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# 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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5 1 **Optimizing diagnosis and treatment of tuberculosis infection in**  
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7 2 **community and primary care settings in two urban provinces of Viet**  
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9 3 **Nam: a cohort study**  
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## 24 ABSTRACT

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

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

36 **Results:** Among 5,837 participants, the indeterminate rate was 0.8% and 30.7% were IGRA-positive. TPT  
37 initiation and completion rates were 63.3% (3HR=61.2% vs. 9H=63.6%; p=0.147) and 80.6% (3HR=85.7% vs.  
38 9H=80.0%; p=0.522), respectively. Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28,  
39 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-  
40 ray (2.23 [1.38, 3.61]; p=0.001) were associated with positive IGRA results. Risk of IGRA-positivity was lower  
41 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  
42 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  
43 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.

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

47  
48 **Keywords:** tuberculosis, infection, community, urban, interferon-gamma release assay, short-course,  
49 tuberculosis preventive therapy

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

## 51 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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

## 61 INTRODUCTION

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

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

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

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

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

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

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

## 109 **METHODS**

### 110 **Study design and objectives**

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

### 117 **Study setting**

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



## 122 **Study population and recruitment**

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

## 135 **Specimen collection and processing**

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

## 151 **TPT initiation and participant follow-up**

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

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3 154 treatment (i.e., with confirmed TBI and active TB ruled out) were invited to present at their respective DTU for  
4 155 pre-treatment counseling and TPT initiation as per national guidelines.[17] TPT regimen varied by province. In  
5 156 HCMC, TPT consisted of nine months of daily isoniazid (9H), while in Hai Phong eligible persons received  
6 157 three months of daily isoniazid and rifampicin (3HR). Individuals on TPT received in-person follow-up during  
7 158 monthly drug pick-up at the DTU. Community TB officers conducted phone or in-person follow-up in regular  
8 159 intervals or as needed. Participants experiencing adverse events were asked to present at the DTU for check-up.

## 13 160 **Statistical analyses**

15 161 The primary measures of interest were QFT-Plus positivity and indeterminate rates. Secondary variables of  
16 162 interest included TPT initiation and completion rates within the study population. Missing data were retrieved  
17 163 through post-event follow-up of participants or excluded from individual analyses. We constructed TBI care  
18 164 cascades in aggregate and segmented by site ranging from persons recruited to participants with a successful  
19 165 TPT completion. We documented losses along the cascade and reported median and interquartile ranges of  
20 166 diagnostic delay, i.e., time from testing to TPT initiation. We calculated descriptive statistics for key sample  
21 167 characteristics by QFT-Plus result and TPT completion and fitted a saturated, mixed-effect logistic regression  
22 168 to assess associations between positivity and participant covariates to adjust for confounding and inherent bias.  
23 169 Study district was the random effect to account for intra-cluster correlation. The survival analysis designated  
24 170 loss to follow-up (LTFU) a failure and censored adherent participants on 3HR and 9H at three and nine months,  
25 171 respectively. We constructed Kaplan-Meier survival curves and conducted log-rank tests to assess the equality  
26 172 of survival between the two TPT regimen. We fitted a saturated Cox model and assessed validity of the  
27 173 proportionality assumption using log-log plots and Schoenfeld residuals. Violations were addressed via  
28 174 stratification or modeling of time-variance for parameters of interest. The final model passed both the global  
29 175 postestimation proportional hazards test and tests of individual parameters. P-values of validation tests were  
30 176 provided in the Supplemental material 2. Hypothesis tests were two-tailed. A threshold of  $p < 0.05$  was  
31 177 considered significant. Analyses were conducted using STATA v17 (Stata Corp.; College Station, TX, USA).

## 43 178 **Patient and public involvement**

45 179 While TB patients and their families were not involved in setting the research question, a consensus building  
46 180 meeting was held at the beginning of the study for government stakeholders and community members to provide  
47 181 feedback and recommendations and reach consensus about the study design and implementation. Patients, their  
48 182 families and public stakeholders were also central to dissemination of study information, which helped to  
49 183 motivate community involvement during and beyond the study.

## 184 RESULTS

### 185 Sample characteristics

186 Of the 5,837 participants in the sample, 59.3% (n=3,463) were female (Table 1). Children under 15 years  
187 constituted 19.5% (1,136/5,834) of the sample and the median participant age was 40 (IQR: 20–55). Overall,  
188 most participants were recruited at community-based ACF events (55.8%; n=3,257), lived in urban areas  
189 (65.6%; n=3,827), were permanent residents (90.5%; 3,116/3,444) and were enrolled on social health insurance  
190 (90.4%; 5,269/5,832). About 2.9% (n=167) were diabetics and 1.1% (n=62) reported a history of TB. Moreover,  
191 39.5% (n=2,306) reported experiencing at least one of the four core TB symptoms (cough, weight loss, fever,  
192 and/or night sweats) during recruitment, while 2.3% (n=134) participants exhibited TB-related CXR  
193 abnormalities.

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

	Total (N = 5,837) N (%) <sup>a</sup>	IGRA(+) <sup>b</sup> (N = 1,792) N (%)	IGRA (-) <sup>b</sup> (N = 4,000) N (%)	Indeterminate (N = 45) N (%)	aOR <sup>b</sup> (95% CI)	p-value <sup>†</sup>
<b>Sex</b>						
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
<b>Age<sup>‡</sup></b>						
<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)		
<b>Study site</b>						
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
<b>Screening location</b>						
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
<b>Target group</b>						
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
<b>Urbanization</b>						
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
<b>Residency status<sup>†,‡</sup></b>						
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
<b>Social health insurance<sup>‡</sup></b>						
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

<b>Diabetes mellitus</b>							
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
<b>Previous history of TB</b>							
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
<b>Any TB symptoms<sup>§,¶</sup></b>							
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
<b>Chest X-ray result</b>							
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

‡ Percent of row total

¥ IGRA=Interferon-Gamma Release Assay; aOR=adjusted Odds Ratio

† Wald test

## 204 TB infection care cascade

205 Of the 16,652 individuals verbally screened in both provinces, 35.1% (n=5,837) agreed to be tested by QFT-  
 206 Plus for the study (Figure 1). The overall indeterminate rate was 0.8% (n=45) and 30.7% (n=1,792) of  
 207 participants were QFT-Plus-positive, of whom 97.5% (n=1,748) were eligible for TPT. About 63.3%  
 208 (1,107/1,748) of eligible participants initiated TPT and 80.6% (892/1,107) completed therapy. The sample  
 209 included 4,840 participants in HCMC and 997 in Hai Phong (Table 2). The indeterminate rate was 0.8% in  
 210 both sites, while positivity rates were 33.1% (1,603/4,840) in HCMC and 19.0% (189/997) in Hai Phong. The  
 211 respective TPT initiation and completion rates in the 9H cohort in HCMC were 63.6% (995/1,565) and 80.0%  
 212 (796/995) compared to 61.2% (112/183) and 85.7% (96/112) in the 3HR cohort in Hai Phong. Neither initiation  
 213 nor completion rates were significantly different between the two regimens (p=0.522 & p=0.147, respectively).

214 **Table 2: TB infection care cascade by TPT cohort**

	Total (N = 5,837) N (%)	HCMC (N = 4,840) N (%)	Hai Phong (N = 997) N (%)
<b>IGRA result &amp; TPT<sup>‡</sup></b>			
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)
<b>--Ineligible for TPT (% of positive)</b>	<b>44 (0.8)</b>	<b>38 (0.8)</b>	<b>6 (0.6)</b>
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)
<b>--Eligible for TPT (% of positive)</b>	<b>1,748 (97.6)</b>	<b>1,565 (97.6)</b>	<b>183 (97.3)</b>
CXR(-)	1,702 (95.0)	1,524 (95.1)	178 (94.7)
CXR(+), MTB(-)	46 (2.6)	41 (2.6)	5 (2.7)
<b>--Initiated on TPT<sup>¶</sup> (% of eligible)</b>	<b>1,107 (63.3)</b>	<b>995 (63.6)</b>	<b>112 (61.2)</b>
<b>--Completed TPT<sup>¶</sup> (% of initiated)</b>	<b>892 (80.6)</b>	<b>796 (80.0)</b>	<b>96 (85.7)</b>

215 Notes:

216 <sup>‡</sup> IGRA=Interferon-Gamma Release Assay; CXR=Chest X-Ray; TPT=TB Preventive Therapy; MTB=*M. tuberculosis*; HCMC=Ho  
 217 Chi Minh City

218 <sup>¶</sup> TPT consisted of 9H in HCMC and of 3HR in Hai Phong

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

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

### 229 Risk factors of IGRA-positivity

230 Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78];  $p<0.001$ ), aged 45-59 years (1.30  
 231 [1.05, 1.60];  $p=0.018$ ), and exhibiting CXR abnormalities suggestive of TB (2.23 [1.38, 3.61];  $p=0.001$ ) were  
 232 associated with higher QFT-Plus positivity (Table 2). Conversely, compared to the reference group (30-44  
 233 years), the risk of QFT-Plus-positivity was significantly lower among children under 15 years (0.18 [0.13, 0.26];  
 234  $p<0.001$ ) 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];  
 235  $p<0.001$ ) and individuals living in peri-urban areas (0.55 [0.36, 0.55];  $p=0.007$ ).

### 236 Survival analysis and risk factors of TPT completion

237 A total of 1,107 participants were followed for a total of 8,211 person-months with 215 recorded LTFUs (Table  
 238 3). There were 7,904 and 307 person-months of observations with mean follow-up times of 7.9 [7.8, 8.1] months  
 239 and 2.7 [2.6, 2.9] months, and 199 and 16 LTFUs in the 9H and 3HR cohorts, respectively. The respective LTFU  
 240 incidence rates were 25.2 and 52.1 per 1,000 person-months. Most LTFUs occurred after the first month of TPT  
 241 in both the 9H (79/199=39.7%) and 3HR (13/16=81.2%) cohorts (Figures 3a and 3b). The survival analysis  
 242 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];  
 243  $p<0.001$ ) were strongly associated with higher risk of LTFU.

244 **Table 3: Participant characteristics and adjusted risk factors associated with TPT loss to follow-up<sup>†</sup>**

	Total (N = 1,107) N (%) <sup>‡</sup>	TPT completed <sup>‡</sup> (N = 892) N (%) <sup>‡</sup>	LTFU <sup>‡</sup> (N = 215) N (%) <sup>‡</sup>	aHR of LTFU <sup>‡</sup> (95% CI)	p-value <sup>†</sup>
<b>TPT regimen</b>					
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
<b>Sex</b>					
Female	645 (58.3)	512 (79.4)	133 (20.6)	Ref	
Male	462 (41.7)	380 (82.3)	82 (17.8)	1.02 [0.94; 1.11]	0.608
<b>Age</b>					
<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)		
<b>Screening location</b>					
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
<b>Target group</b>					
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
<b>Urbanization</b>					
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
<b>Diabetes mellitus</b>					
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
<b>Previous history of TB</b>					
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

‡ 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.



