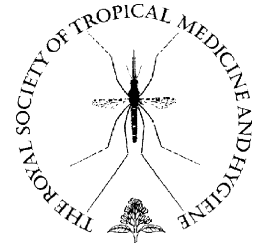




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Voluntary counselling and testing uptake and HIV prevalence among tuberculosis patients in Jogjakarta, Indonesia

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Summary We aimed to establish HIV prevalence and uptake of unlinked anonymous testing and voluntary counselling and testing (VCT) among tuberculosis (TB) patients in Jogjakarta, Indonesia. We introduced unlinked anonymous HIV testing for TB patients attending directly observed treatment, short-course services between April and December 2006. Patients were additionally offered VCT services. Of 1269 TB patients who were offered unlinked anonymous testing, 989 (77.9%; 95% CI 75.6–80.1%) accepted. HIV prevalence was 1.9% (95% CI 1.6–2.2%). HIV infections were less frequently diagnosed among TB patients who attended a public health centre [odds ratio (OR) 0.15; 95% CI 0.03–0.70] rather than public hospital. They were more frequent in TB patients with a university education background (OR 5.16; 95% CI 1.01–26.63) or a history of HIV testing (OR 57.87; 95% CI 9.42–355.62). Of the 989 patients who accepted unlinked anonymous testing, only 133 (13.4%; 95% CI 11.5–15.7%) expressed interest in VCT. Of these, 52 (39.1%; 95% CI 31.2–47.6%) attended VCT, but interest was higher among students and those offered VCT by public health centres. The HIV prevalence in Jogjakarta is higher than expected and needs to be monitored cautiously. Unlinked anonymous HIV testing is well accepted and can be implemented with modest additional efforts.

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1. Introduction

Indonesia's National TB (tuberculosis) Control Programme (NTP) achieved international targets for case detection (>70%) and treatment success rate (>85%) in 2006 (WHO, 2008). However, recent trends suggest the potential for a dual TB–HIV epidemic. The number of reported AIDS cases in Indonesia has increased 15-fold over the past 10 years (MOH-ROI, 2007). Patients with TB-HIV co-infection are reported from hospitals and jails in several provinces. Furthermore, TB is one of the leading opportunistic infections among hospitalized AIDS patients (NIHRD, 2003).

WHO recommends HIV testing among TB patients as a key component of the health sector's response to the intersecting TB and HIV epidemics. HIV testing among TB patients can serve as a pillar for integrated surveillance that is much needed to monitor the dual epidemic trend and to enable the development of sound prevention strategies (WHO, 2004a, 2004b). Moreover, it can facilitate referral for appropriate care, support and treatment for TB patients with HIV infections (Godfrey-Faussett et al., 2002).

In view of the high HIV infection rates in some settings and the improved prospects for HIV/AIDS treatment, an ethical debate has emerged surrounding HIV testing among TB patients, particularly with regard to unlinked anonymous or 'blinded' methods (WHO, 2004b). This led to linked confidential testing through an 'opt in' approach, which has been offered in centres designated for voluntary counselling and testing (VCT) (Bock et al., 2008). Recently, however, WHO encouraged adoption of provider-initiated linked confidential testing and counselling (PITC) (WHO, 2007a). In contrast to VCT, PITC is based on an 'opt out' approach in which the clinician initiates counselling when an individual is seeking medical care with signs or symptoms compatible with HIV infection (Bock et al., 2008).

Ultimately, decisions about whether and how to implement HIV testing in TB patients, particularly in countries with low-level and concentrated epidemics like Indonesia, should be guided by an assessment of the local epidemiological context and the feasibility of alternative testing strategies. This study aimed to determine the HIV prevalence among TB patients in the different types of health facilities in Jogjakarta, Indonesia, and to assess the feasibility of unlinked anonymous HIV testing for routine surveillance and 'opt-in' linked confidential HIV testing as an entry point for integrated TB-HIV care.

