billion TB infections (TBI) must be addressed but achieving global TB preventive therapy (TPT) targets seems unlikely. This study assessed the feasibility of using interferon-gamma release assays (IGRA) at lower healthcare levels and the comparative performance of 3- and 9-month daily TPT regimens (3HR/9H).

Methods: This cohort study was implemented in six districts of Ho Chi Minh City and Hai Phong, Viet Nam, from May-2019 to Sept-2020. Participants included household contacts (HHC), vulnerable community members and healthcare workers (HCW) recruited at community-based TB screening events or HHC investigations at primary care centers, who were followed up throughout TPT. We constructed TBI care cascades describing indeterminate and positivity rates to assess feasibility, and initiation and completion rates to assess performance. We fitted mixed-effect logistic and stratified Cox models to identify factors associated with IGRA-positivity and loss to follow-up (LTFU).

Results: Among 5,837 participants, the indeterminate rate was 0.8% and 30.7% were IGRA-positive. TPT initiation and completion rates were 63.3% (3HR=61.2% vs. 9H=63.6%; p=0.147) and 80.6% (3HR=85.7% vs. 9H=80.0%; p=0.522), respectively. Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78]; p<0.001), aged 45-59 years (1.30 [1.05, 1.60]; p=0.018) and exhibiting TB-related abnormalities on X-ray (2.23 [1.38, 3.61]; p=0.001) were associated with positive IGRA results. Risk of IGRA-positivity was lower in peri-urban districts (0.55 [0.36, 0.55]; p=0.007), aged <15 years (0.18 [0.13, 0.26]; p<0.001), aged 15-29 years (0.56 [0.42, 0.75]; p<0.001), and HCWs (0.34 [0.24, 0.48]; p<0.001). The 3HR regimen (adjusted Hazard Ratio=3.83 [1.49, 9.84]; p=0.005) and HCWs (1.38 [1.25, 1.53]; p<0.001) showed higher hazards of LTFU.

Conclusion: Providing IGRA at lower healthcare levels is feasible and along with shorter regimen may expand access and uptake towards meeting TPT targets, but scale-up may require complementary advocacy and education for beneficiaries and providers.

Keywords: tuberculosis, infection, community, urban, interferon-gamma release assay, short-course, tuberculosis preventive therapy

Running head: Optimizing diagnosis and treatment of TB infection in Viet Nam

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of the study was the large sample size of persons tested by interferon-gamma release assay across two sites with varying characteristics in background tuberculosis infection as well as demographic and clinical characteristics, which enabled comparative analyses of subsegments of the sample.
- The community setting in which participants were recruited and tested using sophisticated diagnostics decentralized to lower care levels further contributes to the evidence base for scale-up of tuberculosis prevention, especially given the size of the sample.
- Embedding the study in routine tuberculosis program activities exposed it to common limitations such as heterogeneity in supply chain as well as health worker knowledge, attitudes and practices commonly experienced by the program.

INTRODUCTION

After a brief relegation due to the COVID-19 pandemic, tuberculosis (TB) is once again the world's leading infectious disease killer.[1] One of the key reasons is the estimated 1.7–2.3 billion people infected with TB without suffering from active disease, whose activation continues to fuel incidence.[2,3] An estimated 5-15% of people with TB infection (TBI) develop active TB disease in their lifetimes, serving as a vast reservoir for future TB disease, even if new TB transmission were completely eliminated today.[4,5] This was also observed by a study in London at the height of the pandemic which showed that social distancing mitigated incidence of several respiratory diseases, but not of TB.[6] Thus, research and modeling suggest that increased emphasis on TBI is needed in order to reduce worldwide TB incidence.[7] However, while efforts to find and treat people with TB who are missed by existing TB care programs have been launched in most high TB burden countries, relatively few are addressing the burden of TBI at scale.[8–11]

This muted response was historically linked to World Health Organization (WHO) guidelines recommending TB preventive therapy (TPT) in high TB burden settings only for people living with HIV (PLHIV), under-5 household contacts (HHC) of persons with bacteriologically-confirmed, pulmonary TB and persons with occupational risk factors for progression to active TB.[12] Beyond conservative guidelines, other commonly cited bottlenecks have included shortages in commodities and particularly diagnostic consumables such as tuberculin, high health system costs of diagnosis, treatment and follow-up depressing TPT uptake, and lack of patient-friendly treatment regimen negatively affecting adherence.[13,14]

In recent years, the WHO has issued updated technical and operational guidelines with expanded TPT eligibility criteria, such as HIV-negative household contacts of all ages.[15,16] However, a key recommendation for this expanded eligibility was the inclusion of an appropriate clinical and laboratory evaluation, which in select settings translated to the prerequisite of immunological confirmation of TBI by tuberculin skin test (TST) or interferon-gamma release assay (IGRA) for TPT within national guidelines.[14,17] The updated WHO guidelines also introduced new short-course TPT regimens with better tolerability and safety profiles, which high TB burden countries have eagerly integrated into national TBI guidelines and national strategic plans.[18,19]

One of these countries is Viet Nam, which ranks 11th among the 30 high TB burden countries. During the first prevalence survey, the annual rate of TB infection was measured to be 1.7% with a TBI prevalence of 16.7% in children aged 6–14 years using TST with a threshold of 10mm.[20] A subsequent study in rural Ca Mau province measured a TBI rate of 36.8% using IGRA.[21] In 2014, Viet Nam passed legislation codifying its goals to drastically reduce TB prevalence in alignment with the WHO End TB Strategy.[22] On World TB Day 2020, the Ministry of Health introduced the country's inaugural guidelines on diagnosis and treatment of TBI. These

guidelines expanded TPT eligibility to all adults with TBI confirmed by recommended diagnostic tools and excluding active TB, permitted the use of various shortened regimen, and described contact investigation and follow-up requirements. Viet Nam further demonstrated its focus on TB prevention by committing at the UN High-Level Meeting on Ending TB to scale-up provision of TPT to 291,500 people by 2022.[23]

However, the country has experienced many of the challenges related to the scale-up of TPT as described above. Specifically, Viet Nam requires TBI confirmation within the expanded eligibility criteria prior to treatment, but has experienced tuberculin supply chain shortages and batch-variance in the positivity threshold. While WHO-recommended IGRAs are commercially available, the National TB Control Programme (NTP) has consigned this assay class to tertiary care facilities due to the delicate specimen handling and sophistical laboratory requirements,[24,25] which is underscored by the lack of published evidence of the assay's deployment at the point-of-care domestically and worldwide. In addition, the prohibitively high costs per test have precluded serious consideration for routine TB program activities.

Nevertheless, the NTP remains committed to the scale-up of TPT through the optimal use of available and new diagnostics and regimens.[26] Given tuberculin supply and staff capacity challenges, and lack of evidence on the impact of recently introduced shorter TPT regimen on uptake and completion, this study assessed the use of the QuantiFERON-TB Gold Plus assay (QFT-Plus; Qiagen, Hilden, Germany) at the community level and the performance of shorter TPT regimen under programmatic conditions. The goal was to inform NTP of Viet Nam and other high TB burden countries in their ambitions to meet their TPT goals.

METHODS

Study design and objectives

This was a cohort study to measure the feasibility of employing IGRA at the community and primary care levels for the diagnosis of TBI. Feasibility was defined by comparing indeterminate and positivity rates with those demonstrated in facility-based studies (primary endpoints). Secondary objectives included measuring the rate of TPT initiation and completion (secondary endpoints) in cohorts provided with two different TPT regimens, and to identify participant covariates associated with IGRA-positivity and loss to follow-up. The study followed the STROBE guideline for reporting observational studies (Supplemental material 1).

Study setting

The study was conducted in six districts of Ho Chi Minh City (HCMC) and Hai Phong municipal provinces. In HCMC, study sites included Districts 6, 8, 12, Binh Chanh, Go Vap, and Tan Binh with a cumulative population

of 2,387,052 and 3,598 TB notifications in 2019. In Hai Phong, the study took place in Do Son with a population of 49,029 and 52 persons with drug-susceptible TB notified in 2019.

Study population and recruitment

The study was embedded into routine contact investigations at primary care commune health posts and community-based active TB case finding (ACF) events. Details of the ACF events are provided elsewhere.[27] The study population included HHC and close contacts, and vulnerable community members at elevated risk of active TB, such as the elderly, urban poor and economic migrants. Briefly, elderly persons were ≥55 years, urban poor were based on national poverty definitions and economic migrants were categorized based on residency registration in rural provinces outside of the intervention districts. [28–30] The HCMC site also included a subgroup of primary- and secondary-level healthcare workers (HCW) based on the request from local authorities. Recruitment and follow-up occurred from May-2019 to Sep-2020. All individuals presenting for screening provided routine demographic and clinical information including age, sex, residency status, history of TB, comorbidities and symptomatic presentation. Following intake, persons belonging to the study population with residency in the study districts were invited to participate in the study. Persons living outside of or intending to relocate away from the study sites, or who declined to consent were excluded. Eligible, consenting participants were recruited consecutively until the quota of available QFT-Plus tests was reached (n=5,000 in HCMC and n=1,000 in Hai Phong). Parents consented on behalf of their children under 18 years.

Specimen collection and processing

Provincial lung hospital (PLH) laboratory staff hosted training sessions on specimen collection and processing for the District TB Unit (DTU) and district-level laboratory staff. The District Health Center (DHC) mobilized participants to attend ACF events or to present at commune health posts. All attendants were systematically screened for TB symptoms and directed to undergo chest radiography (CXR) to rule out active TB. Persons with parenchymal abnormalities suggestive of TB on CXR or strong clinical suspicion of TB were referred for molecular sputum testing, as per contemporary national TB treatment guidelines.[31] Attendants were counseled on TBI and invited to participate. Study staff collected blood specimens from consenting, eligible individuals as per manufacturer recommended procedures. Each participant provided 4ml of venous whole blood in four separate tubes. Blood specimens were processed and analyzed per manufacturer's recommendations. Briefly, all four tubes were immediately shaken ~10 times to dissolve all antigens on the tube's wall coating. Tubes were stored inside dry ice coolers at 17–25°C, which were transported to the PLH biochemistry–hematology departments within six hours, twice a day. Samples were incubated at 37°C for 20 hours (±1 hour) and centrifuged within one hour of completing the incubation stage at 2000-3000g for 14 minutes at room temperature. The twelve-step enzyme linked immunosorbent assay was conducted within 16-24 hours. Results were analyzed by using proprietary QuantiFERON software v2.7.1.

TPT initiation and participant follow-up

QFT-Plus test results were returned to the DHC two days after receipt of the blood specimens. Individuals with negative results were informed via phone by DHC staff. Those with positive results and eligible for preventive treatment (i.e., with confirmed TBI and active TB ruled out by CXR and symptomatic presentation) were invited to present at their respective DTU for pre-treatment counseling and TPT initiation as per national guidelines.[17] TPT regimen varied by province. In HCMC, TPT consisted of nine months of daily isoniazid (9H), while in Hai Phong eligible persons received three months of daily isoniazid and rifampicin (3HR). Individuals on TPT received in-person follow-up during monthly drug pick-up at the DTU. Community TB officers conducted phone or in-person follow-up in regular intervals or as needed, as recommended in national guidelines. Participants experiencing adverse events were asked to present at the DTU for check-up.