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3 269 However, there were patterns in the TBI care cascade indicating that scale-up of available TBI diagnostic tools  
4 270 and regimens requires more than simply decentralization. Fewer than half of the individuals mobilized during  
5 271 these ACF campaigns agreed to or were eligible for an IGRA test and only six out of ten eligible persons initiated  
6 272 TPT, which was concordant with prior studies in Viet Nam.[32] One potential reason for the drop-off may be  
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8 273 process related, since we embedded the study in a programmatic setting, which meant that in general over two  
9 274 weeks elapsed from when participants were tested until eligible persons initiated TPT. Nevertheless, slow  
10 275 turnaround time may only partially explain the pre-treatment LTFU, as TPT initiation rate was consistent across  
11 276 both settings despite the difference in turnaround time.

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16 277 By fielding the study in two separate sites with different TPT regimen and TBI rates in the community, we  
17 278 recorded several noteworthy observations. Specifically, while initiation rates in both sites were similar, there  
18 279 was a slightly higher completion rate in the 3HR cohort. Thus, even though we did not observe a greater uptake  
19 280 of TPT as seen on prior studies, the shorter treatment duration of 3HR may have contributed to higher TPT  
20 281 completion rates.[36–38] However, the survival analysis showed that more persons were lost to follow-up than  
21 282 expected over the shorter period of treatment. Based on informal qualitative feedback from field staff, reasons  
22 283 for the large drop-offs in the cascade included a lack of understanding of the implications of TBI and the benefits  
23 284 of TPT, and the de-prioritization of TPT among providers. Since the 3HR regimen was only used in one province  
24 285 which may have faced site-specific challenges, we cannot generalize these results to other areas of the country.  
25 286 However, they highlight the need for more education and advocacy for providers and participants to improve  
26 287 the acceptance and prioritization of TPT.[39,40]

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34 288 Moreover, advocacy and awareness building may need to be tailored to individual subgroups. Even though  
35 289 positivity, initiation and completion rates did not vary substantially across sites, gender or age category, there  
36 290 were, however, notable differences across study populations. In our study, HCWs exhibited a lower proportion  
37 291 and risk of positivity, higher TPT initiation and significantly higher risk of LTFU compared to HHCs and  
38 292 community members in either site. The low positivity rate was particularly noteworthy for its discordance with  
39 293 published, albeit dated, evidence from Viet Nam[41] and WHO guidelines warranting intervention in this group  
40 294 due to higher occupational risk of TB infection.[42] A potential explanation for the discordance is that a sizeable  
41 295 proportion of HCWs were generalist primary care workers. The more recent EnTIC study (NCT02073240)  
42 296 measured lower TBI rates among Vietnamese HCWs in general hospitals compared to HCWs in TB hospitals  
43 297 (27.9% [22.8%, 33.6%] vs. 41.7% [26.2%, 58.9%]).[43] However, this TBI rate in general hospital HCWs is  
44 298 still higher than the rate among HCWs on this study; a future comparative analyses of TBI in HCWs in  
45 299 tertiary/quaternary general hospitals versus primary care workers may offer further insight.

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54 300 The diagnostic delay was unacceptably long among HCWs and across all groups in Hai Phong. In Hai Phong,  
55 301 the lower burden and more limited TB care capacity as well as greater reliance on the lung hospital in TB care

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3 302 and prevention activities may have contributed to the long delay in treatment initiation. Meanwhile, upon  
4 303 investigation, HCWs indicated a preference to wait for the new 12-dose regimen of isoniazid and rifapentine  
5 304 (3HP), but then agreed to initiate TPT on 9H as concerns over nitrosamine impurities delayed scale-up of 3HP  
6 305 in Viet Nam.[44,45] Nevertheless, despite a delay of almost six weeks, the TPT initiation rate among HCWs  
7 306 was highest across all groups and also above rates measured on prior studies (39.0%-49.6%).[46,47] Conversely,  
8 307 the low completion rate measured on this study was on par with other studies on HCWs receiving 9H for TPT.  
9 308 However, this low rate may have been avoided with shorter regimen as adherence in this study at month 3 was  
10 309 100% and month 8 was still at 80.0%. These results were in line with previous studies that indicated health  
11 310 workers were significantly more likely to complete TPT on 3HR compared to 9H (91.4% vs. 76.7%,  
12 311  $p=0.02$ ).[48–50]

13 312 The use of the 9H regimen in the majority of participants also highlights a key limitation of this study. By  
14 313 conducting it under routine program conditions, the study was exposed to external bias and confounding, such  
15 314 as the variability in the available TPT regimen. HCMC historically has had a substantially larger burden of TB  
16 315 and TBI, as evinced on this study. Thus, 9H was the local regimen of choice due to its greater availability and  
17 316 lower costs. Similarly, we relied on routine diagnostics to rule out active TB rather than more sensitive tools  
18 317 such as culture due to cost implications. With respect to costs, another limitation of our study was the lack of a  
19 318 formal assessment of the cost barrier of IGRAs in our low-resource setting. Operationally, WHO recommends  
20 319 to integrate TPT into routine HHC investigations and ACF.[16] It stands to reason that such integration may  
21 320 also improve value for money as has been well-established for highly vulnerable people living with HIV.[51]  
22 321 There is ample evidence that HHC investigations and community-based ACF campaigns can reach those most  
23 322 vulnerable to active TB and thus most in need of TPT.[52–54] Nevertheless, given the lack of an accompanying  
24 323 health economic evaluation, future research should conduct impact evaluations and cost-effectiveness analyses  
25 324 of integrated TB and TBI testing and treatment on ACF campaigns and differences in incidence and disability-  
26 325 adjusted life years compared to a control cohort. Another limitation is that our cohort design did not include a  
27 326 post-treatment follow-up to assess incidence of TB in those with and without TPT, in part due to the social  
28 327 distancing measures launched in response to the pandemic. The study's convenience sampling and selection of  
29 328 HCMC and Hai Phong as study sites likely introduced bias towards densely populated urban settings, which  
30 329 consequently limits the generalizability of this study. Nevertheless, the study benefitted from its large sample  
31 330 size and integration into routine program operations that may help to translate the findings to recommendations  
32 331 for densely populated, high TB burden settings in general.

## 332 CONCLUSIONS

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

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## 349 COMPETING INTERESTS

350 The authors have no competing interests to declare.

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## 359 **AUTHORS' CONTRIBUTIONS**

- 360 • Conceptualization: LNQV, NN, VVT, HMD, THM
- 361 • Methodology: LNQV, NTTN, TTTD, THM, HMD, VVT
- 362 • Formal analysis: LNQV, PTL
- 363 • Investigation: VVT, NTTN, TTTD, PTL
- 364 • Resources: LHN, HMD, HTT, HBN, NVN
- 365 • Data curation: LNQV, AJC, PTL, KTT
- 366 • Writing – original draft: LNQV, NTTN, TTTD
- 367 • Writing – review and editing: LNQV, AJC, JC, NN, HTT, MC
- 368 • Visualization: LNQV
- 369 • Supervision: JC, MC, LNQV, LHN, THM, HTT, HBN, NVN
- 370 • Project administration: RJF, AJC, VVT, NTTN, TTTD
- 371 • Funding acquisition: LNQV, RJF, AJC
- 372 • Final approval: all authors have read and approved the manuscript

## 373 **DATA AVAILABILITY**

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

## 379 **ETHICAL CONSIDERATIONS**

380 This study was approved by the Pham Ngoc Thach Hospital ethics committee for biomedical research  
381 (897/HDDD-PNT). In addition, QFT-Plus testing is part of national guidelines and activities were approved by  
382 the NTP (1069/BVPTW-DAPCL). Participation was voluntary and did not affect the provision or standard of  
383 care. All personal identifying information was removed from the dataset prior to analysis.

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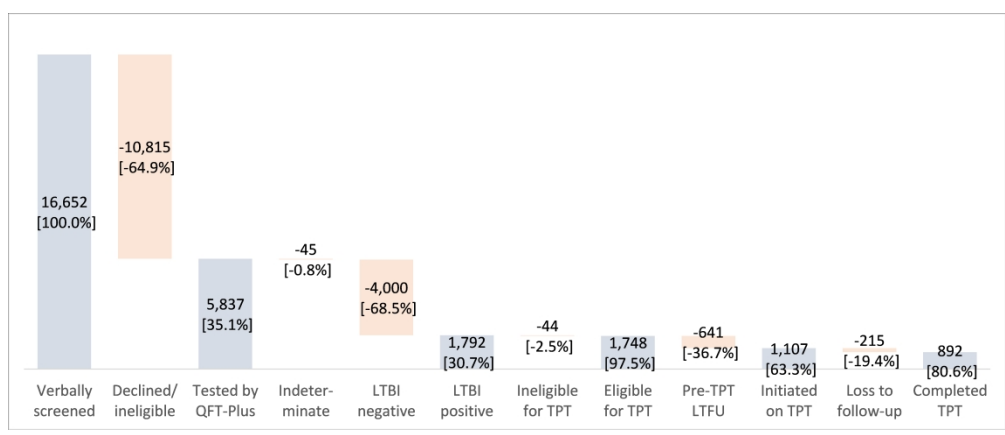
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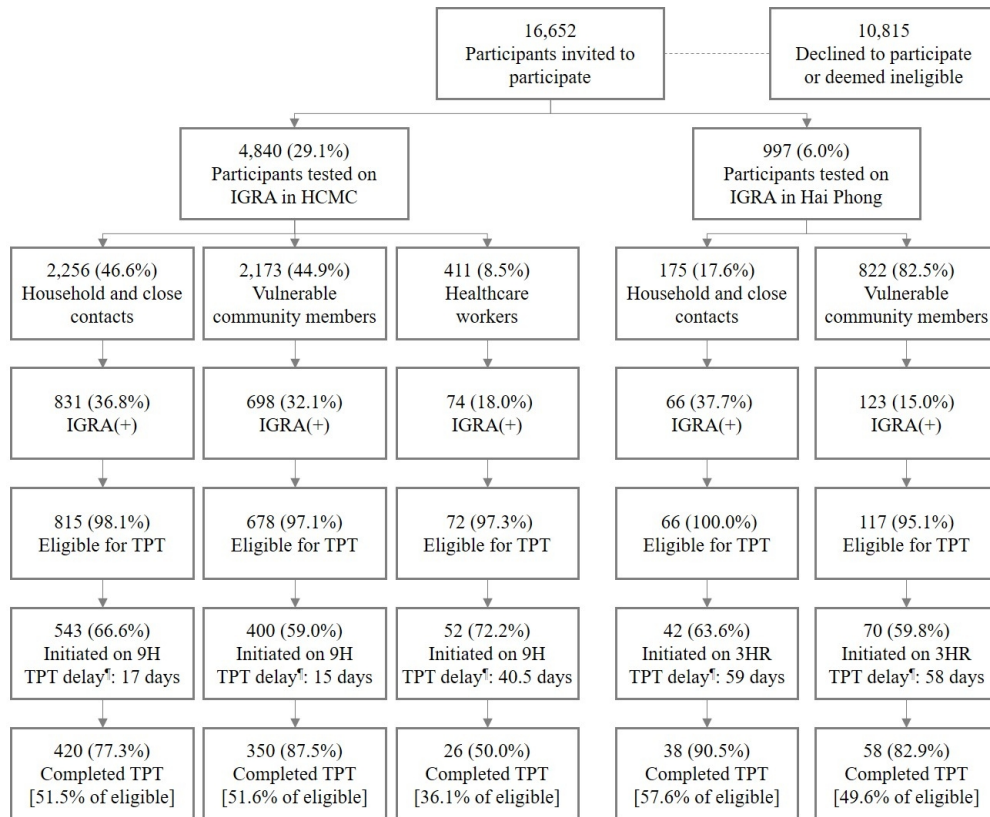
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Notes: ‡ Median number of days between QFT-Plus testing and treatment initiation