2. Methods

2.1. Study context

Jogjakarta province is located in the central part of Java Island, has 3.2 million inhabitants and covers an area of 3185 km². The province's primary care offer consists of some 650 private practices and 117 public community health centres staffed with doctors, midwives and nurses. This first-level network is backed up by nine public and 24 private hospitals. The provincial TB control strategy involves all 117 public health centres, five chest clinics and 18 hospitals (public and private), linking them for monitoring of diag-

nosis and treatment outcomes as well as quality assurance for smear microscopy (Irawati et al., 2007).

The province is currently facing a concentrated HIV epidemic, with 92 AIDS cases (2.3 per 100 000 population) reported as of 2006 (MOH-ROI, 2007). The HIV prevalence among the general adult population in Jogjakarta is estimated at 0.15–2.0% (NAC-MOH, 2006), though much higher among high-risk groups: clients of commercial sex workers (0.69–1.19%), commercial sex workers (3.6–7.4%), prisoners (3.7–8.0%) and injecting drug users (29.0–52.9%) (MOH-ROI, 2007). HIV surveillance in the province is mainly based on routine reporting of AIDS cases by hospitals and on annual seroprevalence surveys among risk groups. VCT services have been established in four hospitals and one non-governmental organization clinic in Jogjakarta municipality. These services are provided free of charge and can be reached from the surrounding districts within 45 min by public transport.

2.2. Study design

We piloted unlinked anonymous HIV testing among TB patients attending directly observed treatment, short-course (DOTS) services in Jogjakarta province and additionally facilitated linked confidential testing. The protocol was developed iteratively in consultation with key stakeholders and informed mainly by the WHO guidelines on TB-HIV surveillance (WHO, 2004b).

A minimum sample size of 916 was required based on the following assumptions: the WHO (2006) estimate of percentage of HIV infection in TB cases in Indonesia (0.6%), a desired precision of 0.05% (with $\alpha = 5.0\%$), and an additional number of subjects to anticipate 5% poor quality blood specimens. Out of five districts in the province, we selected three districts which well represented urban, semi-urban and rural settings. Within the three districts, we involved all 88 DOTS facilities: 68 health centres, 16 hospitals and four chest clinics. We weighted the minimum sample size for each facility type to reflect their contributions per district to TB case finding in 2005.

Between April and December 2006, consecutive new TB patients (smear-positive, smear-negative or extrapulmonary) and relapses, aged 15 years and above, who gave informed consent were recruited into the study until the required sample size was reached. The TB case definitions of the NTP guideline (MOH-ROI, 2003) were employed. The guideline prescribes diagnosis of smear-positive pulmonary TB on the basis of: (1) at least two positive results out of three consecutive sputum samples; or (2) one positive result out of three consecutive sputum samples complemented by chest X-ray indicative of TB. Smear-negative pulmonary TB has to be diagnosed based on: (1) negative results from all three consecutive sputum samples; (2) chest X-ray indicative of TB; (3) no clinical improvement after empirical non-TB antibiotic treatment; and (4) physician's judgement. Persons who were too ill to be counselled or unable to comprehend the procedure were excluded.

Eligible TB patients were recruited during their initial treatment visits and recorded in the TB register to avoid double enrolment. Specifically trained health workers offered TB patients unlinked anonymous HIV testing and addition-

ally the freely available hospital-based VCT services. Their interactions were guided by the content of a brochure covering basic knowledge of HIV transmission and the importance of HIV testing that was subsequently offered to the patient. Access to antiretroviral treatment, as a possible benefit of VCT, was to be explicitly mentioned. If the patient expressed interest in visiting the VCT services, the health worker made an appointment with the testing centre and provided a referral slip as well as a modest incentive to cover two return trips to the VCT centres by public transport.

Blood samples were transported from the TB facilities to the provincial laboratory. HIV was assessed in the provincial laboratory using Entebe HIV dipstick (Hepatika Laboratories, Mataram, Indonesia) and Determine HIV1/2 (Abbott GmbH, Wiesbaden, Germany), according to a WHO standard algorithm (WHO, 2001) already in use for annual HIV serosurveys in the province. The provincial laboratory retested all positive and 10% of the negative HIV tests with Vironostika HIV Uniform II Antigen Ag/Ab (BioMérieux, Marcy l'Étoile, France).