Statistical analyses

The primary measures of interest were QFT-Plus positivity and indeterminate rates. Secondary variables of interest included TPT initiation and completion rates within the study population. Missing data were retrieved through post-event follow-up of participants or excluded from individual analyses. We constructed TBI care cascades in aggregate and segmented by site ranging from persons recruited to participants with a successful TPT completion. We documented losses along the cascade and reported median and interquartile ranges of diagnostic delay, i.e., time from testing to TPT initiation. We calculated descriptive statistics for key sample characteristics by QFT-Plus result and TPT completion and fitted a saturated, mixed-effect logistic regression to assess associations between positivity and participant covariates to adjust for confounding and inherent bias. Study district was the random effect to account for intra-cluster correlation. The survival analysis designated loss to follow-up (LTFU) a failure and censored adherent participants on 3HR and 9H at three and nine months, respectively. We constructed Kaplan-Meier survival curves and conducted log-rank tests to assess the equality of survival between the two TPT regimen. We fitted a saturated Cox model and assessed validity of the proportionality assumption using log-log plots and Schoenfeld residuals. Violations were addressed via stratification or modeling of time-variance for parameters of interest. The final model passed both the global postestimation proportional hazards test and tests of individual parameters. P-values of validation tests were provided in the Supplemental material 2. Hypothesis tests were two-tailed. A threshold of $p<0.05$ was considered significant. Analyses were conducted using STATA v17 (Stata Corp.; College Station, TX, USA).

Patient and public involvement

While TB patients and their families were not involved in setting the research question, a consensus building meeting was held at the beginning of the study for government stakeholders and community members to provide feedback and recommendations and reach consensus about the study design and implementation. Patients, their

families and public stakeholders were also central to dissemination of study information, which helped to motivate community involvement during and beyond the study.

RESULTS

Sample characteristics

Of the 5,837 participants in the sample, 59.3% (n=3,463) were female (Table 1). Children under 15 years constituted 19.5% (1,136/5,834) of the sample and the median participant age was 40 (IQR: 20–55). Overall, most participants were recruited at community-based ACF events (55.8%; n=3,257), lived in urban areas (65.6%; n=3,827), were permanent residents (90.5%; 3,116/3,444) and were enrolled on social health insurance (90.4%; 5,269/5,832). About 2.9% (n=167) were diabetics and 1.1% (n=62) reported a history of TB. Moreover, 39.5% (n=2,306) reported experiencing at least one of the four core TB symptoms (cough, weight loss, fever, and/or night sweats) during recruitment, while 2.3% (n=134) participants exhibited TB-related CXR abnormalities.

199 **Table 1: Participant characteristics and adjusted odds ratios associated with IGRA-positivity**

	Total (N = 5,837) N (%)¤	IGRA(+)¥ (N = 1,792) N (%)	IGRA (-)¥ (N = 4,000) N (%)	Indeterminate (N = 45) N (%)	aOR¥ (95% CI)	p-value†
Sex						
Female	3,463 (59.3)	1,048 (30.3)	2,392 (69.1)	23 (0.7)	Ref	
Male	2,374 (40.7)	744 (31.3)	1,608 (67.7)	22 (0.9)	1.51 [1.28; 1.78]	<0.001
Age¶						
<15 years	1,136 / 5,834 (19.5)	134 / 1,792 (11.8)	997 / 3,997 (87.8)	5 / 45 (0.4)	0.18 [0.13; 0.26]	<0.001
15-29 years	891 / 5,834 (15.3)	195 / 1,792 (21.9)	687 / 3,997 (77.1)	9 / 45 (1.0)	0.56 [0.42; 0.75]	<0.001
30-44 years	1,290 / 5,834 (22.1)	418 / 1,792 (32.4)	864 / 3,997 (67.0)	8 / 45 (0.6)	Ref	
45-59 years	1,679 / 5,834 (28.8)	704 / 1,792 (41.9)	957 / 3,997 (57.0)	18 / 45 (1.1)	1.30 [1.05; 1.60]	0.018
≥60 years	838 / 5,834 (14.4)	341 / 1,792 (40.7)	492 / 3,997 (58.7)	5 / 45 (0.6)	1.06 [0.80; 1.40]	0.673
Median age (IQR)	*40 (20–55)*	*49 (35–58)*	*35 (15–52)*	*45 (24–54)*		
Study site						
Ho Chi Minh City	4,840 (82.9)	1,603 (33.1)	3,200 (66.1)	37 (0.8)	Ref	
Hai Phong	997 (17.1)	189 (19.0)	800 (80.2)	8 (0.8)	0.69 [0.40; 1.20]	0.186
Screening location						
Community screening event	3,257 (55.8)	993 (30.5)	2,244 (68.9)	20 (0.6)	Ref	
Primary care center	2,580 (44.2)	799 (31.0)	1,756 (68.1)	25 (1.0)	0.88 [0.69; 1.13]	0.325
Target group						
Household and close contacts	2,431 (41.7)	897 (36.9)	1,495 (61.5)	39 (1.6)	1.11 [0.67; 1.82]	0.690
Vulnerable community members	2,995 (51.3)	821 (27.4)	2,168 (72.4)	6 (0.2)	Ref	
Healthcare workers	411 (7.0)	74 (18.0)	337 (82.0)	0 (0.0)	0.34 [0.24; 0.48]	<0.001
Urbanization						
Urban	3,827 (65.6)	1,135 (29.7)	2,669 (69.7)	23 (0.6)	Ref	
Peri-urban	2,010 (34.4)	657 (32.7)	1,331 (66.2)	22 (1.1)	0.55 [0.36; 0.85]	0.007
Residency status‡,¶						
Grade 1	3,116 / 3,444 (90.5)	799 / 907 (25.6)	2,294 / 2,511 (73.6)	23 / 26 (0.7)	Ref	
Grade 2	91 / 3,444 (2.6)	27 / 907 (29.7)	62 / 2,511 (68.1)	2 / 26 (2.2)	1.08 [0.66; 1.74]	0.765
Grade 3	202 / 3,444 (5.9)	68 / 907 (33.7)	134 / 2,511 (66.3)	0 / 26 (0.0)	1.36 [0.96; 1.92]	0.083
Grade 4	35 / 3,444 (1.0)	13 / 907 (37.1)	21 / 2,511 (60.0)	1 / 26 (2.9)	1.54 [0.73; 3.26]	0.260
Social health insurance¶						
No	563 / 5,832 (9.7)	180 / 1,790 (32.0)	376 / 3,997 (66.8)	7 / 45 (1.2)	Ref	
Yes	5,269 / 5,832 (90.4)	1,610 / 1,790 (30.6)	3,621 / 3,997 (68.7)	38 / 45 (0.7)	1.11 [0.84; 1.46]	0.473

Diabetes mellitus						
No/Unknown	5,670 (97.1)	1,721 (30.4)	3,906 (68.9)	43 (0.8)	Ref	
Yes	167 (2.9)	71 (42.5)	94 (56.3)	2 (1.2)	1.15 [0.75; 1.76]	0.516
Previous history of TB						
No/Unknown	5,775 (98.9)	1,764 (30.6)	3,967 (68.7)	44 (0.8)	Ref	
Yes	62 (1.1)	28 (45.2)	33 (53.2)	1 (1.6)	1.93 [0.96; 3.86]	0.063
Any TB symptoms[§,¶]						
No	3,531 (60.5)	1,012 (28.7)	2,499 (70.8)	20 (0.6)	Ref	
Yes	2,306 (39.5)	780 (33.8)	1,501 (65.1)	25 (1.1)	0.96 [0.80; 1.15]	0.635
Chest X-ray result						
Normal	5,502 (94.3)	1,693 (30.8)	3,768 (68.5)	41 (0.8)	Ref	
Abnormal	134 (2.3)	78 (58.2)	56 (41.8)	0 (0.0)	2.23 [1.38; 3.61]	0.001
No Chest X-ray	201 (3.4)	21 (10.5)	176 (87.6)	4 (2.0)	0.28 [0.15; 0.51]	<0.001

Notes:
¶ N sizes listed due to missing values;
§ Includes cough, fever, night sweats and weight loss of any duration;
┼ Residency grade definitions: 1=Permanent resident; 2=Long-term intra-province temporary resident; 3=Short-term, intra-province temporary resident; 4=Short-term, inter-province temporary resident
¤ Percent of total
ǂ Percent of row total
¥ IGRA=Interferon-Gamma Release Assay; aOR=adjusted Odds Ratio
† Wald test

TB infection care cascade

Of the 16,652 individuals verbally screened in both provinces, 35.1% (n=5,837) agreed to be tested by QFT-Plus for the study (Figure 1). The overall indeterminate rate was 0.8% (n=45) and 30.7% (n=1,792) of participants were QFT-Plus-positive, of whom 97.5% (n=1,748) were eligible for TPT. About 63.3% (1,107/1,748) of eligible participants initiated TPT and 80.6% (892/1,107) completed therapy. The sample included 4,840 participants in HCMC and 997 in Hai Phong (Table 2). The indeterminate rate was 0.8% in both sites, while positivity rates were 33.1% (1,603/4,840) in HCMC and 19.0% (189/997) in Hai Phong. The respective TPT initiation and completion rates in the 9H cohort in HCMC were 63.6% (995/1,565) and 80.0% (796/995) compared to 61.2% (112/183) and 85.7% (96/112) in the 3HR cohort in Hai Phong. Neither initiation nor completion rates were significantly different between the two regimens (p=0.522 & p=0.147, respectively).

Table 2: TB infection care cascade by TPT cohort

	Total (N = 5,837) N (%)	**HCMC (N = 4,840) N (%)**	**Hai Phong (N = 997) N (%)**
IGRA result & TPT¥			
Indeterminate	45 (0.8)	37 (0.8)	8 (0.8)
Negative	4,000 (68.5)	3,200 (66.1)	800 (80.2)
Positive	1,791 (30.7)	1,603 (33.1)	189 (19.0)
--Ineligible for TPT (% of positive)	**44 (0.8)**	**38 (0.8)**	**6 (0.6)**
No CXR	21 (0.4)	16 (0.3)	5 (0.5)
CXR(+), No MTB test	6 (0.1)	5 (0.1)	1 (0.1)
MTB(+)	17 (0.3)	17 (0.4)	0 (0.0)
--Eligible for TPT (% of positive)	**1,748 (97.6)**	**1,565 (97.6)**	**183 (97.3)**
CXR(-)	1,702 (95.0)	1,524 (95.1)	178 (94.7)
CXR(+), MTB(-)	46 (2.6)	41 (2.6)	5 (2.7)
--Initiated on TPT¶ (% of eligible)	**1,107 (63.3)**	**995 (63.6)**	**112 (61.2)**
--Completed TPT¶ (% of initiated)	**892 (80.6)**	**796 (80.0)**	**96 (85.7)**

Notes:
¥ IGRA=Interferon-Gamma Release Assay; CXR=Chest X-Ray; TPT=TB Preventive Therapy; MTB=*M. tuberculosis*; HCMC=Ho Chi Minh City
¶ TPT consisted of 9H in HCMC and of 3HR in Hai Phong

The sample included 46.6% (n=2,256) HHCs, 44.9% (n=2,173) vulnerable community members and 8.5% (n=411) HCWs in HCMC (Figure 2). In Hai Phong, the sample consisted of 17.6% (n=175) HHCs and 82.5% (n=822) community members. IGRA-positivity among HHCs was similar in both cities, but lower in community members in Hai Phong (123/822=15.0%) compared to HCMC (698/2173=32.1%). Similarly, positivity in HCWs was also comparatively lower (74/411=18.0%). TPT initiation rates in HHCs and community members were similar across sites ranging from 59.0% to 66.6%, and higher among HCWs (52/72=72.2%). Diagnostic delays in HCMC were shorter than in Hai Phong for both HHCs (17 vs. 59 days) and community members (15

vs. 58 days), except among HCWs (40.5). Similarly, TPT completion rates were high among HHCs and community members in both sites ranging from 77.3% to 90.5%, but only half of HCWs completed TPT.

Risk factors of IGRA-positivity

Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78]; p<0.001), aged 45-59 years (1.30 [1.05, 1.60]; p=0.018), and exhibiting CXR abnormalities suggestive of TB (2.23 [1.38, 3.61]; p=0.001) were associated with higher QFT-Plus positivity (Table 2). Conversely, compared to the reference group (30-44 years), the risk of QFT-Plus-positivity was significantly lower among children under 15 years (0.18 [0.13, 0.26]; p<0.001) and persons aged 15-29 years (0.56 [0.42, 0.75]; p<0.001), as well as among HCWs (0.34 [0.24, 0.48]; p<0.001) and individuals living in peri-urban areas (0.55 [0.36, 0.55]; p=0.007).