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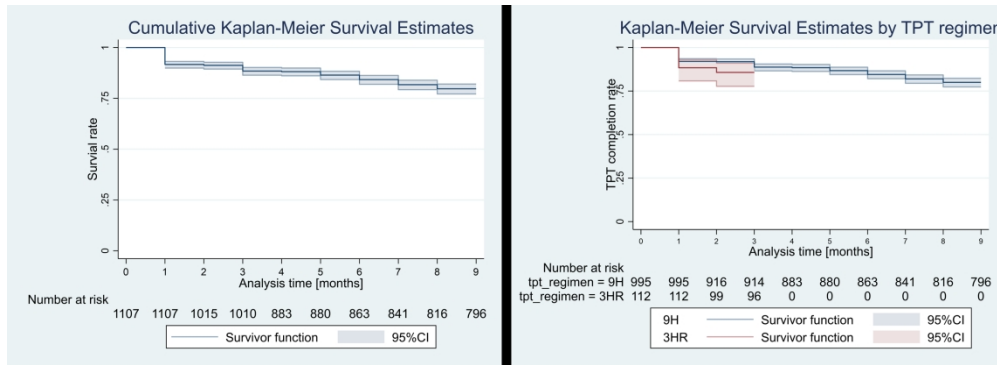


Figure 3a & 3b - Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen

528x190mm (150 x 150 DPI)

## STROBE Statement

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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

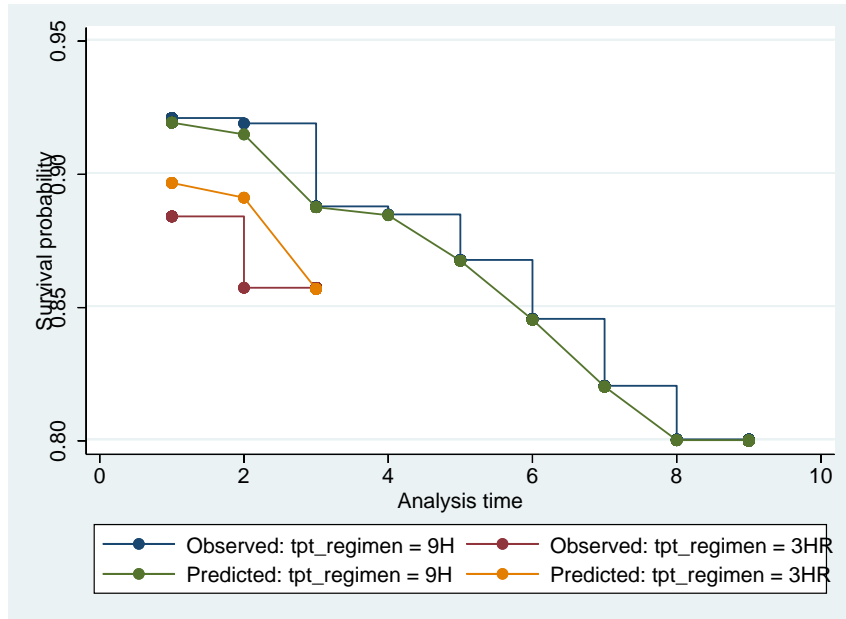
\*Give information separately for exposed and unexposed groups.

**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](http://www.strobe-statement.org).

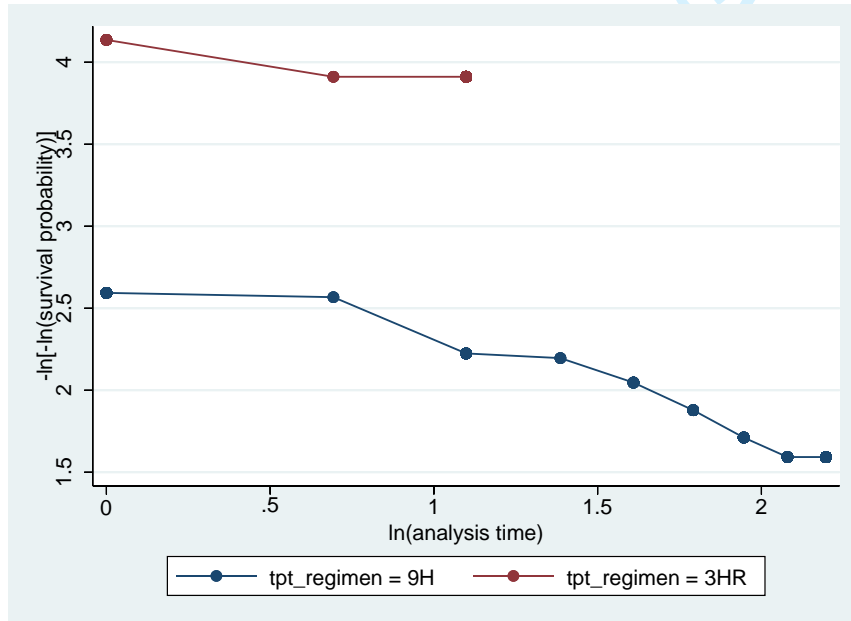
**SUPPLEMENTAL MATERIAL**

**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

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Global health, Public health, Epidemiology
Keywords:	Tuberculosis < INFECTIOUS DISEASES, PREVENTIVE MEDICINE, PUBLIC HEALTH

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5 1 **Optimizing diagnosis and treatment of tuberculosis infection in**  
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7 2 **community and primary care settings in two urban provinces of Viet**  
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9 3 **Nam: a cohort study**  
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11 4 Luan Nguyen Quang Vo<sup>1,\*</sup>, Nhung Viet Nguyen<sup>2</sup>, Nga Thi Thuy Nguyen<sup>1</sup>, Thuy Thi Thu Dong<sup>1</sup>, Andrew  
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13 6 Lan Huu Nguyen<sup>3</sup>, Tuan Huy Mac<sup>4</sup>, Phong Thanh Le<sup>5</sup>, Khoa Tu Tran<sup>1</sup>, Nduku Ndunda<sup>6</sup>, Maxine Caws<sup>7</sup> and  
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## 24 ABSTRACT

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

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

36 **Results:** Among 5,837 participants, the indeterminate rate was 0.8% and 30.7% were IGRA-positive. TPT  
37 initiation and completion rates were 63.3% (3HR=61.2% vs. 9H=63.6%; p=0.147) and 80.6% (3HR=85.7% vs.  
38 9H=80.0%; p=0.522), respectively. Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28,  
39 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-  
40 ray (2.23 [1.38, 3.61]; p=0.001) were associated with positive IGRA results. Risk of IGRA-positivity was lower  
41 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  
42 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  
43 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.

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

47  
48 **Keywords:** tuberculosis, infection, community, urban, interferon-gamma release assay, short-course,  
49 tuberculosis preventive therapy

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

## 51 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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

## 61 INTRODUCTION

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

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

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

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

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3 93 guidelines expanded TPT eligibility to all adults with TBI confirmed by recommended diagnostic tools and  
4 94 excluding active TB, permitted the use of various shortened regimen, and described contact investigation and  
5 95 follow-up requirements. Viet Nam further demonstrated its focus on TB prevention by committing at the UN  
6 96 High-Level Meeting on Ending TB to scale-up provision of TPT to 291,500 people by 2022.[23]  
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10 97 However, the country has experienced many of the challenges related to the scale-up of TPT as described above.  
11 98 Specifically, Viet Nam requires TBI confirmation within the expanded eligibility criteria prior to treatment, but  
12 99 has experienced tuberculin supply chain shortages and batch-variance in the positivity threshold. While WHO-  
13 100 recommended IGRAs are commercially available, the National TB Control Programme (NTP) has consigned  
14 101 this assay class to tertiary care facilities due to the delicate specimen handling and sophisticated laboratory  
15 102 requirements,[24,25] which is underscored by the lack of published evidence of the assay's deployment at the  
16 103 point-of-care domestically and worldwide. In addition, the prohibitively high costs per test have precluded  
17 104 serious consideration for routine TB program activities.  
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23 105 Nevertheless, the NTP remains committed to the scale-up of TPT through the optimal use of available and new  
24 106 diagnostics and regimens.[26] Given tuberculin supply and staff capacity challenges, and lack of evidence on  
25 107 the impact of recently introduced shorter TPT regimen on uptake and completion, this study assessed the use of  
26 108 the QuantiFERON-TB Gold Plus assay (QFT-Plus; Qiagen, Hilden, Germany) at the community level and the  
27 109 performance of shorter TPT regimen under programmatic conditions. The goal was to inform NTP of Viet Nam  
28 110 and other high TB burden countries in their ambitions to meet their TPT goals.  
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## 34 111 **METHODS**

### 35 112 **Study design and objectives**

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37 113 This was a cohort study to measure the feasibility of employing IGRA at the community and primary care levels  
38 114 for the diagnosis of TBI. Feasibility was defined by comparing indeterminate and positivity rates with those  
39 115 demonstrated in facility-based studies (primary endpoints). Secondary objectives included measuring the rate  
40 116 of TPT initiation and completion (secondary endpoints) in cohorts provided with two different TPT regimens,  
41 117 and to identify participant covariates associated with IGRA-positivity and loss to follow-up. The study followed  
42 118 the STROBE guideline for reporting observational studies (Supplemental material 1).  
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### 50 119 **Study setting**

51 120 The study was conducted in six districts of Ho Chi Minh City (HCMC) and Hai Phong municipal provinces. In  
52 121 HCMC, study sites included Districts 6, 8, 12, Binh Chanh, Go Vap, and Tan Binh with a cumulative population  
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3 122 of 2,387,052 and 3,598 TB notifications in 2019. In Hai Phong, the study took place in Do Son with a population  
4 123 of 49,029 and 52 persons with drug-susceptible TB notified in 2019.

## 6 7 124 **Study population and recruitment**

8  
9 125 The study was embedded into routine contact investigations at primary care commune health posts and  
10 126 community-based active TB case finding (ACF) events. Details of the ACF events are provided elsewhere.[27]  
11 127 The study population included HHC and close contacts, and vulnerable community members at elevated risk of  
12 128 active TB, such as the elderly, urban poor and economic migrants. Briefly, elderly persons were  $\geq 55$  years,  
13 129 urban poor were based on national poverty definitions and economic migrants were categorized based on  
14 130 residency registration in rural provinces outside of the intervention districts. [28–30] The HCMC site also  
15 131 included a subgroup of primary- and secondary-level healthcare workers (HCW) based on the request from local  
16 132 authorities. Recruitment and follow-up occurred from May-2019 to Sep-2020. All individuals presenting for  
17 133 screening provided routine demographic and clinical information including age, sex, residency status, history  
18 134 of TB, comorbidities and symptomatic presentation. Following intake, persons belonging to the study population  
19 135 with residency in the study districts were invited to participate in the study. Persons living outside of or intending  
20 136 to relocate away from the study sites, or who declined to consent were excluded. Eligible, consenting  
21 137 participants were recruited consecutively until the quota of available QFT-Plus tests was reached (n=5,000 in  
22 138 HCMC and n=1,000 in Hai Phong). Parents consented on behalf of their children under 18 years.