The health workers who offered HIV testing also administered on site a short questionnaire (available from the corresponding author), which was designed for this study, but with future adoption for routine recording and reporting in mind. The questionnaire identified the type of health facility and collected information on district, age, gender, education, occupation, marital status of the patients, type and duration of TB symptoms and history of HIV testing. All data were double entered and checked for inconsistencies before analysis. Analysis was conducted using SPSS 15.0. (SPSS Inc., Chicago, IL, USA). In univariate analysis, differences between proportions were tested with χ^2 or Fisher's exact test. Logistic regression analysis was performed to identify independent determinants for a positive HIV test and for interest in VCT.

2.3. Ethical considerations

Prior to recruitment, informed consent was obtained from all respondents or their guardian in case of patients aged 15–18 years. Whether or not a patient consented to participate did not influence the standard of care he or she received. Respondents were encouraged, but never forced to consult VCT centres. The Jogjakarta provincial health office had a sufficient supply of courses of highly active antiretroviral treatment (HAART), which were freely available to patients taking up VCT. Patient's anonymity was protected by applying unique codes in place of personal identifiers on the data collection forms.

3. Results

In total, 1681 TB patients were registered by the participating DOTS services in the study districts (Figure 1). Among these, 1269 (75.5%) were invited to participate in the study. The remaining 412 (24.5%) were not invited due to exclusion criteria (26.5%), time constraints within the facility (35.2%) and other reasons (38.3%). The predominant 'other' reason concerned the challenging conditions imposed by the severe earthquake that struck the study area in May 2006. Among the 1269 (77.9%; 95% CI 75.6–80.1%) invited patients, 989

accepted unlinked anonymous testing and were all tested. There were no significant differences between those who accepted or did not in terms of gender, age and district. A significant difference in acceptance rates was only observed with regard to the type of health facility where patients were recruited, with lower acceptance rates in hospitals than public health centres ($P < 0.001$).

HIV prevalence among all tested TB patients was 1.9% (95% CI 1.6–2.2%). There were no significant differences between TB patients who were HIV positive and those who were HIV negative in terms of district, gender, age, occupation, marital/relationship status and TB patient categories (Table 1). The proportion of HIV-positive TB patients was lower in health centres [odds ratio (OR) 0.15; 95% CI 0.03–0.70] and chest clinics (OR 0.19; 95% CI 0.05–0.82) than in public hospitals. It was higher in TB patients with university level education (OR 5.16; 95% CI 1.01–26.63). HIV infections were also more frequently diagnosed in TB patients with a history of HIV testing (OR 57.87; 95% CI 9.42–355.62).

Only 133 (13.4%; 95% CI 11.5–15.7%) of the 989 patients who accepted unlinked anonymous HIV testing expressed interest in attending VCT. Eventually, only 52 (4.1%; 95% CI 3.1–5.3%) of the 1269 patients who were offered unlinked anonymous testing actually attended VCT (Figure 1). Between the three patient groups (those who expressed no interest in VCT; those who expressed interest but did not attend VCT; and those who attended VCT), there were no significant differences observed in terms of district, sex, education, history of HIV testing and patient categories (Table 2). TB patients were more interested in VCT if they were students (OR 2.35; 95% CI 1.24–4.46) or aged between 15 and 44 years old (OR 1.88; 95% CI 1.13–3.13) (Supplementary Table 1). They were also more interested if they had been offered the service by a public health centre (OR 8.02; 95% CI 5.11–12.60).

4. Discussion

This is one of the rare TB-HIV co-infection prevalence studies carried out in a setting with a low prevalence or concentrated epidemic of HIV. Our study is also the first to document TB patients' interest in VCT in such a setting and to establish the acceptability of unlinked anonymous HIV testing in Indonesia.

We limited our study population to those attending DOTS TB services, as these services detected 73% of TB cases in 2006 (WHO, 2008). While one could expect differences between DOTS patients and those TB patients managed in non-DOTS services in terms of socio-economic status, most of the patients with suspected TB attending non-DOTS services in the study area are eventually being referred to DOTS services (Mahendradhata et al., 2007). Some of the TB patients attending DOTS services were not invited to participate due to operational reasons and of those invited, some refused. However, a comparison of tested and not tested patients shows no differences in patient profile.