Survival analysis and risk factors of TPT completion

A total of 1,107 participants were followed for a total of 8,211 person-months with 215 recorded LTFUs (Table 3). There were 7,904 and 307 person-months of observations with mean follow-up times of 7.9 [7.8, 8.1] months and 2.7 [2.6, 2.9] months, and 199 and 16 LTFUs in the 9H and 3HR cohorts, respectively. The respective LTFU incidence rates were 25.2 and 52.1 per 1,000 person-months. Most LTFUs occurred after the first month of TPT in both the 9H (79/199=39.7%) and 3HR (13/16=81.2%) cohorts (Figures 3a and 3b). The survival analysis showed that the 3HR regimen (adjusted Hazard Ratio=3.83 [1.49, 9.84]; p=0.005) and HCWs (1.38 [1.25, 1.53]; p<0.001) were strongly associated with higher risk of LTFU.

Table 3: Participant characteristics and adjusted risk factors associated with TPT loss to follow-up¶

	Total (N = 1,107) N (%)¤	TPT completed¥ (N = 892) N (%)ǂ	LTFU¥ (N = 215) N (%)ǂ	aHR of LTFU¥ (95% CI)	p-value†
TPT regimen					
9H	995 (89.9)	796 (80.0)	199 (20.0)	Ref	
3HR	112 (10.1)	96 (85.7)	16 (14.3)	3.83 [1.49; 9.84]	0.005
Sex					
Female	645 (58.3)	512 (79.4)	133 (20.6)	Ref	
Male	462 (41.7)	380 (82.3)	082 (17.8)	1.02 [0.94; 1.11]	0.608
Age					
<15 years	86 (7.8)	72 (83.7)	14 (16.3)	0.63 [0.22; 1.79]	0.390
15-29 years	116 (10.5)	90 (77.6)	26 (22.4)	1.71 [0.88; 3.35]	0.116
30-44 years	249 (22.5)	195 (78.3)	54 (21.7)	Ref	
45-59 years	426 (38.5)	354 (83.1)	72 (16.9)	0.97 [0.56; 1.69]	0.911
≥60 years	230 (20.8)	181 (78.7)	49 (21.3)	1.14 [0.56; 2.32]	0.723
Median age (IQR)	*50 (35–58)*	*50 (35–58)*	*49 (35–59)*		
Screening location					
Community screening event	627 (56.6)	523 (83.4)	104 (16.6)	Ref	

Primary care center	480 (43.4)	369 (76.9)	111 (23.1)	1.19 [0.62; 2.30]	0.593
Target group					
Household and close contacts	585 (52.9)	458 (78.3)	127 (21.7)	1.03 [0.75; 1.39]	0.874
Vulnerable community members	470 (42.5)	408 (86.8)	62 (13.2)	Ref	
Healthcare workers	52 (4.7)	26 (50.0)	26 (50.0)	1.38 [1.25; 1.53]	<0.001
Urbanization					
Urban	729 (65.9)	598 (82.0)	131 (18.0)	Ref	
Peri-urban	378 (34.2)	294 (77.8)	84 (22.2)	1.00 [0.58; 1.73]	0.990
Diabetes mellitus					
No/Unknown	1,065 (96.2)	859 (80.7)	206 (19.3)	Ref	
Yes	42 (3.8)	33 (78.6)	9 (21.4)	0.74 [0.18; 3.11]	0.679
Previous history of TB					
No/Unknown	1,096 (99.0)	883 (80.6)	213 (19.4)	Ref	
Yes	11 (1.0)	9 (81.8)	2 (18.2)	1.03 [0.14; 7.63]	0.980

Notes:
¶ Model stratified by health insurance and residency status, so these parameters were excluded; parameters of sex and target group fitted as time-varying covariates; includes a total of 8,211 person-months
¤ Percent of total
ǂ Percent of row total
¥ LTFU=Loss to follow-up; aOR=adjusted Hazard Ratio
† Wald test

DISCUSSION

In the array of obstacles to scaling up TPT in Viet Nam, TBI diagnosis remains a critical step in the country's targeted approach. To date, however, it has also represented an insuperable bottleneck. This stems from an overreliance on TST from a single product (PPD-Bulbio), for which there is documented performance deviation compared to other TSTs and IGRA [32]. These issues are in addition to the well-understood range of confounders affecting clinical performance of TSTs in comparison to IGRAs.[33] Despite its shortcomings, TST remains the programmatic standard of care partly due to the perceived operational challenges in deploying IGRAs outside of hospital settings.

This evaluation builds on the evidence base that it is possible to deploy IGRAs at lower healthcare levels.[21] As shown previously, fidelity to manufacturer recommended procedures in terms of handling, timing and temperature-control throughout collection, transport and processing of specimens from the community to the laboratory resulted in positivity[34] and indeterminate rates[35,36] that were comparable to those of facility-based studies. Our measured positivity was also aligned with previously published IGRA-positivity measured in the community in Viet Nam (pooled positivity: 37.7%; n=2,706).[21,37] We also observed the expected dose-response pattern of rising positivity and risk of TBI in older individuals as well as the higher risk of QFT-Plus positivity in males.[20,21] Concordant with these results, our study highlighted that IGRA can be used at the community level as another option for TBI diagnosis and accelerating scale-up of TPT.

However, there were patterns in the TBI care cascade indicating that scale-up of available TBI diagnostic tools and regimens requires more than simply decentralization. Fewer than half of the individuals mobilized during these ACF campaigns agreed to or were eligible for an IGRA test and only six out of ten eligible persons initiated TPT, which was concordant with prior studies in Viet Nam.[34] One potential reason for the drop-off may be process related, since we embedded the study in a programmatic setting, which meant that in general over two weeks elapsed from when participants were tested until eligible persons initiated TPT. Nevertheless, slow turnaround time may only partially explain the pre-treatment LTFU, as TPT initiation rate was consistent across both settings despite the difference in turnaround time.

By fielding the study in two separate sites with different TPT regimen and TBI rates in the community, we recorded several noteworthy observations. Specifically, while initiation rates in both sites were similar, there was a slightly higher completion rate in the 3HR cohort. Thus, even though we did not observe a greater uptake of TPT as seen on prior studies, the shorter treatment duration of 3HR may have contributed to higher TPT completion rates.[38–40] However, the survival analysis showed that more persons were lost to follow-up than expected over the shorter period of treatment. Based on informal qualitative feedback from field staff, reasons for the large drop-offs in the cascade included a lack of understanding of the risk of progression from TBI to active TB and the benefits of TPT in the general population, but also among healthcare providers, which leads to the de-prioritization of TPT as optional prophylaxis rather than valuable intervention. Since the 3HR regimen was only used in one province which may have faced site-specific challenges, we cannot generalize these results to other areas of the country. However, they highlight the need for more education and advocacy for providers and participants to improve the acceptance and prioritization of TPT.[41,42]

Moreover, advocacy and awareness building may need to be tailored to individual subgroups. Even though positivity, initiation and completion rates did not vary substantially across sites, gender or age category, there were, however, notable differences across study populations. In our study, HCWs exhibited a lower proportion and risk of positivity, higher TPT initiation and significantly higher risk of LTFU compared to HHCs and community members in either site. The low positivity rate was particularly noteworthy for its discordance with published, albeit dated, evidence from Viet Nam[43] and WHO guidelines warranting intervention in this group due to higher occupational risk of TB infection.[44] A potential explanation for the discordance is that a sizeable proportion of HCWs were generalist primary care workers. The more recent EnTIC study (NCT02073240) measured lower TBI rates among Vietnamese HCWs in general hospitals compared to HCWs in TB hospitals (27.9% [22.8%, 33.6%] vs. 41.7% [26.2%, 58.9%]).[45] However, this TBI rate in general hospital HCWs is still higher than the rate among HCWs on this study; a future comparative analyses of TBI in HCWs in tertiary/quaternary general hospitals versus primary care workers may offer further insight.

The diagnostic delay was unacceptably long among HCWs and across all groups in Hai Phong. In Hai Phong, the lower burden and more limited TB care capacity as well as greater reliance on the lung hospital in TB care and prevention activities may have contributed to the long delay in treatment initiation. Meanwhile, upon investigation, HCWs indicated a preference to wait for the new 12-dose regimen of isoniazid and rifapentine (3HP), but then agreed to initiate TPT on 9H as concerns over nitrosamine impurities delayed scale-up of 3HP in Viet Nam.[46,47] Nevertheless, despite a delay of almost six weeks, the TPT initiation rate among HCWs was highest across all groups and also above rates measured on prior studies (39.0%-49.6%).[48,49] Conversely, the low completion rate measured on this study was on par with other studies on HCWs receiving 9H for TPT. However, this low rate may have been avoided with shorter regimen as adherence in this study at month 3 was 100% and month 8 was still at 80.0%. These results were in line with previous studies that indicated health workers were significantly more likely to complete TPT on 3HR compared to 9H (91.4% *vs.* 76.7%, p=0.02).[50–52]

The use of the 9H regimen in the majority of participants also highlights a key limitation of this study. By conducting it under routine program conditions, the study was exposed to external bias and confounding, such as the variability in the available TPT regimen. HCMC historically has had a substantially larger burden of TB and TBI, as evinced on this study. Thus, 9H was the local regimen of choice due to its greater availability and lower costs. Similarly, we relied on routine diagnostics to rule out active TB rather than more sensitive tools such as culture due to cost implications. With respect to costs, another limitation of our study was the lack of a formal assessment of the cost barrier of IGRAs in our low-resource setting with limited program budgets. Operationally, WHO recommends to integrate TPT into routine HHC investigations and ACF.[16] It stands to reason that such integration may also improve value for money as has been well-established for highly vulnerable people living with HIV.[53] There is ample evidence that HHC investigations and community-based ACF campaigns can reach those most vulnerable to active TB and thus most in need of TPT.[29,54,55] Nevertheless, given the lack of an accompanying health economic evaluation, future research should conduct impact evaluations and cost-effectiveness analyses of integrated TB and TBI testing and treatment on ACF campaigns and differences in incidence and disability-adjusted life years compared to a control cohort. Another limitation is that our cohort design did not include a post-treatment follow-up to assess incidence of TB in those with and without TPT, in part due to the social distancing measures launched in response to the pandemic. The study's convenience sampling and selection of HCMC and Hai Phong as study sites likely introduced bias towards densely populated urban settings, which consequently limits the generalizability of this study. Nevertheless, the study benefitted from its large sample size and integration into routine program operations that may help to translate the findings to recommendations for densely populated, high TB burden settings in general.

CONCLUSIONS

WHO's End TB Strategy highlights the need for increased testing and treatment of TB infection as a core intervention to reduce transmission and thus achieve incidence targets. While many high TB burden countries have incorporated this emphasis into their national strategic plans, operationalization of these plans is often hindered by the suboptimal application of available tools. IGRAs are the current gold standard for TBI testing, but are often underutilized, particularly at the lower healthcare levels. Shorter TPT regimen are recommended, but require further studies to assess their potential to support broad-scale TPT. This study elucidated the potential to decentralize and leverage these tools for wider and more cost-effective deployment towards meeting TPT targets, but also highlighted that scale-up of these tools, as well as overall TPT access and uptake, will likely require complementary, tailored advocacy and education for both beneficiaries and providers.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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AUTHORS' CONTRIBUTIONS

LNQV, NN, VVT, HMD and THM contributed to the conceptualization of the study. The methodology was developed by LNQV, NTTN, TTTD, THM, HMD, and VVT. LNQV and PTL conducted the formal analysis. The investigation was conducted VVT, NTTN, TTTD and PTL. Resources for the study were provided by LHN, HMD, HTT, HBN and NVN. Data were curated by LNQV, AJC, PTL and KTT and LNQV visualized the data. LNQV, NTTN, TTTD wrote the original draft, while the manuscript was reviewed and edited by LNQV, AJC, JC, NN, HTT and MC. Study supervision was provided by JC, MC, LNQV, LHN, THM, HTT, HBN and NVN, while RJF, AJC, VVT, NTTN and TTTD were responsible for project administration. Funding acquisition was led by LNQV, RJF and AJC. All authors have read and approved the final manuscript.