## 23 139 **Specimen collection and processing**

24 140 Provincial lung hospital (PLH) laboratory staff hosted training sessions on specimen collection and processing  
25 141 for the District TB Unit (DTU) and district-level laboratory staff. The District Health Center (DHC) mobilized  
26 142 participants to attend ACF events or to present at commune health posts. All attendants were systematically  
27 143 screened for TB symptoms and directed to undergo chest radiography (CXR) to rule out active TB. Persons with  
28 144 parenchymal abnormalities suggestive of TB on CXR or strong clinical suspicion of TB were referred for  
29 145 molecular sputum testing, as per contemporary national TB treatment guidelines.[31] Attendants were counseled  
30 146 on TBI and invited to participate. Study staff collected blood specimens from consenting, eligible individuals  
31 147 as per manufacturer recommended procedures. Each participant provided 4ml of venous whole blood in four  
32 148 separate tubes. Blood specimens were processed and analyzed per manufacturer's recommendations. Briefly,  
33 149 all four tubes were immediately shaken ~10 times to dissolve all antigens on the tube's wall coating. Tubes were  
34 150 stored inside dry ice coolers at 17–25°C, which were transported to the PLH biochemistry–hematology  
35 151 departments within six hours, twice a day. Samples were incubated at 37°C for 20 hours ( $\pm 1$  hour) and  
36 152 centrifuged within one hour of completing the incubation stage at 2000–3000g for 14 minutes at room  
37 153 temperature. The twelve-step enzyme linked immunosorbent assay was conducted within 16–24 hours. Results  
38 154 were analyzed by using proprietary QuantiFERON software v2.7.1.

## 155 TPT initiation and participant follow-up

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

## 165 Statistical analyses

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

## 183 Patient and public involvement

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

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

## 189 **RESULTS**

### 190 **Sample characteristics**

191 Of the 5,837 participants in the sample, 59.3% (n=3,463) were female (Table 1). Children under 15 years  
192 constituted 19.5% (1,136/5,834) of the sample and the median participant age was 40 (IQR: 20–55). Overall,  
193 most participants were recruited at community-based ACF events (55.8%; n=3,257), lived in urban areas  
194 (65.6%; n=3,827), were permanent residents (90.5%; 3,116/3,444) and were enrolled on social health insurance  
195 (90.4%; 5,269/5,832). About 2.9% (n=167) were diabetics and 1.1% (n=62) reported a history of TB. Moreover,  
196 39.5% (n=2,306) reported experiencing at least one of the four core TB symptoms (cough, weight loss, fever,  
197 and/or night sweats) during recruitment, while 2.3% (n=134) participants exhibited TB-related CXR  
198 abnormalities.



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

	Total (N = 5,837) N (%) <sup>a</sup>	IGRA(+) <sup>b</sup> (N = 1,792) N (%)	IGRA (-) <sup>b</sup> (N = 4,000) N (%)	Indeterminate (N = 45) N (%)	aOR <sup>b</sup> (95% CI)	p-value <sup>†</sup>
<b>Sex</b>						
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
<b>Age<sup>‡</sup></b>						
<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)		
<b>Study site</b>						
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
<b>Screening location</b>						
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
<b>Target group</b>						
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
<b>Urbanization</b>						
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
<b>Residency status<sup>†,‡</sup></b>						
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
<b>Social health insurance<sup>‡</sup></b>						
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

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<b>Diabetes mellitus</b>							
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
<b>Previous history of TB</b>							
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
<b>Any TB symptoms<sup>§,¶</sup></b>							
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
<b>Chest X-ray result</b>							
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  
 ‡ Percent of row total  
 ¥ IGRA=Interferon-Gamma Release Assay; aOR=adjusted Odds Ratio  
 † Wald test

## 209 TB infection care cascade

210 Of the 16,652 individuals verbally screened in both provinces, 35.1% (n=5,837) agreed to be tested by QFT-  
 211 Plus for the study (Figure 1). The overall indeterminate rate was 0.8% (n=45) and 30.7% (n=1,792) of  
 212 participants were QFT-Plus-positive, of whom 97.5% (n=1,748) were eligible for TPT. About 63.3%  
 213 (1,107/1,748) of eligible participants initiated TPT and 80.6% (892/1,107) completed therapy. The sample  
 214 included 4,840 participants in HCMC and 997 in Hai Phong (Table 2). The indeterminate rate was 0.8% in  
 215 both sites, while positivity rates were 33.1% (1,603/4,840) in HCMC and 19.0% (189/997) in Hai Phong. The  
 216 respective TPT initiation and completion rates in the 9H cohort in HCMC were 63.6% (995/1,565) and 80.0%  
 217 (796/995) compared to 61.2% (112/183) and 85.7% (96/112) in the 3HR cohort in Hai Phong. Neither initiation  
 218 nor completion rates were significantly different between the two regimens (p=0.522 & p=0.147, respectively).

219 **Table 2: TB infection care cascade by TPT cohort**

	<b>Total</b> (N = 5,837) N (%)	<b>HCMC</b> (N = 4,840) N (%)	<b>Hai Phong</b> (N = 997) N (%)
<b>IGRA result &amp; TPT<sup>‡</sup></b>			
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)
<b>--Ineligible for TPT (% of positive)</b>	<b>44 (0.8)</b>	<b>38 (0.8)</b>	<b>6 (0.6)</b>
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)
<b>--Eligible for TPT (% of positive)</b>	<b>1,748 (97.6)</b>	<b>1,565 (97.6)</b>	<b>183 (97.3)</b>
CXR(-)	1,702 (95.0)	1,524 (95.1)	178 (94.7)
CXR(+), MTB(-)	46 (2.6)	41 (2.6)	5 (2.7)
<b>--Initiated on TPT<sup>¶</sup> (% of eligible)</b>	<b>1,107 (63.3)</b>	<b>995 (63.6)</b>	<b>112 (61.2)</b>
<b>--Completed TPT<sup>¶</sup> (% of initiated)</b>	<b>892 (80.6)</b>	<b>796 (80.0)</b>	<b>96 (85.7)</b>

220 Notes:

221 <sup>‡</sup> IGRA=Interferon-Gamma Release Assay; CXR=Chest X-Ray; TPT=TB Preventive Therapy; MTB=*M. tuberculosis*; HCMC=Ho  
 222 Chi Minh City

223 <sup>¶</sup> TPT consisted of 9H in HCMC and of 3HR in Hai Phong

224  
 225 The sample included 46.6% (n=2,256) HHCs, 44.9% (n=2,173) vulnerable community members and 8.5%  
 226 (n=411) HCWs in HCMC (Figure 2). In Hai Phong, the sample consisted of 17.6% (n=175) HHCs and 82.5%  
 227 (n=822) community members. IGRA-positivity among HHCs was similar in both cities, but lower in community  
 228 members in Hai Phong (123/822=15.0%) compared to HCMC (698/2173=32.1%). Similarly, positivity in  
 229 HCWs was also comparatively lower (74/411=18.0%). TPT initiation rates in HHCs and community members  
 230 were similar across sites ranging from 59.0% to 66.6%, and higher among HCWs (52/72=72.2%). Diagnostic  
 231 delays in HCMC were shorter than in Hai Phong for both HHCs (17 vs. 59 days) and community members (15

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

### 234 Risk factors of IGRA-positivity

235 Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78];  $p<0.001$ ), aged 45-59 years (1.30  
 236 [1.05, 1.60];  $p=0.018$ ), and exhibiting CXR abnormalities suggestive of TB (2.23 [1.38, 3.61];  $p=0.001$ ) were  
 237 associated with higher QFT-Plus positivity (Table 2). Conversely, compared to the reference group (30-44  
 238 years), the risk of QFT-Plus-positivity was significantly lower among children under 15 years (0.18 [0.13, 0.26];  
 239  $p<0.001$ ) 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];  
 240  $p<0.001$ ) and individuals living in peri-urban areas (0.55 [0.36, 0.55];  $p=0.007$ ).

### 241 Survival analysis and risk factors of TPT completion

242 A total of 1,107 participants were followed for a total of 8,211 person-months with 215 recorded LTFUs (Table  
 243 3). There were 7,904 and 307 person-months of observations with mean follow-up times of 7.9 [7.8, 8.1] months  
 244 and 2.7 [2.6, 2.9] months, and 199 and 16 LTFUs in the 9H and 3HR cohorts, respectively. The respective LTFU  
 245 incidence rates were 25.2 and 52.1 per 1,000 person-months. Most LTFUs occurred after the first month of TPT  
 246 in both the 9H (79/199=39.7%) and 3HR (13/16=81.2%) cohorts (Figures 3a and 3b). The survival analysis  
 247 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];  
 248  $p<0.001$ ) were strongly associated with higher risk of LTFU.

249 **Table 3: Participant characteristics and adjusted risk factors associated with TPT loss to follow-up<sup>†</sup>**

	Total (N = 1,107) N (%) <sup>‡</sup>	TPT completed <sup>‡</sup> (N = 892) N (%) <sup>‡</sup>	LTFU <sup>‡</sup> (N = 215) N (%) <sup>‡</sup>	aHR of LTFU <sup>‡</sup> (95% CI)	p-value <sup>†</sup>
<b>TPT regimen</b>					
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
<b>Sex</b>					
Female	645 (58.3)	512 (79.4)	133 (20.6)	Ref	
Male	462 (41.7)	380 (82.3)	82 (17.8)	1.02 [0.94; 1.11]	0.608
<b>Age</b>					
<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)		
<b>Screening location</b>					
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
<b>Target group</b>					
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
<b>Urbanization</b>					
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
<b>Diabetes mellitus</b>					
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
<b>Previous history of TB</b>					
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

‡ 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.

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3 274 However, there were patterns in the TBI care cascade indicating that scale-up of available TBI diagnostic tools  
4 275 and regimens requires more than simply decentralization. Fewer than half of the individuals mobilized during  
5 276 these ACF campaigns agreed to or were eligible for an IGRA test and only six out of ten eligible persons initiated  
6 277 TPT, which was concordant with prior studies in Viet Nam.[34] One potential reason for the drop-off may be  
7 278 process related, since we embedded the study in a programmatic setting, which meant that in general over two  
8 279 weeks elapsed from when participants were tested until eligible persons initiated TPT. Nevertheless, slow  
9 280 turnaround time may only partially explain the pre-treatment LTFU, as TPT initiation rate was consistent across  
10 281 both settings despite the difference in turnaround time.