The acceptance rate of unlinked anonymous HIV testing among our TB patients is high (77.9%). There exist no comparable data on unlinked anonymous testing uptake among TB patients as other studies utilized VCT as the entry point

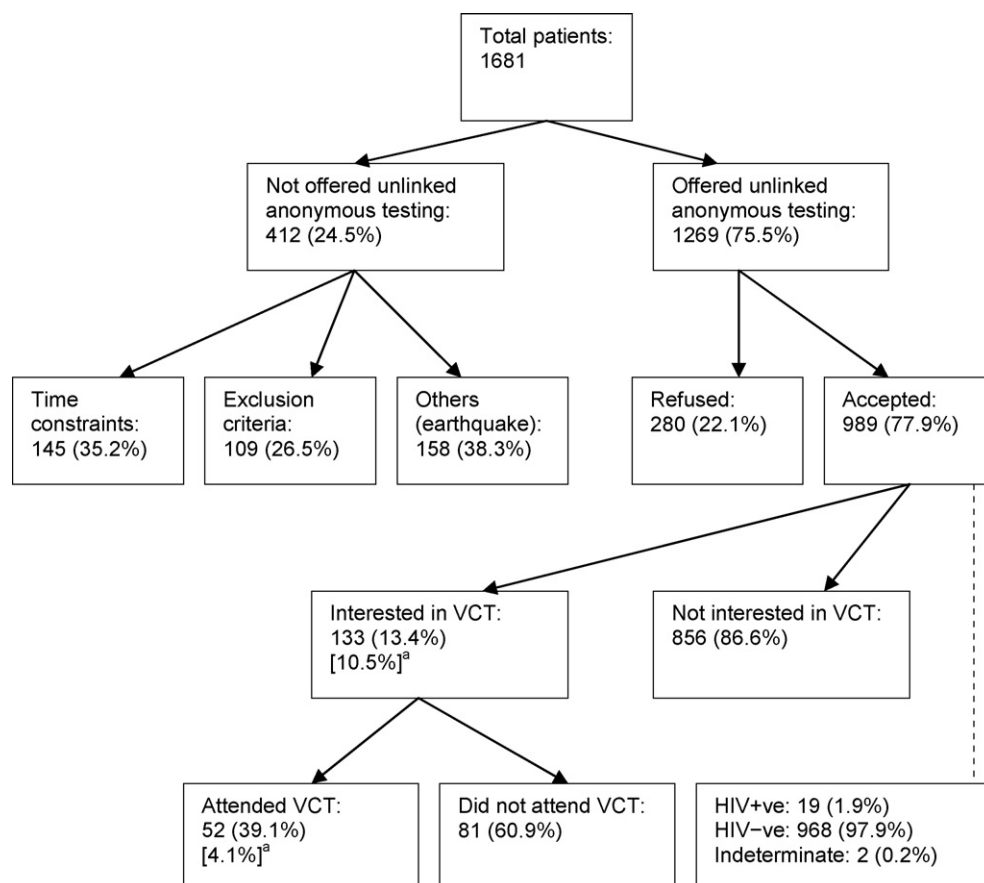


Figure 1 Acceptability of unlinked anonymous HIV testing and voluntary counselling and testing (VCT) among tuberculosis patients in Jogjakarta province, Indonesia in 2006. ^a Denominator = 1269 (offered unlinked anonymous testing).

(Jerene et al., 2007; Ramachandran et al., 2003; Trinh et al., 2007; Van der Werf et al., 2006; Zachariah et al., 2003). Studies in another target population, women attending antenatal clinics in Uganda (Mpairwe et al., 2005), observed on the one hand a low uptake of unlinked anonymous testing (27%) and on the other hand a high uptake of VCT (73%). In settings where HIV is generalized, one can expect more demand for VCT services than for unlinked testing that does not lead to any direct individual benefit. Moreover, many other differences across settings such as coverage and effectiveness of VCT campaigns, service quality and accessibility, and availability of HAART can influence uptake. Notwithstanding, our findings support the use of an unlinked anonymous HIV surveillance strategy among TB patients in Indonesia, where HIV has not gained high visibility. It could be introduced with relatively modest additional inputs: one day of training for health workers, specimen collection kits and linkage to the provincial laboratory. This should be accompanied by promotion for VCT in the now existing centres, raising issues that will be discussed below.