DATA AVAILABILITY

The data that support the findings of this study are available from the Viet Nam National TB Control Program, Hai Phong Provincial Lung Hospital and Pham Ngoc Thach Provincial TB Hospital, but restrictions apply to their availability. Data are can be made available from the authors upon reasonable request and with permission of the Viet Nam National TB Control Program, Hai Phong Provincial Lung Hospital and Pham Ngoc Thach Provincial TB Hospital.

ETHICAL CONSIDERATIONS

This study was approved by the Pham Ngoc Thach Hospital ethics committee for biomedical research (897/HDDD-PNT). In addition, QFT-Plus testing is part of national guidelines and activities were approved by the NTP (1069/BVPTW-DAPCL). Participation was voluntary and did not affect the provision or standard of care. All personal identifying information was removed from the dataset prior to analysis.

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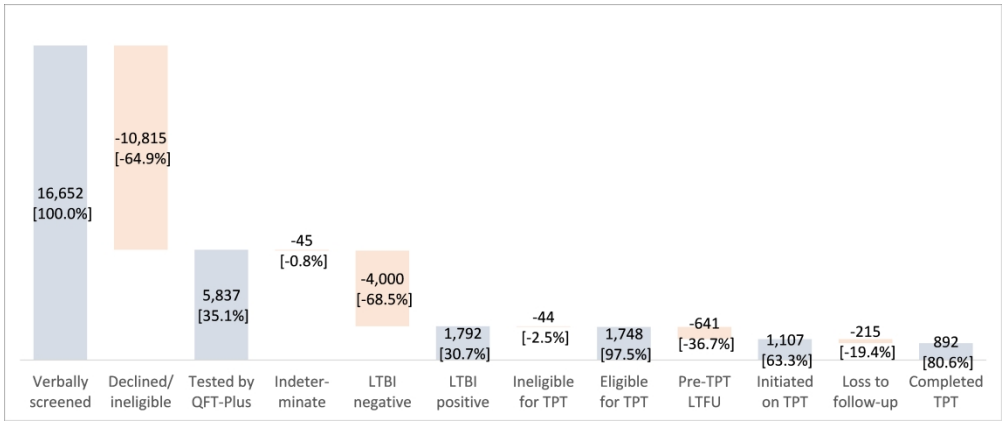
55 Morishita F, Garfin AMCG, Lew W, *et al.* Bringing state-of-The-Art diagnostics to vulnerable populations: The use of a mobile screening unit in active case finding for tuberculosis in Palawan, the Philippines. *PLoS One* 2017;**12**:1–21. doi:10.1371/journal.pone.0171310

FIGURE LEGENDS

Figure 1. Aggregate TB infection care cascade.

Figure 2. TB infection care cascade by site and target group.

Figure 3. Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen.



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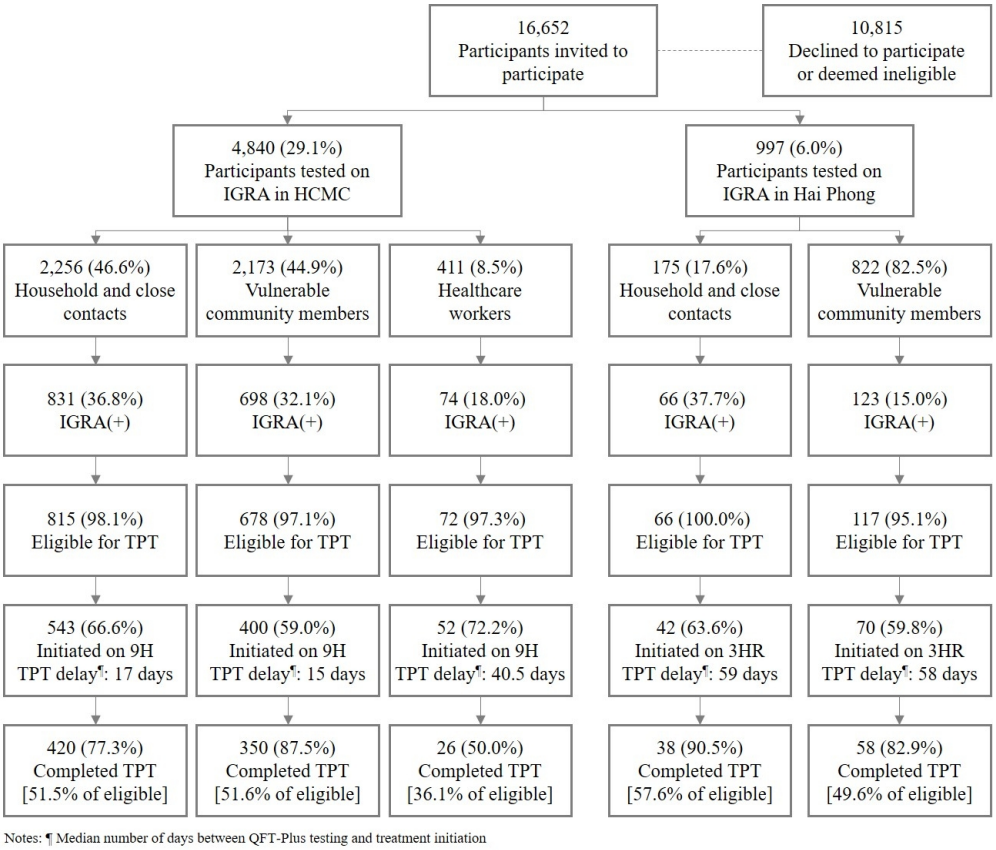

Notes: ¶ Median number of days between QFT-Plus testing and treatment initiation

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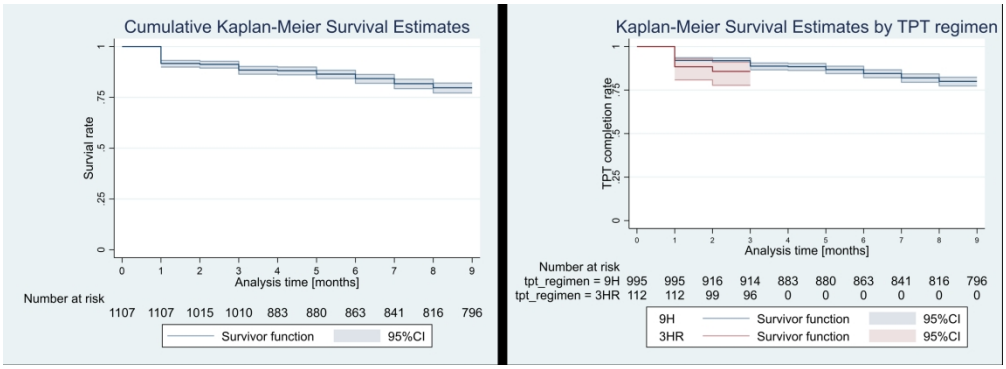


Figure 3a & 3b - Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen

528x190mm (150 x 150 DPI)

STROBE Statement

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	8-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-12
		(b) Indicate number of participants with missing data for each variable of interest	10-12
Outcome data	15*	Report numbers of outcome events or summary measures	8-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12

		(*b*) Report category boundaries when continuous variables were categorized	10, 12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

SUPPLEMENTAL MATERIAL

Model specification validation results

Figure S1: Kaplan-Meier observed survival curve of TPT regimen

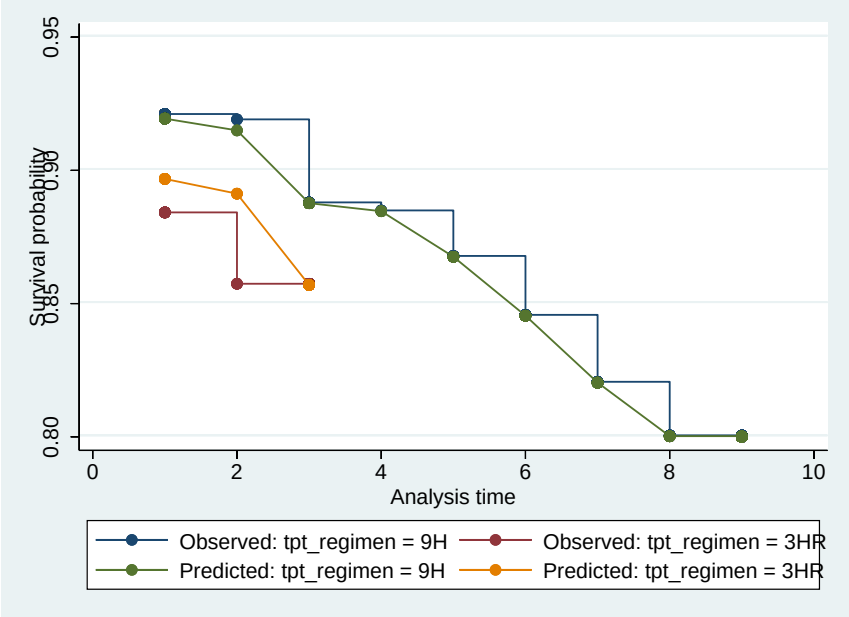
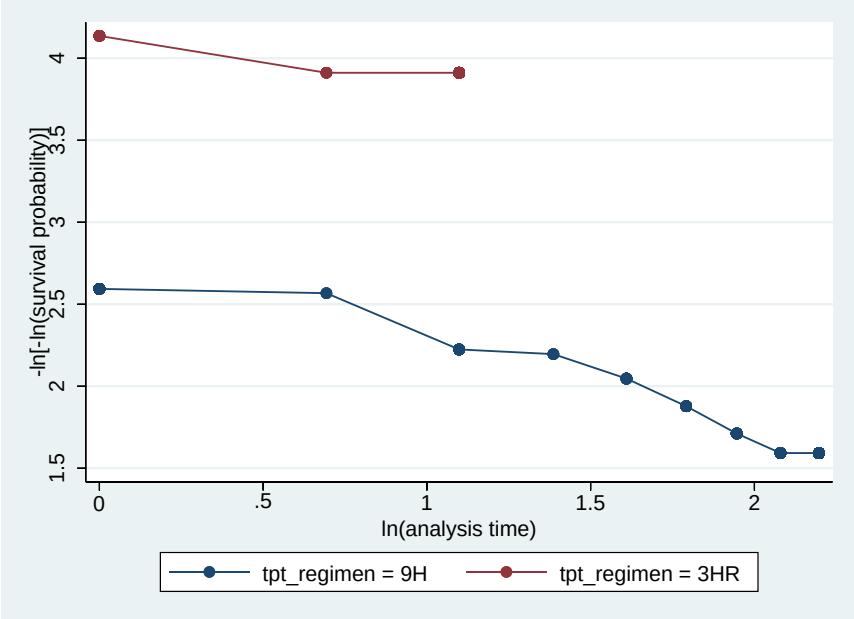


Figure S2: Log-log plot of the final Cox model



The log-rank test result to assess the equality of survival between the two TPT regimen was p=0.319.

The p-value of the global postestimation proportional hazards test 0.644 and tests of individual parameters produced p-values of 0.112<p<0.955.