11 282 By fielding the study in two separate sites with different TPT regimen and TBI rates in the community, we  
12 283 recorded several noteworthy observations. Specifically, while initiation rates in both sites were similar, there  
13 284 was a slightly higher completion rate in the 3HR cohort. Thus, even though we did not observe a greater uptake  
14 285 of TPT as seen on prior studies, the shorter treatment duration of 3HR may have contributed to higher TPT  
15 286 completion rates.[38–40] However, the survival analysis showed that more persons were lost to follow-up than  
16 287 expected over the shorter period of treatment. Based on informal qualitative feedback from field staff, reasons  
17 288 for the large drop-offs in the cascade included a lack of understanding of the risk of progression from TBI to  
18 289 active TB and the benefits of TPT in the general population, but also among healthcare providers, which leads  
19 290 to the de-prioritization of TPT as optional prophylaxis rather than valuable intervention. Since the 3HR regimen  
20 291 was only used in one province which may have faced site-specific challenges, we cannot generalize these results  
21 292 to other areas of the country. However, they highlight the need for more education and advocacy for providers  
22 293 and participants to improve the acceptance and prioritization of TPT.[41,42]

23 294 Moreover, advocacy and awareness building may need to be tailored to individual subgroups. Even though  
24 295 positivity, initiation and completion rates did not vary substantially across sites, gender or age category, there  
25 296 were, however, notable differences across study populations. In our study, HCWs exhibited a lower proportion  
26 297 and risk of positivity, higher TPT initiation and significantly higher risk of LTFU compared to HHCs and  
27 298 community members in either site. The low positivity rate was particularly noteworthy for its discordance with  
28 299 published, albeit dated, evidence from Viet Nam[43] and WHO guidelines warranting intervention in this group  
29 300 due to higher occupational risk of TB infection.[44] A potential explanation for the discordance is that a sizeable  
30 301 proportion of HCWs were generalist primary care workers. The more recent EnTIC study (NCT02073240)  
31 302 measured lower TBI rates among Vietnamese HCWs in general hospitals compared to HCWs in TB hospitals  
32 303 (27.9% [22.8%, 33.6%] vs. 41.7% [26.2%, 58.9%]).[45] However, this TBI rate in general hospital HCWs is  
33 304 still higher than the rate among HCWs on this study; a future comparative analyses of TBI in HCWs in  
34 305 tertiary/quaternary general hospitals versus primary care workers may offer further insight.

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3 306 The diagnostic delay was unacceptably long among HCWs and across all groups in Hai Phong. In Hai Phong,  
4 307 the lower burden and more limited TB care capacity as well as greater reliance on the lung hospital in TB care  
5 308 and prevention activities may have contributed to the long delay in treatment initiation. Meanwhile, upon  
6 309 investigation, HCWs indicated a preference to wait for the new 12-dose regimen of isoniazid and rifapentine  
7 310 (3HP), but then agreed to initiate TPT on 9H as concerns over nitrosamine impurities delayed scale-up of 3HP  
8 311 in Viet Nam.[46,47] Nevertheless, despite a delay of almost six weeks, the TPT initiation rate among HCWs  
9 312 was highest across all groups and also above rates measured on prior studies (39.0%-49.6%).[48,49] Conversely,  
10 313 the low completion rate measured on this study was on par with other studies on HCWs receiving 9H for TPT.  
11 314 However, this low rate may have been avoided with shorter regimen as adherence in this study at month 3 was  
12 315 100% and month 8 was still at 80.0%. These results were in line with previous studies that indicated health  
13 316 workers were significantly more likely to complete TPT on 3HR compared to 9H (91.4% vs. 76.7%,  
14 317  $p=0.02$ ).[50–52]

15  
16 318 The use of the 9H regimen in the majority of participants also highlights a key limitation of this study. By  
17 319 conducting it under routine program conditions, the study was exposed to external bias and confounding, such  
18 320 as the variability in the available TPT regimen. HCMC historically has had a substantially larger burden of TB  
19 321 and TBI, as evinced on this study. Thus, 9H was the local regimen of choice due to its greater availability and  
20 322 lower costs. Similarly, we relied on routine diagnostics to rule out active TB rather than more sensitive tools  
21 323 such as culture due to cost implications. With respect to costs, another limitation of our study was the lack of a  
22 324 formal assessment of the cost barrier of IGRAs in our low-resource setting with limited program budgets.  
23 325 Operationally, WHO recommends to integrate TPT into routine HHC investigations and ACF.[16] It stands to  
24 326 reason that such integration may also improve value for money as has been well-established for highly  
25 327 vulnerable people living with HIV.[53] There is ample evidence that HHC investigations and community-based  
26 328 ACF campaigns can reach those most vulnerable to active TB and thus most in need of TPT.[29,54,55]  
27 329 Nevertheless, given the lack of an accompanying health economic evaluation, future research should conduct  
28 330 impact evaluations and cost-effectiveness analyses of integrated TB and TBI testing and treatment on ACF  
29 331 campaigns and differences in incidence and disability-adjusted life years compared to a control cohort. Another  
30 332 limitation is that our cohort design did not include a post-treatment follow-up to assess incidence of TB in those  
31 333 with and without TPT, in part due to the social distancing measures launched in response to the pandemic. The  
32 334 study's convenience sampling and selection of HCMC and Hai Phong as study sites likely introduced bias  
33 335 towards densely populated urban settings, which consequently limits the generalizability of this study.  
34 336 Nevertheless, the study benefitted from its large sample size and integration into routine program operations  
35 337 that may help to translate the findings to recommendations for densely populated, high TB burden settings in  
36 338 general.

## 339 CONCLUSIONS

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

## 349 ACKNOWLEDGMENTS

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352 their support. We would also like to thank the Ho Chi Minh City Public Health Association for their support.  
353 Lastly, we feel a debt of gratitude to our patients, family members and communities for their participation and  
354 support. We would like to especially thank the site coordinators and CHWs for their tireless efforts to care for  
355 their patients and contribute to ending TB in Viet Nam.

## 356 COMPETING INTERESTS

357 The authors have no competing interests to declare.

## 358 FUNDING

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365 design of the study, in collection, analysis, and interpretation of data, or in writing the manuscript.



## 366 **AUTHORS' CONTRIBUTIONS**

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

## 375 **DATA AVAILABILITY**

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

## 381 **ETHICAL CONSIDERATIONS**

382 This study was approved by the Pham Ngoc Thach Hospital ethics committee for biomedical research  
383 (897/HDDD-PNT). In addition, QFT-Plus testing is part of national guidelines and activities were approved by  
384 the NTP (1069/BVPTW-DAPCL). Participation was voluntary and did not affect the provision or standard of  
385 care. All personal identifying information was removed from the dataset prior to analysis.

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522 **FIGURE LEGENDS**

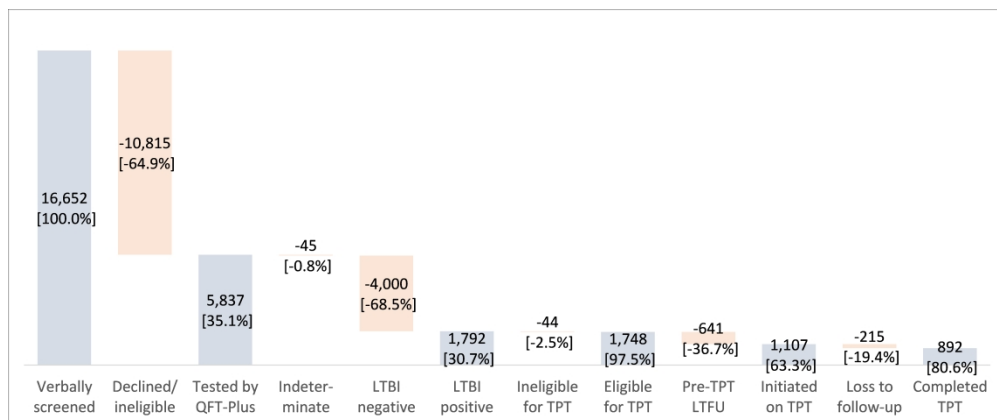
523 Figure 1. Aggregate TB infection care cascade.

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

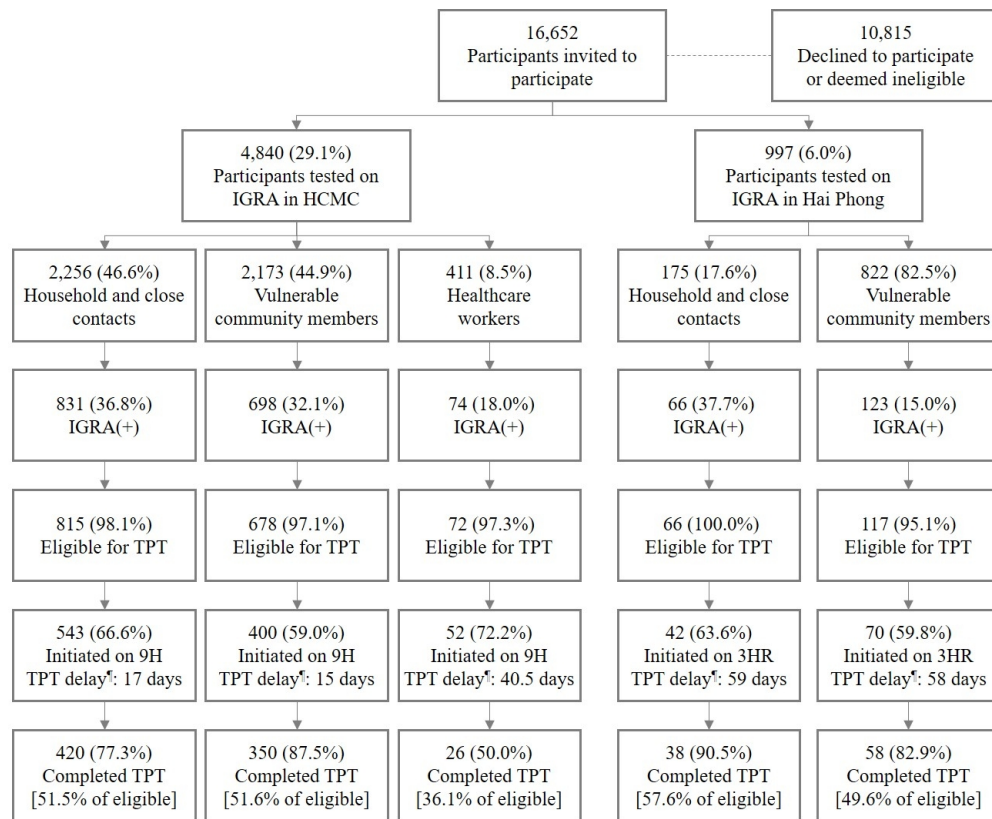
525 Figure 3. Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen.

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

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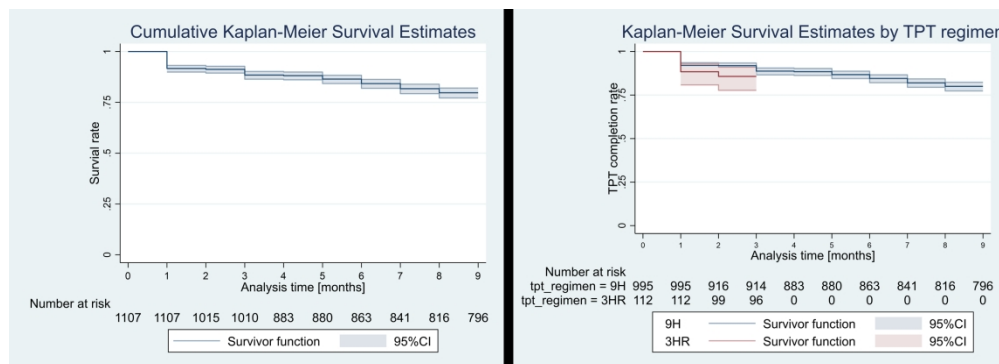


Figure 3a & 3b - Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen

528x190mm (150 x 150 DPI)

## STROBE Statement

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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

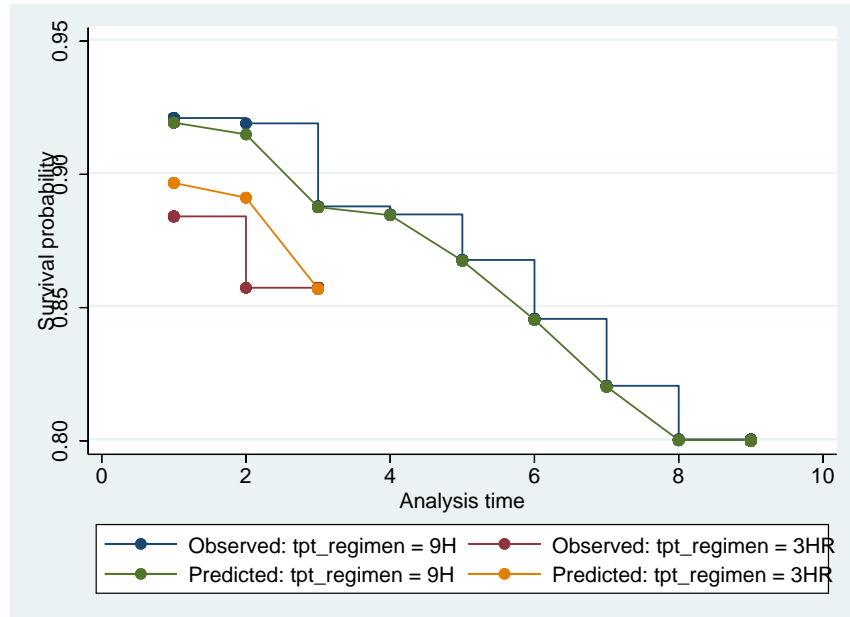
\*Give information separately for exposed and unexposed groups.