Due to methodological differences our prevalence result may not be directly comparable to results from other studies. Furthermore, HIV testing in TB suspects, rather than in TB cases, would possibly return higher HIV prevalence rates. The difference could be marked in a generalized HIV setting (Srikantiah et al., 2007) where the diagnosis of TB is a challenge, but it is probably negligible in Jogjakarta. At any rate, our data suggests that HIV preva-

lence among TB patients in Jogjakarta is significantly higher than the national (0.14–0.18%) and provincial (0.15–0.20%) estimates for the general adult population (NAC-MOH, 2006; UNAIDS/WHO, 2006). The prevalence we found in TB patients is close to the HIV prevalence in risk populations such as commercial sex workers and injecting drug users, which is 2.42–5.44% in the province (NAC-MOH, 2006). It is also considerably higher than the estimated HIV prevalence of 0.6% among all new adult TB patients in Indonesia (WHO, 2007b). This implies that the magnitude of co-infection in other Indonesian provinces with concentrated HIV epidemics could also be substantially higher than the national average. This further implies that TB patients in Jogjakarta and similar settings in Indonesia should be considered as an important target group for HIV care and prevention.

Potential risk factors for HIV infection in TB patients that could easily and reliably be assessed were investigated, but in the interpretation one has to take into account possible (residual) confounding and endogenous effects. Few were found to be significant. This might, however, reflect the study's lack of power to detect moderate differences at the subgroup level. HIV prevalence was slightly higher among those aged 15–44 years in our study population, but this was not statistically significant. A study in Ukraine did not identify age as a risk factor (Van der Werf et al., 2006), while others (Haar et al., 2006; Ramachandran et al., 2003; Trinh et al., 2007) did. In our study, the proportion of female TB

Table 1 Characteristics of tuberculosis (TB) patients and HIV test result in Jogjakarta province, Indonesia in 2006 (*n* = 987)^a

Variable	Total	HIV-positive <i>n</i> (%)	Univariate		Multivariate	
			Odds ratio (95% CI)	Odds ratio (95% CI)		
All	987	19 (1.9)	—	—	—	—
District						
Sleman	309	9 (2.9)	1		1	
Jogjakarta	532	9 (1.7)	0.57	(0.23–1.46)	1.07	(0.30–3.77)
Bantul	146	1 (0.7)	0.23	(0.03–1.83)	0.94	(0.10–9.04)
Health facility where TB patient was diagnosed						
Public hospital	232	11 (4.7)	1		1	
Private hospital	69	1 (1.4)	0.30	(0.04–2.33)	0.20	(0.19–2.15)
Health centre	360	3 (0.8)	0.17	(0.05–0.61)	0.15	(0.03–0.70)
Chest clinic	322	4 (1.2)	0.25	(0.08–0.80)	0.19	(0.05–0.82)
Sex						
Male	596	13 (2.2)	1		1	
Female	390	6 (1.5)	0.70	(0.26–1.86)	0.52	(0.13–2.05)
Age group (years)						
15–24	222	6 (2.7)	1		1	
25–34	249	7 (2.8)	1.04	(0.34–3.13)	0.93	(0.21–4.06)
35–44	147	4 (2.7)	1.03	(0.29–3.69)	1.21	(0.20–7.12)
>44	367	2 (0.5)	0.20	(0.03–1.09)	0.20	(0.23–1.59)
Education level						
No education, elementary or junior high school	471	4 (0.8)	1		1	
High school	370	8 (2.2)	2.58	(0.77–8.64)	2.86	(0.72–11.40)
University	146	7 (4.8)	5.88	(1.70–20.4)	5.16	(1.01–26.63)
Occupation						
Unemployed/informal	527	10 (1.9)	1		1	
Student	117	4 (3.4)	1.83	(0.56–5.94)	0.36	(0.06–2.36)
Employed	203	2 (1.0)	0.51	(0.11–2.37)	0.25	(0.05–1.37)
Housewife	140	3 (2.1)	1.13	(0.30–4.17)	2.17	(0.36–13.20)
Married/in relationship						
No	302	8 (2.6)	1		1	
Yes	682	11 (1.6)	0.60	(0.24–1.51)	1.51	(0.34–6.66)
History of HIV testing						
No	962	15 (1.6)	1		1	
Yes	8	4 (50.0)	63.1	(14.4–276.5)	57.87	(9.42–355.62)
Patient category 1						
Relapse/failure	54	1 (1.9)	1		1	
New/intensive phase	932	18 (1.9)	1.04	(0.14–7.97)	1.08	(0.09–13.04)
Patient category 2						
Pulmonary smear positive	606	10 (1.7)	1		1	
Pulmonary smear negative/extrapulmonary	380	9 (2.4)	1.45	(0.54–3.89)	0.74	(0.90–13.04)