BMJ Open

Optimizing diagnosis and treatment of tuberculosis infection in community and primary care settings in two urban provinces of Viet Nam: a cohort study

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Global health, Public health, Epidemiology
Keywords:	Tuberculosis < INFECTIOUS DISEASES, PREVENTIVE MEDICINE, PUBLIC HEALTH

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Optimizing diagnosis and treatment of tuberculosis infection in community and primary care settings in two urban provinces of Viet Nam: a cohort study

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Word count: 3,954

ABSTRACT

Objectives: To end tuberculosis (TB), the vast reservoir of 1.7-2.3 billion TB infections (TBI) must be addressed but achieving global TB preventive therapy (TPT) targets seems unlikely. This study assessed the feasibility of using interferon-gamma release assays (IGRA) at lower healthcare levels and the comparative performance of 3- and 9-month daily TPT regimens (3HR/9H).

Design, setting and participants: This cohort study was implemented in two provinces of Viet Nam from May-2019 to Sept-2020. Participants included household contacts (HHC), vulnerable community members and healthcare workers (HCW) recruited at community-based TB screening events or HHC investigations at primary care centers, who were followed up throughout TPT.

Primary and secondary outcomes: We constructed TBI care cascades describing indeterminate and positivity rates to assess feasibility, and initiation and completion rates to assess performance. We fitted mixed-effect logistic and stratified Cox models to identify factors associated with IGRA-positivity and loss to follow-up (LTFU).

Results: Among 5,837 participants, the indeterminate rate was 0.8% and 30.7% were IGRA-positive. TPT initiation and completion rates were 63.3% (3HR=61.2% vs. 9H=63.6%; p=0.147) and 80.6% (3HR=85.7% vs. 9H=80.0%; p=0.522), respectively. Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78]; p<0.001), aged 45-59 years (1.30 [1.05, 1.60]; p=0.018) and exhibiting TB-related abnormalities on X-ray (2.23 [1.38, 3.61]; p=0.001) were associated with positive IGRA results. Risk of IGRA-positivity was lower in peri-urban districts (0.55 [0.36, 0.55]; p=0.007), aged <15 years (0.18 [0.13, 0.26]; p<0.001), aged 15-29 years (0.56 [0.42, 0.75]; p<0.001), and HCWs (0.34 [0.24, 0.48]; p<0.001). The 3HR regimen (adjusted Hazard Ratio=3.83 [1.49, 9.84]; p=0.005) and HCWs (1.38 [1.25, 1.53]; p<0.001) showed higher hazards of LTFU.

Conclusion: Providing IGRA at lower healthcare levels is feasible and along with shorter regimen may expand access and uptake towards meeting TPT targets, but scale-up may require complementary advocacy and education for beneficiaries and providers.

Keywords: tuberculosis, infection, community, urban, interferon-gamma release assay, short-course, tuberculosis preventive therapy

Running head: Optimizing diagnosis and treatment of TB infection in Viet Nam

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A strength of the study was the large sample size of persons tested by interferon-gamma release assay across two sites with varying characteristics in background tuberculosis infection as well as demographic and clinical characteristics, which enabled comparative analyses of subsegments of the sample.
- The community setting in which participants were recruited and tested using sophisticated diagnostics decentralized to lower care levels further contributes to the evidence base for scale-up of tuberculosis prevention, especially given the size of the sample.
- Embedding the study in routine tuberculosis program activities exposed it to common limitations such as heterogeneity in supply chain as well as health worker knowledge, attitudes and practices commonly experienced by the program.

INTRODUCTION

After a brief relegation due to the COVID-19 pandemic, tuberculosis (TB) is once again the world's leading infectious disease killer.[1] One of the key reasons is the estimated 1.7–2.3 billion people infected with TB without suffering from active disease, whose activation continues to fuel incidence.[2,3] An estimated 5-15% of people with TB infection (TBI) develop active TB disease in their lifetimes, serving as a vast reservoir for future TB disease, even if new TB transmission were completely eliminated today.[4,5] This was also observed by a study in London at the height of the pandemic which showed that social distancing mitigated incidence of several respiratory diseases, but not of TB.[6] Thus, research and modeling suggest that increased emphasis on TBI is needed in order to reduce worldwide TB incidence.[7] However, while efforts to find and treat people with TB who are missed by existing TB care programs have been launched in most high TB burden countries, relatively few are addressing the burden of TBI at scale.[8–11]

This muted response was historically linked to World Health Organization (WHO) guidelines recommending TB preventive therapy (TPT) in high TB burden settings only for people living with HIV (PLHIV), under-5 household contacts (HHC) of persons with bacteriologically-confirmed, pulmonary TB and persons with occupational risk factors for progression to active TB.[12] Beyond conservative guidelines, other commonly cited bottlenecks have included shortages in commodities and particularly diagnostic consumables such as tuberculin, high health system costs of diagnosis, treatment and follow-up depressing TPT uptake, and lack of patient-friendly treatment regimen negatively affecting adherence.[13,14]

In recent years, the WHO has issued updated technical and operational guidelines with expanded TPT eligibility criteria, such as HIV-negative household contacts of all ages.[15,16] However, a key recommendation for this expanded eligibility was the inclusion of an appropriate clinical and laboratory evaluation, which in select settings translated to the prerequisite of immunological confirmation of TBI by tuberculin skin test (TST) or interferon-gamma release assay (IGRA) for TPT within national guidelines.[14,17] The updated WHO guidelines also introduced new short-course TPT regimens with better tolerability and safety profiles, which high TB burden countries have eagerly integrated into national TBI guidelines and national strategic plans.[18,19]

One of these countries is Viet Nam, which ranks 11th among the 30 high TB burden countries. During the first prevalence survey, the annual rate of TB infection was measured to be 1.7% with a TBI prevalence of 16.7% in children aged 6–14 years using TST with a threshold of 10mm.[20] A subsequent study in rural Ca Mau province measured a TBI rate of 36.8% using IGRA.[21] In 2014, Viet Nam passed legislation codifying its goals to drastically reduce TB prevalence in alignment with the WHO End TB Strategy.[22] On World TB Day 2020, the Ministry of Health introduced the country's inaugural guidelines on diagnosis and treatment of TBI. These

guidelines expanded TPT eligibility to all adults with TBI confirmed by recommended diagnostic tools and excluding active TB, permitted the use of various shortened regimen, and described contact investigation and follow-up requirements. Viet Nam further demonstrated its focus on TB prevention by committing at the UN High-Level Meeting on Ending TB to scale-up provision of TPT to 291,500 people by 2022.[23]

However, the country has experienced many of the challenges related to the scale-up of TPT as described above. Specifically, Viet Nam requires TBI confirmation within the expanded eligibility criteria prior to treatment, but has experienced tuberculin supply chain shortages and batch-variance in the positivity threshold. While WHO-recommended IGRAs are commercially available, the National TB Control Programme (NTP) has consigned this assay class to tertiary care facilities due to the delicate specimen handling and sophistical laboratory requirements,[24,25] which is underscored by the lack of published evidence of the assay's deployment at the point-of-care domestically and worldwide. In addition, the prohibitively high costs per test have precluded serious consideration for routine TB program activities.

Nevertheless, the NTP remains committed to the scale-up of TPT through the optimal use of available and new diagnostics and regimens.[26] Given tuberculin supply and staff capacity challenges, and lack of evidence on the impact of recently introduced shorter TPT regimen on uptake and completion, this study assessed the use of the QuantiFERON-TB Gold Plus assay (QFT-Plus; Qiagen, Hilden, Germany) at the community level and the performance of shorter TPT regimen under programmatic conditions. The goal was to inform NTP of Viet Nam and other high TB burden countries in their ambitions to meet their TPT goals.

METHODS

Study design and objectives

This was a cohort study to measure the feasibility of employing IGRA at the community and primary care levels for the diagnosis of TBI. Feasibility was defined by comparing indeterminate and positivity rates with those demonstrated in facility-based studies (primary endpoints). Secondary objectives included measuring the rate of TPT initiation and completion (secondary endpoints) in cohorts provided with two different TPT regimens, and to identify participant covariates associated with IGRA-positivity and loss to follow-up. The study followed the STROBE guideline for reporting observational studies (Supplemental material 1).

Study setting

The study was conducted in six districts of Ho Chi Minh City (HCMC) and Hai Phong municipal provinces. In HCMC, study sites included Districts 6, 8, 12, Binh Chanh, Go Vap, and Tan Binh with a cumulative population

of 2,387,052 and 3,598 TB notifications in 2019. In Hai Phong, the study took place in Do Son with a population of 49,029 and 52 persons with drug-susceptible TB notified in 2019.

Study population and recruitment

The study was embedded into routine contact investigations at primary care commune health posts and community-based active TB case finding (ACF) events. Details of the ACF events are provided elsewhere.[27] The study population included HHC and close contacts, and vulnerable community members at elevated risk of active TB, such as the elderly, urban poor and economic migrants. Briefly, elderly persons were ≥55 years, urban poor were based on national poverty definitions and economic migrants were categorized based on residency registration in rural provinces outside of the intervention districts. [28–30] The HCMC site also included a subgroup of primary- and secondary-level healthcare workers (HCW) based on the request from local authorities. Recruitment and follow-up occurred from May-2019 to Sep-2020. All individuals presenting for screening provided routine demographic and clinical information including age, sex, residency status, history of TB, comorbidities and symptomatic presentation. Following intake, persons belonging to the study population with residency in the study districts were invited to participate in the study. Persons living outside of or intending to relocate away from the study sites, or who declined to consent were excluded. Eligible, consenting participants were recruited consecutively until the quota of available QFT-Plus tests was reached (n=5,000 in HCMC and n=1,000 in Hai Phong). Parents consented on behalf of their children under 18 years.

Sample size

We calculated the sample size to power a 1-sample Z-test of proportions for non-inferiority between a literature-based indeterminate rate of p=2.9% and a null hypothesis of p_0=3.5% with a non-inferiority margin δ=0.1%. With a confidence level of α=95% and a power of β=90%, the estimated sample size was n=4,915. We included a 15% contingency for attrition, data losses and post-hoc exclusion for a final sample size of n=5,653.

Specimen collection and processing

Provincial lung hospital (PLH) laboratory staff hosted training sessions on specimen collection and processing for the District TB Unit (DTU) and district-level laboratory staff. The District Health Center (DHC) mobilized participants to attend ACF events or to present at commune health posts. All attendants were systematically screened for TB symptoms and directed to undergo chest radiography (CXR) to rule out active TB. Persons with parenchymal abnormalities suggestive of TB on CXR or strong clinical suspicion of TB were referred for molecular sputum testing, as per contemporary national TB treatment guidelines.[31] Attendants were counseled on TBI and invited to participate. Study staff collected blood specimens from consenting, eligible individuals as per manufacturer recommended procedures. Each participant provided 4ml of venous whole blood in four separate tubes. Blood specimens were processed and analyzed per manufacturer's recommendations. Briefly,

all four tubes were immediately shaken ~10 times to dissolve all antigens on the tube's wall coating. Tubes were stored inside dry ice coolers at 17–25°C, which were transported to the PLH biochemistry–hematology departments within six hours, twice a day. Samples were incubated at 37°C for 20 hours (±1 hour) and centrifuged within one hour of completing the incubation stage at 2000-3000g for 14 minutes at room temperature. The twelve-step enzyme linked immunosorbent assay was conducted within 16-24 hours. Results were analyzed by using proprietary QuantiFERON software v2.7.1.

TPT initiation and participant follow-up

QFT-Plus test results were returned to the DHC two days after receipt of the blood specimens. Individuals with negative results were informed via phone by DHC staff. Those with positive results and eligible for preventive treatment (i.e., with confirmed TBI and active TB ruled out by CXR and symptomatic presentation) were invited to present at their respective DTU for pre-treatment counseling and TPT initiation as per national guidelines.[17] TPT regimen varied by province. In HCMC, TPT consisted of nine months of daily isoniazid (9H), while in Hai Phong eligible persons received three months of daily isoniazid and rifampicin (3HR). Individuals on TPT received in-person follow-up during monthly drug pick-up at the DTU. Community TB officers conducted phone or in-person follow-up in regular intervals or as needed, as recommended in national guidelines. Participants experiencing adverse events were asked to present at the DTU for check-up.