**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](http://www.strobe-statement.org).

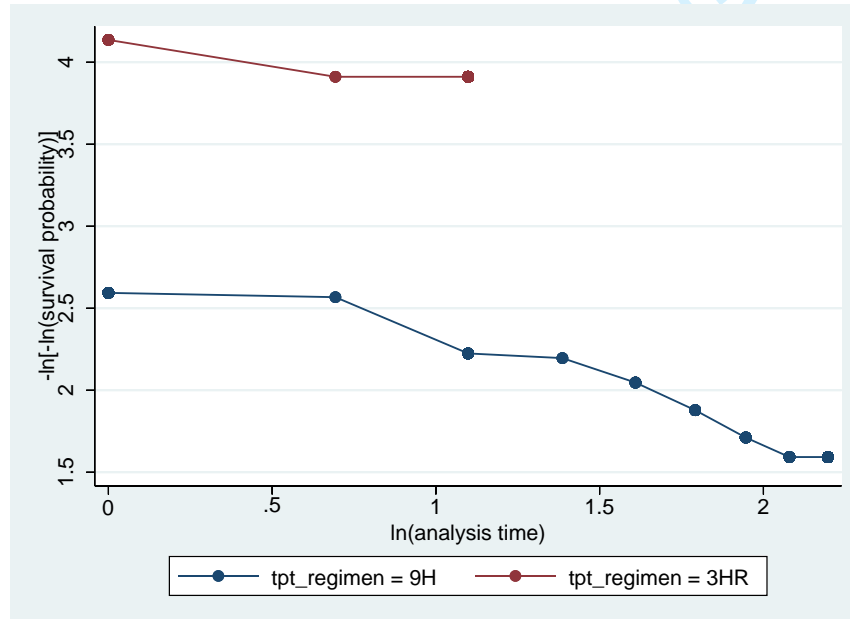
## SUPPLEMENTAL MATERIAL

### 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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5 1 **Optimizing diagnosis and treatment of tuberculosis infection in**  
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7 2 **community and primary care settings in two urban provinces of Viet**  
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9 3 **Nam: a cohort study**  
10

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## 24 ABSTRACT

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

29 **Design, setting and participants:** This cohort study was implemented in two provinces of Viet Nam from May-  
30 2019 to Sept-2020. Participants included household contacts (HHC), vulnerable community members and  
31 healthcare workers (HCW) recruited at community-based TB screening events or HHC investigations at primary  
32 care centers, who were followed up throughout TPT.

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

37 **Results:** Among 5,837 participants, the indeterminate rate was 0.8% and 30.7% were IGRA-positive. TPT  
38 initiation and completion rates were 63.3% (3HR=61.2% vs. 9H=63.6%;  $p=0.147$ ) and 80.6% (3HR=85.7% vs.  
39 9H=80.0%;  $p=0.522$ ), respectively. Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28,  
40 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-  
41 ray (2.23 [1.38, 3.61];  $p=0.001$ ) were associated with positive IGRA results. Risk of IGRA-positivity was lower  
42 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  
43 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  
44 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.

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

48  
49 **Keywords:** tuberculosis, infection, community, urban, interferon-gamma release assay, short-course,  
50 tuberculosis preventive therapy

51 **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.

## 62 INTRODUCTION

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

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

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

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

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3 94 guidelines expanded TPT eligibility to all adults with TBI confirmed by recommended diagnostic tools and  
4 95 excluding active TB, permitted the use of various shortened regimen, and described contact investigation and  
5 96 follow-up requirements. Viet Nam further demonstrated its focus on TB prevention by committing at the UN  
6 97 High-Level Meeting on Ending TB to scale-up provision of TPT to 291,500 people by 2022.[23]  
9

10 98 However, the country has experienced many of the challenges related to the scale-up of TPT as described above.  
11 99 Specifically, Viet Nam requires TBI confirmation within the expanded eligibility criteria prior to treatment, but  
12 100 has experienced tuberculin supply chain shortages and batch-variance in the positivity threshold. While WHO-  
13 101 recommended IGRAs are commercially available, the National TB Control Programme (NTP) has consigned  
14 102 this assay class to tertiary care facilities due to the delicate specimen handling and sophisticated laboratory  
15 103 requirements,[24,25] which is underscored by the lack of published evidence of the assay's deployment at the  
16 104 point-of-care domestically and worldwide. In addition, the prohibitively high costs per test have precluded  
17 105 serious consideration for routine TB program activities.

18 106 Nevertheless, the NTP remains committed to the scale-up of TPT through the optimal use of available and new  
19 107 diagnostics and regimens.[26] Given tuberculin supply and staff capacity challenges, and lack of evidence on  
20 108 the impact of recently introduced shorter TPT regimen on uptake and completion, this study assessed the use of  
21 109 the QuantiFERON-TB Gold Plus assay (QFT-Plus; Qiagen, Hilden, Germany) at the community level and the  
22 110 performance of shorter TPT regimen under programmatic conditions. The goal was to inform NTP of Viet Nam  
23 111 and other high TB burden countries in their ambitions to meet their TPT goals.

## 112 **METHODS**

### 113 **Study design and objectives**

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

### 120 **Study setting**

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

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3 123 of 2,387,052 and 3,598 TB notifications in 2019. In Hai Phong, the study took place in Do Son with a population  
4 124 of 49,029 and 52 persons with drug-susceptible TB notified in 2019.

## 7 125 **Study population and recruitment**

9 126 The study was embedded into routine contact investigations at primary care commune health posts and  
10 127 community-based active TB case finding (ACF) events. Details of the ACF events are provided elsewhere.[27]  
11 128 The study population included HHC and close contacts, and vulnerable community members at elevated risk of  
12 129 active TB, such as the elderly, urban poor and economic migrants. Briefly, elderly persons were  $\geq 55$  years,  
13 130 urban poor were based on national poverty definitions and economic migrants were categorized based on  
14 131 residency registration in rural provinces outside of the intervention districts. [28–30] The HCMC site also  
15 132 included a subgroup of primary- and secondary-level healthcare workers (HCW) based on the request from local  
16 133 authorities. Recruitment and follow-up occurred from May-2019 to Sep-2020. All individuals presenting for  
17 134 screening provided routine demographic and clinical information including age, sex, residency status, history  
18 135 of TB, comorbidities and symptomatic presentation. Following intake, persons belonging to the study population  
19 136 with residency in the study districts were invited to participate in the study. Persons living outside of or intending  
20 137 to relocate away from the study sites, or who declined to consent were excluded. Eligible, consenting  
21 138 participants were recruited consecutively until the quota of available QFT-Plus tests was reached ( $n=5,000$  in  
22 139 HCMC and  $n=1,000$  in Hai Phong). Parents consented on behalf of their children under 18 years.

## 32 140 **Sample size**

34 141 We calculated the sample size to power a 1-sample Z-test of proportions for non-inferiority between a literature-  
35 142 based indeterminate rate of  $p=2.9\%$  and a null hypothesis of  $p_0=3.5\%$  with a non-inferiority margin  $\delta=0.1\%$ .  
36 143 With a confidence level of  $\alpha=95\%$  and a power of  $\beta=90\%$ , the estimated sample size was  $n=4,915$ . We included  
37 144 a 15% contingency for attrition, data losses and post-hoc exclusion for a final sample size of  $n=5,653$ .

## 41 145 **Specimen collection and processing**

43 146 Provincial lung hospital (PLH) laboratory staff hosted training sessions on specimen collection and processing  
44 147 for the District TB Unit (DTU) and district-level laboratory staff. The District Health Center (DHC) mobilized  
45 148 participants to attend ACF events or to present at commune health posts. All attendants were systematically  
46 149 screened for TB symptoms and directed to undergo chest radiography (CXR) to rule out active TB. Persons with  
47 150 parenchymal abnormalities suggestive of TB on CXR or strong clinical suspicion of TB were referred for  
48 151 molecular sputum testing, as per contemporary national TB treatment guidelines.[31] Attendants were counseled  
49 152 on TBI and invited to participate. Study staff collected blood specimens from consenting, eligible individuals  
50 153 as per manufacturer recommended procedures. Each participant provided 4ml of venous whole blood in four  
51 154 separate tubes. Blood specimens were processed and analyzed per manufacturer's recommendations. Briefly,

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3 155 all four tubes were immediately shaken ~10 times to dissolve all antigens on the tube's wall coating. Tubes were  
4 156 stored inside dry ice coolers at 17–25°C, which were transported to the PLH biochemistry–hematology  
5 157 departments within six hours, twice a day. Samples were incubated at 37°C for 20 hours (±1 hour) and  
6 158 centrifuged within one hour of completing the incubation stage at 2000–3000g for 14 minutes at room  
7 159 temperature. The twelve-step enzyme linked immunosorbent assay was conducted within 16–24 hours. Results  
8 160 were analyzed by using proprietary QuantiFERON software v2.7.1.

### 161 **TPT initiation and participant follow-up**

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

### 171 **Statistical analyses**

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

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

## 189 Patient and public involvement

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

## 195 RESULTS

### 196 Sample characteristics

197 Of the 5,837 participants in the sample, 59.3% ( $n=3,463$ ) were female (Table 1). Children under 15 years  
198 constituted 19.5% (1,136/5,834) of the sample and the median participant age was 40 (IQR: 20–55). Overall,  
199 most participants were recruited at community-based ACF events (55.8%;  $n=3,257$ ), lived in urban areas  
200 (65.6%;  $n=3,827$ ), were permanent residents (90.5%; 3,116/3,444) and were enrolled on social health insurance  
201 (90.4%; 5,269/5,832). About 2.9% ( $n=167$ ) were diabetics and 1.1% ( $n=62$ ) reported a history of TB. Moreover,  
202 39.5% ( $n=2,306$ ) reported experiencing at least one of the four core TB symptoms (cough, weight loss, fever,  
203 and/or night sweats) during recruitment, while 2.3% ( $n=134$ ) participants exhibited TB-related CXR  
204 abnormalities.