^a Patients with indeterminate HIV test results and with missing values excluded.

patients infected with HIV is slightly lower than the male TB patients. This, however, was also not statistically significant. Other TB-HIV co-infection studies have reported no association (Ramachandran et al., 2003; Van der Werf et al., 2006, 2007), or that HIV infection was significantly more frequent in males (Haar et al., 2006; Trinh et al., 2007) or in women (Jerene et al., 2007). We also observed a higher HIV prevalence among TB patients with higher education levels. This is in line with the study conducted by Van der Werf et al. (2007) in Eritrea. The above, sometimes contrasting,

findings between studies indicate that the importance of demographic characteristics as risk factors for HIV infection in TB patients is largely context-bound and related to the dynamics of the local HIV epidemiology.

We found no significant difference in HIV rates between smear-positive and smear-negative TB patients. Studies in India (Ramachandran et al., 2003) and Vietnam (Trinh et al., 2007) documented that HIV prevalence was higher among smear-positive patients. These conflicting results could be attributed to the difficulty of diagnosing smear-negative TB,

Table 2 Characteristics of tuberculosis (TB) patients and response to voluntary counselling and testing (VCT) offer in Jogjakarta province, Indonesia in 2006 (*n* = 989)

Variable	Total	Response (%)			P-value
		Attended VCT (<i>n</i> = 52)	Interested but did not attend VCT (<i>n</i> = 81)	Not interested in VCT (<i>n</i> = 856)	
All	989	—	—	—	—
District					0.31
Sleman	309	6.8	7.1	86.1	
Jogjakarta	533	4.5	7.9	87.6	
Bantul	147	4.8	11.6	83.7	
Health facility offering VCT to TB patient					<0.001
Public hospital	228	3.1	3.5	93.4	
Private hospital	65	6.2	4.6	89.2	
Health centre	365	9.9	16.4	73.7	
Chest clinic	331	1.5	3.0	95.5	
Sex					0.53
Male	598	5.9	8.4	85.8	
Female	390	4.4	7.7	87.9	
Age group (years)					0.05
15–24	222	6.3	12.2	81.5	
25–34	250	6.0	8.4	85.6	
35–44	147	3.4	9.5	87.1	
>44	368	4.9	4.9	90.2	
Education					0.19
No education, elementary or junior high school	473	4.6	6.6	88.8	
High school	370	5.7	8.6	85.7	
University	146	6.2	12.3	81.5	
Occupation					0.02
Unemployed/informal	528	4.9	8.0	87.1	
Student	117	8.5	14.5	76.9	
Employed	204	4.4	8.8	86.8	
Housewife	140	5.0	2.9	92.1	
Married/in relationship					0.04
No	302	5.3	11.6	83.1	
Yes	684	5.3	6.7	88.0	
History of HIV testing					0.56
No	964	5.1	8.2	86.7	
Yes	8	12.5	12.5	75.0	
Patient category 1					0.40
Relapse/failure	54	9.3	7.4	83.3	
New/intensive phase	934	5.0	8.2	86.7	
Sex					0.94
Pulmonary smear positive	606	5.4	8.3	86.3	
Pulmonary smear negative/extrapulmonary	382	5.0	8.1	86.9	

particularly in HIV patients (Siddiqi et al., 2006). HIV infection is most often found among TB patients with a history of previous HIV testing in our study. This comes as no surprise, as those who had been interested in being tested in the past probably considered themselves at risk. HIV is also more often diagnosed among TB patients attending public hospitals. This indicates that public referral hospitals in major Indonesian towns could be a strategic entry point for integrated TB–HIV care and surveillance.