Statistical analyses

The primary measures of interest were QFT-Plus positivity and indeterminate rates. Secondary variables of interest included TPT initiation and completion rates within the study population. Missing data were retrieved through post-event follow-up of participants or excluded from individual analyses. We constructed TBI care cascades in aggregate and segmented by site ranging from persons recruited to participants with a successful TPT completion. We documented losses along the cascade and reported median and interquartile ranges of diagnostic delay, i.e., time from testing to TPT initiation. We calculated descriptive statistics for key sample characteristics by QFT-Plus result and TPT completion and fitted a saturated, mixed-effect logistic regression to assess associations between positivity and participant covariates to adjust for confounding and inherent bias. Study district was the random effect to account for intra-cluster correlation. The survival analysis designated loss to follow-up (LTFU) a failure and censored adherent participants on 3HR and 9H at three and nine months, respectively. We constructed Kaplan-Meier survival curves and conducted log-rank tests to assess the equality of survival between the two TPT regimen. We fitted a saturated Cox model and assessed validity of the proportionality assumption using log-log plots and Schoenfeld residuals. Violations were addressed via stratification or modeling of time-variance for parameters of interest. The final model passed both the global postestimation proportional hazards test and tests of individual parameters. P-values of validation tests were

provided in the Supplemental material 2. Hypothesis tests were two-tailed. A threshold of $p<0.05$ was considered significant. Analyses were conducted using STATA v17 (Stata Corp.; College Station, TX, USA).

Patient and public involvement

While TB patients and their families were not involved in setting the research question, a consensus building meeting was held at the beginning of the study for government stakeholders and community members to provide feedback and recommendations and reach consensus about the study design and implementation. Patients, their families and public stakeholders were also central to dissemination of study information, which helped to motivate community involvement during and beyond the study.

RESULTS

Sample characteristics

Of the 5,837 participants in the sample, 59.3% (n=3,463) were female (Table 1). Children under 15 years constituted 19.5% (1,136/5,834) of the sample and the median participant age was 40 (IQR: 20–55). Overall, most participants were recruited at community-based ACF events (55.8%; n=3,257), lived in urban areas (65.6%; n=3,827), were permanent residents (90.5%; 3,116/3,444) and were enrolled on social health insurance (90.4%; 5,269/5,832). About 2.9% (n=167) were diabetics and 1.1% (n=62) reported a history of TB. Moreover, 39.5% (n=2,306) reported experiencing at least one of the four core TB symptoms (cough, weight loss, fever, and/or night sweats) during recruitment, while 2.3% (n=134) participants exhibited TB-related CXR abnormalities.

Table 1: Participant characteristics and adjusted odds ratios associated with IGRA-positivity

	Total (N = 5,837) N (%)¤	IGRA(+)¥ (N = 1,792) N (%)	IGRA (-)¥ (N = 4,000) N (%)	Indeterminate (N = 45) N (%)	aOR¥ (95% CI)	p-value†
Sex						
Female	3,463 (59.3)	1,048 (30.3)	2,392 (69.1)	23 (0.7)	Ref	
Male	2,374 (40.7)	744 (31.3)	1,608 (67.7)	22 (0.9)	1.51 [1.28; 1.78]	<0.001
Age¶						
<15 years	1,136 / 5,834 (19.5)	134 / 1,792 (11.8)	997 / 3,997 (87.8)	5 / 45 (0.4)	0.18 [0.13; 0.26]	<0.001
15-29 years	891 / 5,834 (15.3)	195 / 1,792 (21.9)	687 / 3,997 (77.1)	9 / 45 (1.0)	0.56 [0.42; 0.75]	<0.001
30-44 years	1,290 / 5,834 (22.1)	418 / 1,792 (32.4)	864 / 3,997 (67.0)	8 / 45 (0.6)	Ref	
45-59 years	1,679 / 5,834 (28.8)	704 / 1,792 (41.9)	957 / 3,997 (57.0)	18 / 45 (1.1)	1.30 [1.05; 1.60]	0.018
≥60 years	838 / 5,834 (14.4)	341 / 1,792 (40.7)	492 / 3,997 (58.7)	5 / 45 (0.6)	1.06 [0.80; 1.40]	0.673
Median age (IQR)	*40 (20–55)*	*49 (35–58)*	*35 (15–52)*	*45 (24–54)*		
Study site						
Ho Chi Minh City	4,840 (82.9)	1,603 (33.1)	3,200 (66.1)	37 (0.8)	Ref	
Hai Phong	997 (17.1)	189 (19.0)	800 (80.2)	8 (0.8)	0.69 [0.40; 1.20]	0.186
Screening location						
Community screening event	3,257 (55.8)	993 (30.5)	2,244 (68.9)	20 (0.6)	Ref	
Primary care center	2,580 (44.2)	799 (31.0)	1,756 (68.1)	25 (1.0)	0.88 [0.69; 1.13]	0.325
Target group						
Household and close contacts	2,431 (41.7)	897 (36.9)	1,495 (61.5)	39 (1.6)	1.11 [0.67; 1.82]	0.690
Vulnerable community members	2,995 (51.3)	821 (27.4)	2,168 (72.4)	6 (0.2)	Ref	
Healthcare workers	411 (7.0)	74 (18.0)	337 (82.0)	0 (0.0)	0.34 [0.24; 0.48]	<0.001
Urbanization						
Urban	3,827 (65.6)	1,135 (29.7)	2,669 (69.7)	23 (0.6)	Ref	
Peri-urban	2,010 (34.4)	657 (32.7)	1,331 (66.2)	22 (1.1)	0.55 [0.36; 0.85]	0.007
Residency status‡,¶						
Grade 1	3,116 / 3,444 (90.5)	799 / 907 (25.6)	2,294 / 2,511 (73.6)	23 / 26 (0.7)	Ref	
Grade 2	91 / 3,444 (2.6)	27 / 907 (29.7)	62 / 2,511 (68.1)	2 / 26 (2.2)	1.08 [0.66; 1.74]	0.765
Grade 3	202 / 3,444 (5.9)	68 / 907 (33.7)	134 / 2,511 (66.3)	0 / 26 (0.0)	1.36 [0.96; 1.92]	0.083
Grade 4	35 / 3,444 (1.0)	13 / 907 (37.1)	21 / 2,511 (60.0)	1 / 26 (2.9)	1.54 [0.73; 3.26]	0.260
Social health insurance¶						
No	563 / 5,832 (9.7)	180 / 1,790 (32.0)	376 / 3,997 (66.8)	7 / 45 (1.2)	Ref	
Yes	5,269 / 5,832 (90.4)	1,610 / 1,790 (30.6)	3,621 / 3,997 (68.7)	38 / 45 (0.7)	1.11 [0.84; 1.46]	0.473

Diabetes mellitus						
No/Unknown	5,670 (97.1)	1,721 (30.4)	3,906 (68.9)	43 (0.8)	Ref	
Yes	167 (2.9)	71 (42.5)	94 (56.3)	2 (1.2)	1.15 [0.75; 1.76]	0.516
Previous history of TB						
No/Unknown	5,775 (98.9)	1,764 (30.6)	3,967 (68.7)	44 (0.8)	Ref	
Yes	62 (1.1)	28 (45.2)	33 (53.2)	1 (1.6)	1.93 [0.96; 3.86]	0.063
Any TB symptoms[§,¶]						
No	3,531 (60.5)	1,012 (28.7)	2,499 (70.8)	20 (0.6)	Ref	
Yes	2,306 (39.5)	780 (33.8)	1,501 (65.1)	25 (1.1)	0.96 [0.80; 1.15]	0.635
Chest X-ray result						
Normal	5,502 (94.3)	1,693 (30.8)	3,768 (68.5)	41 (0.8)	Ref	
Abnormal	134 (2.3)	78 (58.2)	56 (41.8)	0 (0.0)	2.23 [1.38; 3.61]	0.001
No Chest X-ray	201 (3.4)	21 (10.5)	176 (87.6)	4 (2.0)	0.28 [0.15; 0.51]	<0.001

Notes:
¶ N sizes listed due to missing values;
§ Includes cough, fever, night sweats and weight loss of any duration;
┼ Residency grade definitions: 1=Permanent resident; 2=Long-term intra-province temporary resident; 3=Short-term, intra-province temporary resident; 4=Short-term, inter-province temporary resident
¤ Percent of total
ǂ Percent of row total
¥ IGRA=Interferon-Gamma Release Assay; aOR=adjusted Odds Ratio
† Wald test

TB infection care cascade

Of the 16,652 individuals verbally screened in both provinces, 35.1% (n=5,837) agreed to be tested by QFT-Plus for the study (Figure 1). The overall indeterminate rate was 0.8% (n=45) and 30.7% (n=1,792) of participants were QFT-Plus-positive, of whom 97.5% (n=1,748) were eligible for TPT. About 63.3% (1,107/1,748) of eligible participants initiated TPT and 80.6% (892/1,107) completed therapy. The sample included 4,840 participants in HCMC and 997 in Hai Phong (Table 2). The indeterminate rate was 0.8% in both sites, while positivity rates were 33.1% (1,603/4,840) in HCMC and 19.0% (189/997) in Hai Phong. The respective TPT initiation and completion rates in the 9H cohort in HCMC were 63.6% (995/1,565) and 80.0% (796/995) compared to 61.2% (112/183) and 85.7% (96/112) in the 3HR cohort in Hai Phong. Neither initiation nor completion rates were significantly different between the two regimens (p=0.522 & p=0.147, respectively).

Table 2: TB infection care cascade by TPT cohort

	Total (N = 5,837) N (%)	**HCMC (N = 4,840) N (%)**	**Hai Phong (N = 997) N (%)**
IGRA result & TPT¥			
Indeterminate	45 (0.8)	37 (0.8)	8 (0.8)
Negative	4,000 (68.5)	3,200 (66.1)	800 (80.2)
Positive	1,791 (30.7)	1,603 (33.1)	189 (19.0)
--Ineligible for TPT (% of positive)	**44 (0.8)**	**38 (0.8)**	**6 (0.6)**
No CXR	21 (0.4)	16 (0.3)	5 (0.5)
CXR(+), No MTB test	6 (0.1)	5 (0.1)	1 (0.1)
MTB(+)	17 (0.3)	17 (0.4)	0 (0.0)
--Eligible for TPT (% of positive)	**1,748 (97.6)**	**1,565 (97.6)**	**183 (97.3)**
CXR(-)	1,702 (95.0)	1,524 (95.1)	178 (94.7)
CXR(+), MTB(-)	46 (2.6)	41 (2.6)	5 (2.7)
--Initiated on TPT¶ (% of eligible)	**1,107 (63.3)**	**995 (63.6)**	**112 (61.2)**
--Completed TPT¶ (% of initiated)	**892 (80.6)**	**796 (80.0)**	**96 (85.7)**

Notes:
¥ IGRA=Interferon-Gamma Release Assay; CXR=Chest X-Ray; TPT=TB Preventive Therapy; MTB=*M. tuberculosis*; HCMC=Ho Chi Minh City
¶ TPT consisted of 9H in HCMC and of 3HR in Hai Phong

The sample included 46.6% (n=2,256) HHCs, 44.9% (n=2,173) vulnerable community members and 8.5% (n=411) HCWs in HCMC (Figure 2). In Hai Phong, the sample consisted of 17.6% (n=175) HHCs and 82.5% (n=822) community members. IGRA-positivity among HHCs was similar in both cities, but lower in community members in Hai Phong (123/822=15.0%) compared to HCMC (698/2173=32.1%). Similarly, positivity in HCWs was also comparatively lower (74/411=18.0%). TPT initiation rates in HHCs and community members were similar across sites ranging from 59.0% to 66.6%, and higher among HCWs (52/72=72.2%). Diagnostic delays in HCMC were shorter than in Hai Phong for both HHCs (17 vs. 59 days) and community members (15

vs. 58 days), except among HCWs (40.5). Similarly, TPT completion rates were high among HHCs and community members in both sites ranging from 77.3% to 90.5%, but only half of HCWs completed TPT.