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

	Total (N = 5,837) N (%) <sup>a</sup>	IGRA(+) <sup>b</sup> (N = 1,792) N (%)	IGRA (-) <sup>b</sup> (N = 4,000) N (%)	Indeterminate (N = 45) N (%)	aOR <sup>b</sup> (95% CI)	p-value <sup>†</sup>
<b>Sex</b>						
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
<b>Age<sup>‡</sup></b>						
<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)		
<b>Study site</b>						
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
<b>Screening location</b>						
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
<b>Target group</b>						
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
<b>Urbanization</b>						
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
<b>Residency status<sup>†,¶</sup></b>						
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
<b>Social health insurance<sup>¶</sup></b>						
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

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<b>Diabetes mellitus</b>						
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
<b>Previous history of TB</b>						
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
<b>Any TB symptoms<sup>§,¶</sup></b>						
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
<b>Chest X-ray result</b>						
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

‡ Percent of row total

¥ IGRA=Interferon-Gamma Release Assay; aOR=adjusted Odds Ratio

† Wald test



## 215 TB infection care cascade

216 Of the 16,652 individuals verbally screened in both provinces, 35.1% (n=5,837) agreed to be tested by QFT-  
 217 Plus for the study (Figure 1). The overall indeterminate rate was 0.8% (n=45) and 30.7% (n=1,792) of  
 218 participants were QFT-Plus-positive, of whom 97.5% (n=1,748) were eligible for TPT. About 63.3%  
 219 (1,107/1,748) of eligible participants initiated TPT and 80.6% (892/1,107) completed therapy. The sample  
 220 included 4,840 participants in HCMC and 997 in Hai Phong (Table 2). The indeterminate rate was 0.8% in  
 221 both sites, while positivity rates were 33.1% (1,603/4,840) in HCMC and 19.0% (189/997) in Hai Phong. The  
 222 respective TPT initiation and completion rates in the 9H cohort in HCMC were 63.6% (995/1,565) and 80.0%  
 223 (796/995) compared to 61.2% (112/183) and 85.7% (96/112) in the 3HR cohort in Hai Phong. Neither initiation  
 224 nor completion rates were significantly different between the two regimens (p=0.522 & p=0.147, respectively).

225 **Table 2: TB infection care cascade by TPT cohort**

	Total (N = 5,837) N (%)	HCMC (N = 4,840) N (%)	Hai Phong (N = 997) N (%)
<b>IGRA result &amp; TPT<sup>‡</sup></b>			
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)
<b>--Ineligible for TPT (% of positive)</b>	<b>44 (0.8)</b>	<b>38 (0.8)</b>	<b>6 (0.6)</b>
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)
<b>--Eligible for TPT (% of positive)</b>	<b>1,748 (97.6)</b>	<b>1,565 (97.6)</b>	<b>183 (97.3)</b>
CXR(-)	1,702 (95.0)	1,524 (95.1)	178 (94.7)
CXR(+), MTB(-)	46 (2.6)	41 (2.6)	5 (2.7)
<b>--Initiated on TPT<sup>¶</sup> (% of eligible)</b>	<b>1,107 (63.3)</b>	<b>995 (63.6)</b>	<b>112 (61.2)</b>
<b>--Completed TPT<sup>¶</sup> (% of initiated)</b>	<b>892 (80.6)</b>	<b>796 (80.0)</b>	<b>96 (85.7)</b>

226 Notes:

227 <sup>‡</sup> IGRA=Interferon-Gamma Release Assay; CXR=Chest X-Ray; TPT=TB Preventive Therapy; MTB=*M. tuberculosis*; HCMC=Ho  
 228 Chi Minh City

229 <sup>¶</sup> TPT consisted of 9H in HCMC and of 3HR in Hai Phong

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

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

### 240 Risk factors of IGRA-positivity

241 Being male (adjusted Odds Ratio=1.51; 95% confidence interval: [1.28, 1.78];  $p<0.001$ ), aged 45-59 years (1.30  
 242 [1.05, 1.60];  $p=0.018$ ), and exhibiting CXR abnormalities suggestive of TB (2.23 [1.38, 3.61];  $p=0.001$ ) were  
 243 associated with higher QFT-Plus positivity (Table 2). Conversely, compared to the reference group (30-44  
 244 years), the risk of QFT-Plus-positivity was significantly lower among children under 15 years (0.18 [0.13, 0.26];  
 245  $p<0.001$ ) 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];  
 246  $p<0.001$ ) and individuals living in peri-urban areas (0.55 [0.36, 0.55];  $p=0.007$ ).

### 247 Survival analysis and risk factors of TPT completion

248 A total of 1,107 participants were followed for a total of 8,211 person-months with 215 recorded LTFUs (Table  
 249 3). There were 7,904 and 307 person-months of observations with mean follow-up times of 7.9 [7.8, 8.1] months  
 250 and 2.7 [2.6, 2.9] months, and 199 and 16 LTFUs in the 9H and 3HR cohorts, respectively. The respective LTFU  
 251 incidence rates were 25.2 and 52.1 per 1,000 person-months. Most LTFUs occurred after the first month of TPT  
 252 in both the 9H (79/199=39.7%) and 3HR (13/16=81.2%) cohorts (Figures 3a and 3b). The survival analysis  
 253 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];  
 254  $p<0.001$ ) were strongly associated with higher risk of LTFU.

255 **Table 3: Participant characteristics and adjusted risk factors associated with TPT loss to follow-up<sup>†</sup>**

	Total (N = 1,107) N (%) <sup>‡</sup>	TPT completed <sup>‡</sup> (N = 892) N (%) <sup>‡</sup>	LTFU <sup>‡</sup> (N = 215) N (%) <sup>‡</sup>	aHR of LTFU <sup>‡</sup> (95% CI)	p-value <sup>†</sup>
<b>TPT regimen</b>					
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
<b>Sex</b>					
Female	645 (58.3)	512 (79.4)	133 (20.6)	Ref	
Male	462 (41.7)	380 (82.3)	82 (17.8)	1.02 [0.94; 1.11]	0.608
<b>Age</b>					
<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)		
<b>Screening location</b>					
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
<b>Target group</b>					
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
<b>Urbanization</b>					
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
<b>Diabetes mellitus</b>					
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
<b>Previous history of TB</b>					
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

‡ 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.

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3 280 However, there were patterns in the TBI care cascade indicating that scale-up of available TBI diagnostic tools  
4 281 and regimens requires more than simply decentralization. Fewer than half of the individuals mobilized during  
5 282 these ACF campaigns agreed to or were eligible for an IGR test and only six out of ten eligible persons initiated  
6 283 TPT, which was concordant with prior studies in Viet Nam.[34] One potential reason for the drop-off may be  
7 284 process related, since we embedded the study in a programmatic setting, which meant that in general over two  
8 285 weeks elapsed from when participants were tested until eligible persons initiated TPT. Nevertheless, slow  
9 286 turnaround time may only partially explain the pre-treatment LTFU, as TPT initiation rate was consistent across  
10 287 both settings despite the difference in turnaround time.

11 288 By fielding the study in two separate sites with different TPT regimen and TBI rates in the community, we  
12 289 recorded several noteworthy observations. Specifically, while initiation rates in both sites were similar, there  
13 290 was a slightly higher completion rate in the 3HR cohort. Thus, even though we did not observe a greater uptake  
14 291 of TPT as seen on prior studies, the shorter treatment duration of 3HR may have contributed to higher TPT  
15 292 completion rates.[38–40] However, the survival analysis showed that more persons were lost to follow-up than  
16 293 expected over the shorter period of treatment. Based on informal qualitative feedback from field staff, reasons  
17 294 for the large drop-offs in the cascade included a lack of understanding of the risk of progression from TBI to  
18 295 active TB and the benefits of TPT in the general population, but also among healthcare providers, which leads  
19 296 to the de-prioritization of TPT as optional prophylaxis rather than valuable intervention. Since the 3HR regimen  
20 297 was only used in one province which may have faced site-specific challenges, we cannot generalize these results  
21 298 to other areas of the country. However, they highlight the need for more education and advocacy for providers  
22 299 and participants to improve the acceptance and prioritization of TPT.[41,42]

23 300 Moreover, advocacy and awareness building may need to be tailored to individual subgroups. Even though  
24 301 positivity, initiation and completion rates did not vary substantially across sites, gender or age category, there  
25 302 were, however, notable differences across study populations. In our study, HCWs exhibited a lower proportion  
26 303 and risk of positivity, higher TPT initiation and significantly higher risk of LTFU compared to HHCs and  
27 304 community members in either site. The low positivity rate was particularly noteworthy for its discordance with  
28 305 published, albeit dated, evidence from Viet Nam[43] and WHO guidelines warranting intervention in this group  
29 306 due to higher occupational risk of TB infection.[44] A potential explanation for the discordance is that a sizeable  
30 307 proportion of HCWs were generalist primary care workers. The more recent EnTIC study (NCT02073240)  
31 308 measured lower TBI rates among Vietnamese HCWs in general hospitals compared to HCWs in TB hospitals  
32 309 (27.9% [22.8%, 33.6%] vs. 41.7% [26.2%, 58.9%]).[45] However, this TBI rate in general hospital HCWs is  
33 310 still higher than the rate among HCWs on this study; a future comparative analyses of TBI in HCWs in  
34 311 tertiary/quaternary general hospitals versus primary care workers may offer further insight.

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3 312 The diagnostic delay was unacceptably long among HCWs and across all groups in Hai Phong. In Hai Phong,  
4 313 the lower burden and more limited TB care capacity as well as greater reliance on the lung hospital in TB care  
5 314 and prevention activities may have contributed to the long delay in treatment initiation. Meanwhile, upon  
6 315 investigation, HCWs indicated a preference to wait for the new 12-dose regimen of isoniazid and rifapentine  
7 316 (3HP), but then agreed to initiate TPT on 9H as concerns over nitrosamine impurities delayed scale-up of 3HP  
8 317 in Viet Nam.[46,47] Nevertheless, despite a delay of almost six weeks, the TPT initiation rate among HCWs  
9 318 was highest across all groups and also above rates measured on prior studies (39.0%-49.6%).[48,49] Conversely,  
10 319 the low completion rate measured on this study was on par with other studies on HCWs receiving 9H for TPT.  
11 320 However, this low rate may have been avoided with shorter regimen as adherence in this study at month 3 was  
12 321 100% and month 8 was still at 80.0%. These results were in line with previous studies that indicated health  
13 322 workers were significantly more likely to complete TPT on 3HR compared to 9H (91.4% vs. 76.7%,  
14 323 p=0.02).[50–52]

15  
16 324 The use of the 9H regimen in the majority of participants also highlights a key limitation of this study. By  
17 325 conducting it under routine program conditions, the study was exposed to external bias and confounding, such  
18 326 as the variability in the available TPT regimen. HCMC historically has had a substantially larger burden of TB  
19 327 and TBI, as evinced on this study. Thus, 9H was the local regimen of choice due to its greater availability and  
20 328 lower costs. Similarly, we relied on routine diagnostics to rule out active TB rather than more sensitive tools  
21 329 such as culture due to cost implications. With respect to costs, another limitation of our study was the lack of a  
22 330 formal assessment of the cost barrier of IGRAs in our low-resource setting with limited program budgets.  
23 331 Operationally, WHO recommends to integrate TPT into routine HHC investigations and ACF.[16] It stands to  
24 332 reason that such integration may also improve value for money as has been well-established for highly  
25 333 vulnerable people living with HIV.[53] There is ample evidence that HHC investigations and community-based  
26 334 ACF campaigns can reach those most vulnerable to active TB and thus most in need of TPT.[29,54,55]  
27 335 Nevertheless, given the lack of an accompanying health economic evaluation, future research should conduct  
28 336 impact evaluations and cost-effectiveness analyses of integrated TB and TBI testing and treatment on ACF  
29 337 campaigns and differences in incidence and disability-adjusted life years compared to a control cohort. Another  
30 338 limitation is that our cohort design did not include a post-treatment follow-up to assess incidence of TB in those  
31 339 with and without TPT, in part due to the social distancing measures launched in response to the pandemic. The  
32 340 study's convenience sampling and selection of HCMC and Hai Phong as study sites likely introduced bias  
33 341 towards densely populated urban settings, which consequently limits the generalizability of this study.  
34 342 Nevertheless, the study benefitted from its large sample size and integration into routine program operations  
35 343 that may help to translate the findings to recommendations for densely populated, high TB burden settings in  
36 344 general.