Interest in VCT is very low in Jogjakarta. Studies in settings with generalized HIV epidemics reported much higher rates (Jerene et al., 2007; Van der Werf et al.,

2006; Zachariah et al., 2003). Only Jerene et al. (2007) in Ethiopia reported individual determinants of VCT interest in TB patients. While some other studies were conducted in other sub-populations, mainly pregnant women, better education (Matovu et al., 2005; Mpairwe et al., 2005) self-perceived risk (Jerene et al., 2007; Mpairwe et al., 2005), marital status (Matovu et al., 2005) and history of VCT utilization (Matovu et al., 2005) were reported as predictors. We observe greater interest among TB patients who were students or young. This suggests that introduction of VCT testing strategy would be more fruitful if targeted to TB patients with these characteristics.

TB patients offered VCT in a public health centre were notably much more likely to be interested. This points to the importance of structural conditions for effective VCT. As health centres tend to see fewer TB patients than other facilities, health centre workers have more time to communicate about VCT services. The importance of structural factors for interest in VCT was also noted in other studies on TB patients (Jerene et al., 2007; Zachariah et al., 2003). There is a need to ensure supportive conditions, particularly in hospitals, to move forward with integrated TB–HIV surveillance and care.

Finally, referral to VCT services in our study was organized in four central hospitals located in Jogjakarta municipality. Patients interested in VCT were offered incentives for transport. However, this may not have offset the opportunity costs (e.g. being away from work) when travelling to VCT, waiting for the counsellor, undertaking the counselling and testing process, and returning for the results the next day. All this poses barriers to attendance. It has, in particular, been shown that providing the result on the same day increases VCT uptake among clients of a sexually transmitted disease clinic (Kassler et al., 1997) and an AIDS information centre (Kassler et al., 1998). A strong effect of VCT location on uptake was also observed in studies among groups other than TB patients (Corbett et al., 2006; Fylkesnes and Siziya, 2004; Wolff et al., 2005). Expansion of VCT sites into the decentralized DOTS services or establishing mobile VCT units to visit DOTS services may therefore provide substantial leverage.

We have demonstrated that acceptability of unlinked anonymous HIV testing among TB patients is high, and that such surveillance schemes can be implemented in low prevalence settings without much additional effort. However, if Indonesian health authorities want to adopt the current WHO recommendation for linked confidential testing, they must first boost acceptance of this strategy among TB patients. This requires improving access and ensuring availability of time, skills and facilities for VCT services. Taking into account the available resources, such a large undertaking should initially be targeted at students diagnosed in referral hospitals and prioritize provinces with a more advanced HIV epidemic. Likewise, Ministries of Health in other countries with emerging TB–HIV epidemics should not delay introduction of HIV testing among TB patients, after thoughtfully considering the appropriate testing modalities.

Authors' contributions: YM, RAA, TAK, MB, MJW, MEK and PVDS contributed to conception and design of the study; YM, RAA and TAK carried out the field work; MJW and MEK supervised the field work; YM, RAA, MB, MJW, MEK and PVDS contributed to analysis and interpretation of data; YM drafted the paper; RAA, TAK, MB, MJW, MEK and PVDS revised the draft critically for intellectual content. All authors read and approved the final manuscript. YM and PVDS are guarantors of the paper.

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Conflicts of interest: None declared.

Ethical approval: The study protocol was approved by the ethical review committee of the Faculty of Medicine, Gadjah Mada University, Indonesia and endorsed by the Expert Committee of the National TB Control Programme, Republic of Indonesia.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.trstmh.2008.04.042](https://doi.org/10.1016/j.trstmh.2008.04.042).

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