Risk factors of IGRA-positivity

Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78]; p<0.001), aged 45-59 years (1.30 [1.05, 1.60]; p=0.018), and exhibiting CXR abnormalities suggestive of TB (2.23 [1.38, 3.61]; p=0.001) were associated with higher QFT-Plus positivity (Table 2). Conversely, compared to the reference group (30-44 years), the risk of QFT-Plus-positivity was significantly lower among children under 15 years (0.18 [0.13, 0.26]; p<0.001) and persons aged 15-29 years (0.56 [0.42, 0.75]; p<0.001), as well as among HCWs (0.34 [0.24, 0.48]; p<0.001) and individuals living in peri-urban areas (0.55 [0.36, 0.55]; p=0.007).

Survival analysis and risk factors of TPT completion

A total of 1,107 participants were followed for a total of 8,211 person-months with 215 recorded LTFUs (Table 3). There were 7,904 and 307 person-months of observations with mean follow-up times of 7.9 [7.8, 8.1] months and 2.7 [2.6, 2.9] months, and 199 and 16 LTFUs in the 9H and 3HR cohorts, respectively. The respective LTFU incidence rates were 25.2 and 52.1 per 1,000 person-months. Most LTFUs occurred after the first month of TPT in both the 9H (79/199=39.7%) and 3HR (13/16=81.2%) cohorts (Figures 3a and 3b). The survival analysis showed that the 3HR regimen (adjusted Hazard Ratio=3.83 [1.49, 9.84]; p=0.005) and HCWs (1.38 [1.25, 1.53]; p<0.001) were strongly associated with higher risk of LTFU.

Table 3: Participant characteristics and adjusted risk factors associated with TPT loss to follow-up¶

	Total (N = 1,107) N (%)¤	TPT completed¥ (N = 892) N (%)ǂ	LTFU¥ (N = 215) N (%)ǂ	aHR of LTFU¥ (95% CI)	p-value†
TPT regimen					
9H	995 (89.9)	796 (80.0)	199 (20.0)	Ref	
3HR	112 (10.1)	96 (85.7)	16 (14.3)	3.83 [1.49; 9.84]	0.005
Sex					
Female	645 (58.3)	512 (79.4)	133 (20.6)	Ref	
Male	462 (41.7)	380 (82.3)	082 (17.8)	1.02 [0.94; 1.11]	0.608
Age					
<15 years	86 (7.8)	72 (83.7)	14 (16.3)	0.63 [0.22; 1.79]	0.390
15-29 years	116 (10.5)	90 (77.6)	26 (22.4)	1.71 [0.88; 3.35]	0.116
30-44 years	249 (22.5)	195 (78.3)	54 (21.7)	Ref	
45-59 years	426 (38.5)	354 (83.1)	72 (16.9)	0.97 [0.56; 1.69]	0.911
≥60 years	230 (20.8)	181 (78.7)	49 (21.3)	1.14 [0.56; 2.32]	0.723
Median age (IQR)	*50 (35–58)*	*50 (35–58)*	*49 (35–59)*		
Screening location					
Community screening event	627 (56.6)	523 (83.4)	104 (16.6)	Ref	

Primary care center	480 (43.4)	369 (76.9)	111 (23.1)	1.19 [0.62; 2.30]	0.593
Target group					
Household and close contacts	585 (52.9)	458 (78.3)	127 (21.7)	1.03 [0.75; 1.39]	0.874
Vulnerable community members	470 (42.5)	408 (86.8)	62 (13.2)	Ref	
Healthcare workers	52 (4.7)	26 (50.0)	26 (50.0)	1.38 [1.25; 1.53]	<0.001
Urbanization					
Urban	729 (65.9)	598 (82.0)	131 (18.0)	Ref	
Peri-urban	378 (34.2)	294 (77.8)	84 (22.2)	1.00 [0.58; 1.73]	0.990
Diabetes mellitus					
No/Unknown	1,065 (96.2)	859 (80.7)	206 (19.3)	Ref	
Yes	42 (3.8)	33 (78.6)	9 (21.4)	0.74 [0.18; 3.11]	0.679
Previous history of TB					
No/Unknown	1,096 (99.0)	883 (80.6)	213 (19.4)	Ref	
Yes	11 (1.0)	9 (81.8)	2 (18.2)	1.03 [0.14; 7.63]	0.980

Notes:
¶ Model stratified by health insurance and residency status, so these parameters were excluded; parameters of sex and target group fitted as time-varying covariates; includes a total of 8,211 person-months
¤ Percent of total
ǂ Percent of row total
¥ LTFU=Loss to follow-up; aOR=adjusted Hazard Ratio
† Wald test

DISCUSSION

In the array of obstacles to scaling up TPT in Viet Nam, TBI diagnosis remains a critical step in the country's targeted approach. To date, however, it has also represented an insuperable bottleneck. This stems from an overreliance on TST from a single product (PPD-Bulbio), for which there is documented performance deviation compared to other TSTs and IGRA [32]. These issues are in addition to the well-understood range of confounders affecting clinical performance of TSTs in comparison to IGRAs.[33] Despite its shortcomings, TST remains the programmatic standard of care partly due to the perceived operational challenges in deploying IGRAs outside of hospital settings.

This evaluation builds on the evidence base that it is possible to deploy IGRAs at lower healthcare levels.[21] As shown previously, fidelity to manufacturer recommended procedures in terms of handling, timing and temperature-control throughout collection, transport and processing of specimens from the community to the laboratory resulted in positivity[34] and indeterminate rates[35,36] that were comparable to those of facility-based studies. Our measured positivity was also aligned with previously published IGRA-positivity measured in the community in Viet Nam (pooled positivity: 37.7%; n=2,706).[21,37] We also observed the expected dose-response pattern of rising positivity and risk of TBI in older individuals as well as the higher risk of QFT-Plus positivity in males.[20,21] Concordant with these results, our study highlighted that IGRA can be used at the community level as another option for TBI diagnosis and accelerating scale-up of TPT.

However, there were patterns in the TBI care cascade indicating that scale-up of available TBI diagnostic tools and regimens requires more than simply decentralization. Fewer than half of the individuals mobilized during these ACF campaigns agreed to or were eligible for an IGRA test and only six out of ten eligible persons initiated TPT, which was concordant with prior studies in Viet Nam.[34] One potential reason for the drop-off may be process related, since we embedded the study in a programmatic setting, which meant that in general over two weeks elapsed from when participants were tested until eligible persons initiated TPT. Nevertheless, slow turnaround time may only partially explain the pre-treatment LTFU, as TPT initiation rate was consistent across both settings despite the difference in turnaround time.

By fielding the study in two separate sites with different TPT regimen and TBI rates in the community, we recorded several noteworthy observations. Specifically, while initiation rates in both sites were similar, there was a slightly higher completion rate in the 3HR cohort. Thus, even though we did not observe a greater uptake of TPT as seen on prior studies, the shorter treatment duration of 3HR may have contributed to higher TPT completion rates.[38–40] However, the survival analysis showed that more persons were lost to follow-up than expected over the shorter period of treatment. Based on informal qualitative feedback from field staff, reasons for the large drop-offs in the cascade included a lack of understanding of the risk of progression from TBI to active TB and the benefits of TPT in the general population, but also among healthcare providers, which leads to the de-prioritization of TPT as optional prophylaxis rather than valuable intervention. Since the 3HR regimen was only used in one province which may have faced site-specific challenges, we cannot generalize these results to other areas of the country. However, they highlight the need for more education and advocacy for providers and participants to improve the acceptance and prioritization of TPT.[41,42]

Moreover, advocacy and awareness building may need to be tailored to individual subgroups. Even though positivity, initiation and completion rates did not vary substantially across sites, gender or age category, there were, however, notable differences across study populations. In our study, HCWs exhibited a lower proportion and risk of positivity, higher TPT initiation and significantly higher risk of LTFU compared to HHCs and community members in either site. The low positivity rate was particularly noteworthy for its discordance with published, albeit dated, evidence from Viet Nam[43] and WHO guidelines warranting intervention in this group due to higher occupational risk of TB infection.[44] A potential explanation for the discordance is that a sizeable proportion of HCWs were generalist primary care workers. The more recent EnTIC study (NCT02073240) measured lower TBI rates among Vietnamese HCWs in general hospitals compared to HCWs in TB hospitals (27.9% [22.8%, 33.6%] vs. 41.7% [26.2%, 58.9%]).[45] However, this TBI rate in general hospital HCWs is still higher than the rate among HCWs on this study; a future comparative analyses of TBI in HCWs in tertiary/quaternary general hospitals versus primary care workers may offer further insight.

The diagnostic delay was unacceptably long among HCWs and across all groups in Hai Phong. In Hai Phong, the lower burden and more limited TB care capacity as well as greater reliance on the lung hospital in TB care and prevention activities may have contributed to the long delay in treatment initiation. Meanwhile, upon investigation, HCWs indicated a preference to wait for the new 12-dose regimen of isoniazid and rifapentine (3HP), but then agreed to initiate TPT on 9H as concerns over nitrosamine impurities delayed scale-up of 3HP in Viet Nam.[46,47] Nevertheless, despite a delay of almost six weeks, the TPT initiation rate among HCWs was highest across all groups and also above rates measured on prior studies (39.0%-49.6%).[48,49] Conversely, the low completion rate measured on this study was on par with other studies on HCWs receiving 9H for TPT. However, this low rate may have been avoided with shorter regimen as adherence in this study at month 3 was 100% and month 8 was still at 80.0%. These results were in line with previous studies that indicated health workers were significantly more likely to complete TPT on 3HR compared to 9H (91.4% *vs.* 76.7%, p=0.02).[50–52]

The use of the 9H regimen in the majority of participants also highlights a key limitation of this study. By conducting it under routine program conditions, the study was exposed to external bias and confounding, such as the variability in the available TPT regimen. HCMC historically has had a substantially larger burden of TB and TBI, as evinced on this study. Thus, 9H was the local regimen of choice due to its greater availability and lower costs. Similarly, we relied on routine diagnostics to rule out active TB rather than more sensitive tools such as culture due to cost implications. With respect to costs, another limitation of our study was the lack of a formal assessment of the cost barrier of IGRAs in our low-resource setting with limited program budgets. Operationally, WHO recommends to integrate TPT into routine HHC investigations and ACF.[16] It stands to reason that such integration may also improve value for money as has been well-established for highly vulnerable people living with HIV.[53] There is ample evidence that HHC investigations and community-based ACF campaigns can reach those most vulnerable to active TB and thus most in need of TPT.[29,54,55] Nevertheless, given the lack of an accompanying health economic evaluation, future research should conduct impact evaluations and cost-effectiveness analyses of integrated TB and TBI testing and treatment on ACF campaigns and differences in incidence and disability-adjusted life years compared to a control cohort. Another limitation is that our cohort design did not include a post-treatment follow-up to assess incidence of TB in those with and without TPT, in part due to the social distancing measures launched in response to the pandemic. The study's convenience sampling and selection of HCMC and Hai Phong as study sites likely introduced bias towards densely populated urban settings, which consequently limits the generalizability of this study. Nevertheless, the study benefitted from its large sample size and integration into routine program operations that may help to translate the findings to recommendations for densely populated, high TB burden settings in general.