## 345 CONCLUSIONS

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

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## 362 COMPETING INTERESTS

363 The authors have no competing interests to declare.

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371 design of the study, in collection, analysis, and interpretation of data, or in writing the manuscript.

## 372 **AUTHORS' CONTRIBUTIONS**

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

## 381 **DATA AVAILABILITY**

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

## 387 **ETHICAL CONSIDERATIONS**

388 This study was approved by the Pham Ngoc Thach Hospital ethics committee for biomedical research  
389 (897/HDDD-PNT). In addition, QFT-Plus testing is part of national guidelines and activities were approved by  
390 the NTP (1069/BVPTW-DAPCL). Participation was voluntary and did not affect the provision or standard of  
391 care. All personal identifying information was removed from the dataset prior to analysis.

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528 **FIGURE LEGENDS**

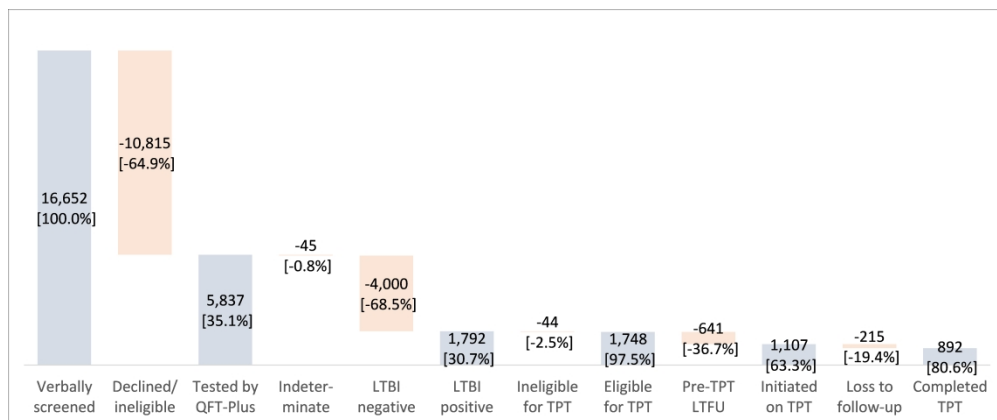
529 Figure 1. Aggregate TB infection care cascade.

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

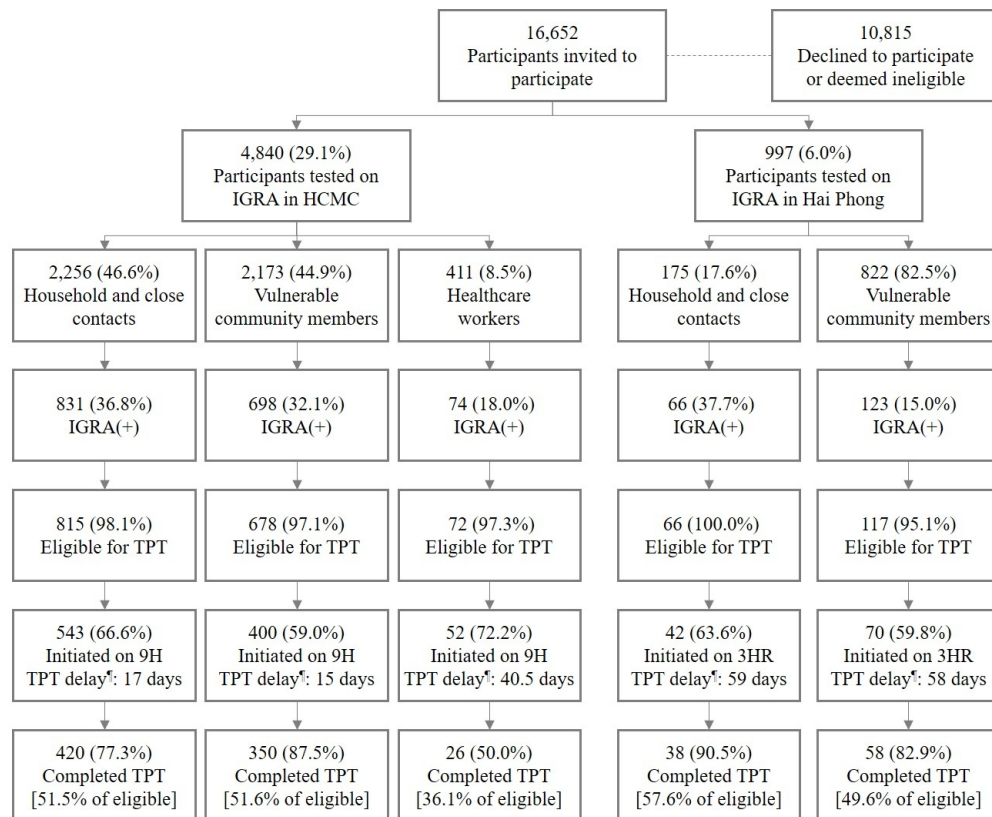
531 Figure 3. Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen.

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Notes: <sup>‡</sup> Median number of days between QFT-Plus testing and treatment initiation

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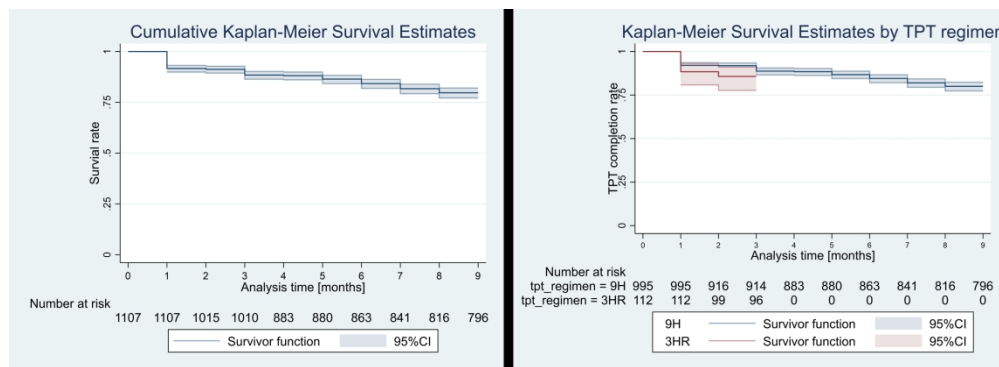


Figure 3a & 3b - Kaplan-Meier TPT survival curves a) for all participants and b) by TPT regimen

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## STROBE Statement

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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

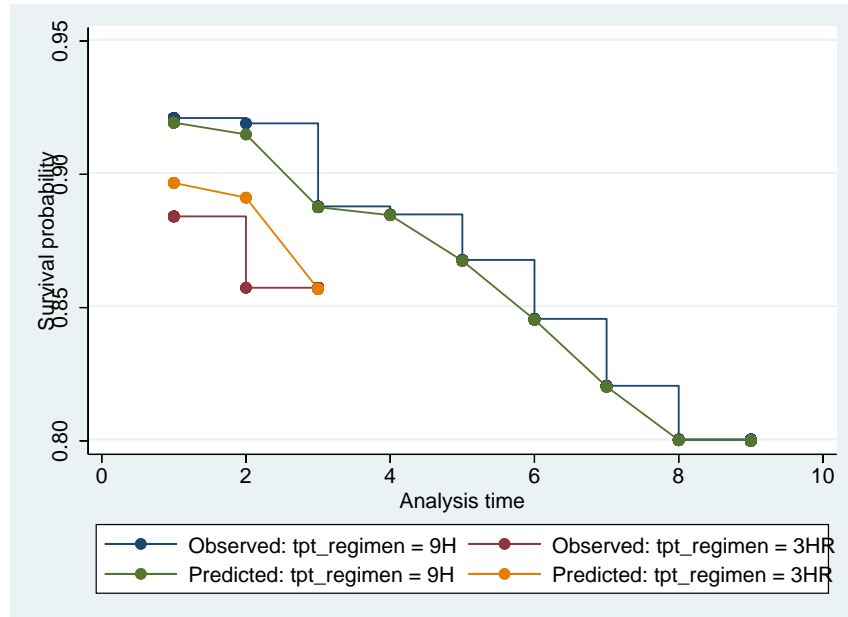
\*Give information separately for exposed and unexposed groups.

**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](http://www.strobe-statement.org).

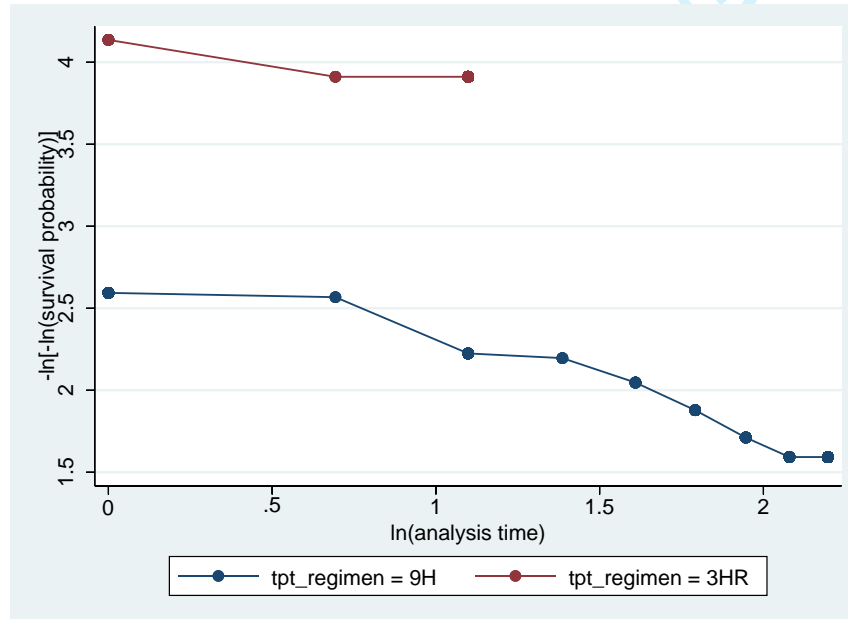
## SUPPLEMENTAL MATERIAL

### 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  $0.112 < p < 0.955$ .