CONCLUSIONS

WHO's End TB Strategy highlights the need for increased testing and treatment of TB infection as a core intervention to reduce transmission and thus achieve incidence targets. While many high TB burden countries have incorporated this emphasis into their national strategic plans, operationalization of these plans is often hindered by the suboptimal application of available tools. IGRAs are the current gold standard for TBI testing, but are often underutilized, particularly at the lower healthcare levels. Shorter TPT regimen are recommended, but require further studies to assess their potential to support broad-scale TPT. This study elucidated the potential to decentralize and leverage these tools for wider and more cost-effective deployment towards meeting TPT targets, but also highlighted that scale-up of these tools, as well as overall TPT access and uptake, will likely require complementary, tailored advocacy and education for both beneficiaries and providers.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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AUTHORS' CONTRIBUTIONS

LNQV, NN, VVT, HMD and THM contributed to the conceptualization of the study. The methodology was developed by LNQV, NTTN, TTTD, THM, HMD, and VVT. LNQV and PTL conducted the formal analysis. The investigation was conducted VVT, NTTN, TTTD and PTL. Resources for the study were provided by LHN, HMD, HTT, HBN and NVN. Data were curated by LNQV, AJC, PTL and KTT and LNQV visualized the data. LNQV, NTTN, TTTD wrote the original draft, while the manuscript was reviewed and edited by LNQV, AJC, JC, NN, HTT and MC. Study supervision was provided by JC, MC, LNQV, LHN, THM, HTT, HBN and NVN, while RJF, AJC, VVT, NTTN and TTTD were responsible for project administration. Funding acquisition was led by LNQV, RJF and AJC. All authors have read and approved the final manuscript.

DATA AVAILABILITY

The data that support the findings of this study are available from the Viet Nam National TB Control Program, Hai Phong Provincial Lung Hospital and Pham Ngoc Thach Provincial TB Hospital, but restrictions apply to their availability. Data are can be made available from the authors upon reasonable request and with permission of the Viet Nam National TB Control Program, Hai Phong Provincial Lung Hospital and Pham Ngoc Thach Provincial TB Hospital.

ETHICAL CONSIDERATIONS

This study was approved by the Pham Ngoc Thach Hospital ethics committee for biomedical research (897/HDDD-PNT). In addition, QFT-Plus testing is part of national guidelines and activities were approved by the NTP (1069/BVPTW-DAPCL). Participation was voluntary and did not affect the provision or standard of care. All personal identifying information was removed from the dataset prior to analysis.

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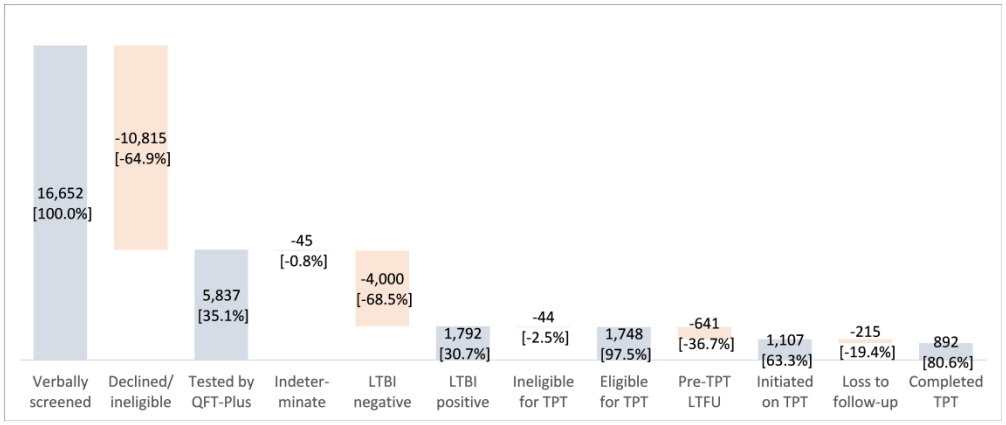
FIGURE LEGENDS

Figure 1. Aggregate TB infection care cascade.

Figure 2. TB infection care cascade by site and target group.

Figure 3. Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen.



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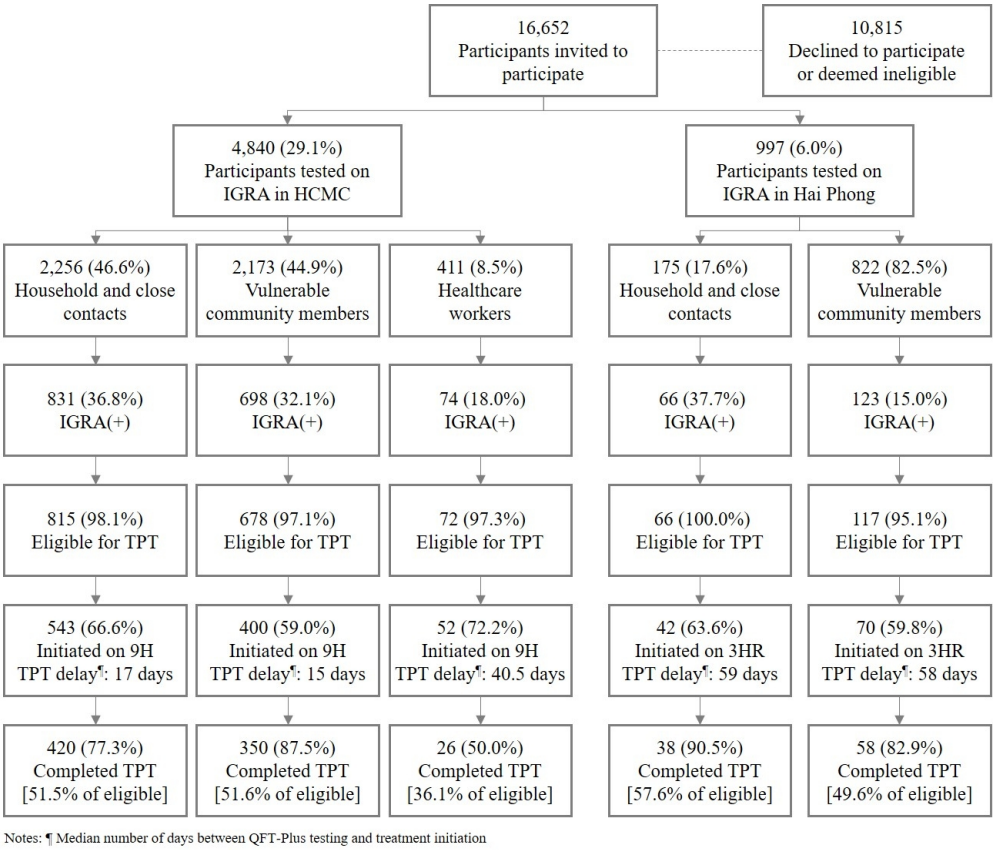

Notes: ¶ Median number of days between QFT-Plus testing and treatment initiation

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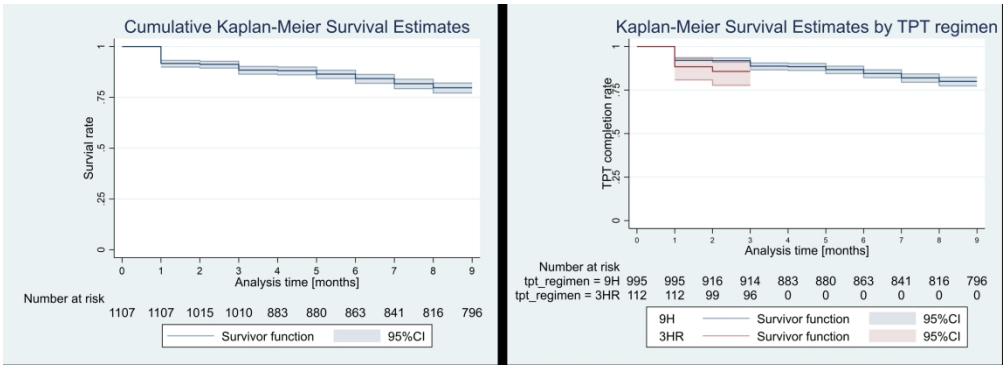


Figure 3a & 3b - Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen

528x190mm (150 x 150 DPI)

STROBE Statement

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	8-9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-12
		(b) Indicate number of participants with missing data for each variable of interest	10-12
Outcome data	15*	Report numbers of outcome events or summary measures	8-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12

		(*b*) Report category boundaries when continuous variables were categorized	10, 12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

SUPPLEMENTAL MATERIAL

Model specification validation results

Figure S1: Kaplan-Meier observed survival curve of TPT regimen

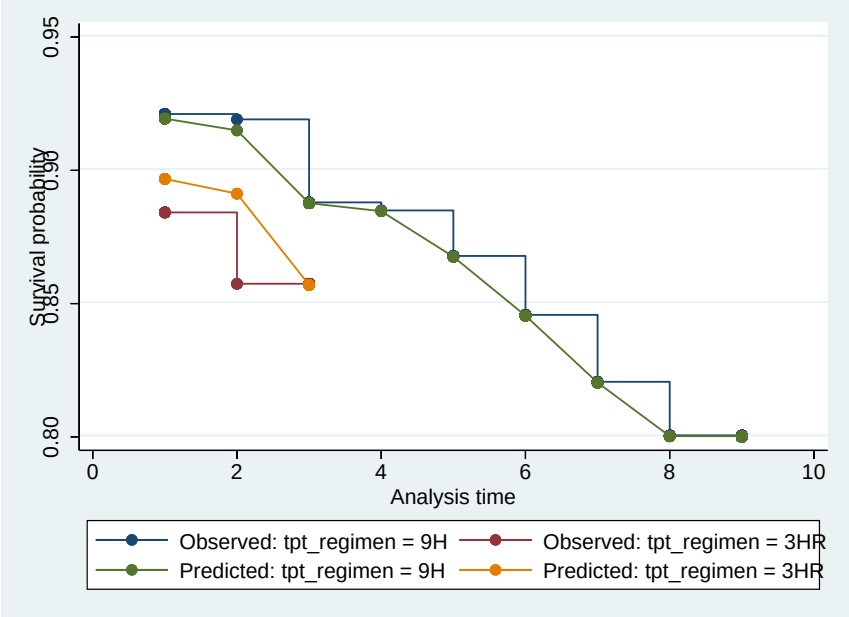
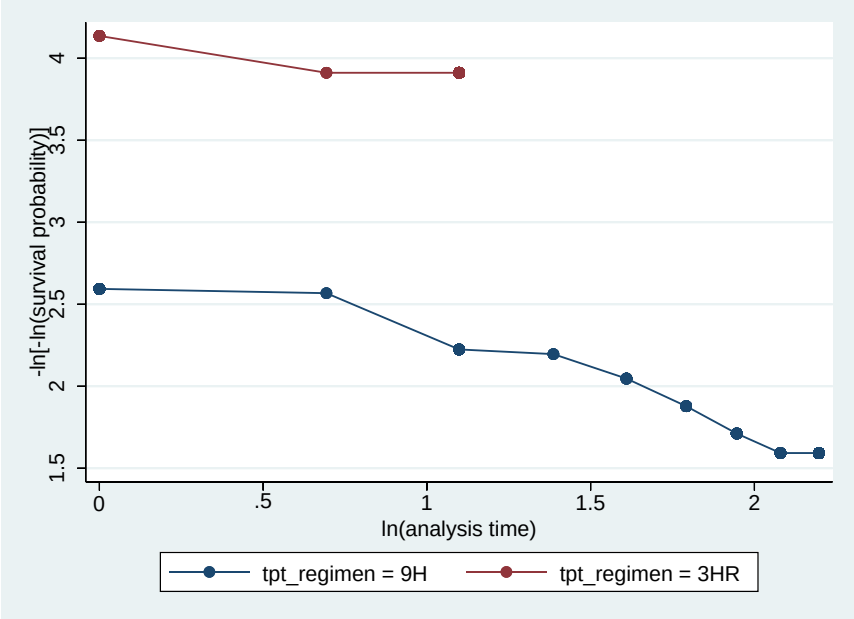


Figure S2: Log-log plot of the final Cox model



The log-rank test result to assess the equality of survival between the two TPT regimen was p=0.319.

The p-value of the global postestimation proportional hazards test 0.644 and tests of individual parameters produced p-values of 0.112<p<0.955.