Increasing Tuberculosis Notification Rates Among Young Adults are Not Associated with Migration in Da Nang, Vietnam

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Abstract: Tuberculosis (TB) case notification rates in Vietnam have stabilized since 2000, but in 2007 were increasing among young adults. The emerging HIV epidemic only partly explains this increase. Other factors are probably involved. We aimed to assess whether rural-to-urban migration is such a factor.

We conducted a case-control study at district TB units (DTUs) in Da Nang province, Vietnam, recruiting equal numbers (170) of TB patients aged 15-35 years, TB suspects of the same age in whom TB was excluded, and TB patients of 35 years and older. Risk factors for TB were assessed through interviews using pre-structured questionnaires.

Among persons seeking care at DTUs, migration was not a significant risk factor for TB. Young male migrants had a lower risk of TB than other young adults (odds ratio (OR) 0.4; 95% confidence interval (95%CI) 0.03-0.64). Instead, TB was associated with male sex and a higher level of education. Compared to older TB patients, younger TB patients were more likely to be female, have a higher education level and a job involving indoor contacts with other people.

Migration does not account for the increase in TB case notification rates among young adults in Vietnam. However, migration cannot be excluded as a risk factor for TB in Vietnam, because migrants may not seek diagnosis and treatment for TB at DTUs.

Keywords: Case control, epidemiology, risk factors, rural-urban migration, tuberculosis, Vietnam, KNCV.

INTRODUCTION

Background

With an annual incidence of 180 new tuberculosis (TB) cases (all forms) per 100,00 inhabitants, Vietnam is one of the 22 high burden countries that account for 80% of all new TB cases each year worldwide [1].

The recommended strategy to fight TB, called the directly observed therapy, short course (DOTS) strategy (later revised and broadened to the Stop TB Strategy [2]) was implemented in 1986 in Vietnam. Full country coverage was achieved in 1999 [3]. Since 1996, Vietnam has reached the Stop TB targets (i.e., detection of at least 70% of all new smear-positive TB cases and cure of at least 85% of these) [2]. Meeting these targets was thought to lead to 11% annual reduction in TB incidence rate [4]. However, since 1990 the case notification rates in Vietnam stabilized rather than declined [5]. After 2007, a weak decrease in case notification and estimated incidence rates becomes visible [1].

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Vree *et al.* [5] showed that stabilization in case notification rates was due to a statistically significant increase in case notification rates among young adults, mainly among men aged between 15 and 34 years in urban and remote areas. This increase compensated the decrease in case notification rates observed for other sex and age groups, specially among older women. Correction for diagnostic efforts (defined as the number of TB suspects evaluated per 10,000 inhabitants) did not change the reported trends in case notification rates [5].

In Da Nang, Vietnam, steep increases in TB case notification rates were observed among men aged between 15 and 44 years, most notably in the industrialized districts [6]. The authors speculated that these increases may be related to migration. Migrants often suffer from poverty, malnutrition, crowding, and stress, which may lead to alcohol abuse and smoking [7]. All these are known risk factors for TB [8]. Within-country migration was a risk factor for TB in different studies in Africa and Asia [9,10]. In Vietnam, between 2004 and 2009, 1.9 million people migrated from rural to urban areas, whereas 0.5 million migrated from urban to rural areas. This resulted in a net rural-to-urban migration number of 1.4 million and an urban population growth of 0.57% compared with a decrease of the rural population of 0.23% [11]. The number of rural-to-urban

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migrants is rapidly growing with about 9% per year [12]. In 2009, with a proportion of >10%, Da Nang was among the provinces with the highest proportion of migrants in its population in Vietnam [12].

Technical Assistance Provided by KNCV

In a workshop jointly organized by the Ministry of Health and the national tuberculosis control program (NTP) of Vietnam and KNCV Tuberculosis Foundation (KNCV), the potential reasons for the stabilizing case notification rates overall and the increasing case notification rates among young adults were discussed. Also, an agenda with research questions to be answered was developed. Subsequently, KNCV assisted in different studies to investigate potential causes for stabilizing case notification rates. The emerging HIV epidemic was one of these risk factors. Research indicated that, in high HIV prevalence areas, it is only partly responsible for this increase [13,14].

In a joint project with NTP Vietnam, Da Nang Hospital for Tuberculosis and Lung Diseases, and KNCV, we assessed risk factors for TB among young adults. The project focused on migration and associated factors in order to inform NTP about specific risk factors for TB in Vietnam that could be used for targeting interventions for subgroups experiencing the highest risks of TB.

MATERIALS AND METHODS

Study Site

Da Nang province was selected for this study because it has the second highest net migration rate (after Ho Chi Minh City) [11], with a low HIV prevalence [15] and a well-organized TB control program. Local NTP staff had experience in operational research and had successfully collaborated with KNCV in previous projects.

Study Population and Setting

To identify risk factors for TB in young adults as compared to older TB patients and to TB-free persons of the same age, we conducted a case-control study including three groups. Young adults were aged between 15 and 34 years, as the Vietnamese TB case notification rates showed the largest increase in this age band [5]. Among those visiting a district TB unit (DTU) in Da Nang province for TB suggestive symptoms, we recruited young adults aged 15-34 years diagnosed with TB, TB patients aged 35 years and over, and young adults aged 15-34 years who were found not to suffer from TB based on chest X-ray (CXR) result and sputum smear examination (TB suspects). We included TB suspects in whom TB was excluded rather than a random sample of the general population with the same age for two reasons. First, not everyone in the general population will seek care for cough symptoms at DTUs [16] and therefore, this cannot be regarded as the base population from which the TB cases emerge. Second, TB cannot be excluded in a random sample of population controls.

The study population was prospectively enrolled between December 2008 and December 2009 at all seven DTUs on the mainland of Da Nang province proportional to the DTU's TB case load in 2007. Per DTU, equal numbers of young and older newly diagnosed patients with new smear-positive TB, and young TB-free controls were recruited using TB-suspect registers kept at the DTUs, thus applying frequency matching by DTU. Young TB patients (<35 y) were consecutively enrolled. We intended to recruit all groups over the same recruitment period. Because there were more TB patients aged 35 years and above and TB free controls than young TB patients, every 2nd older TB patient and every 10th TB free control was invited to participate. We enrolled 170 participants per group. This number was calculated using the formula for differences in proportions [17], a desired study power of 80%, a two-sided alpha-level of 5%, and assuming an odds ratio (OR) for specific risk factors of 2, and a risk factor prevalence (i.e., migration) in the control group of 25% assuming that the response rate would be 90% in all groups. Enrolment continued until either the target number of 170 participants per group was reached or the end of data collection, whichever came first.

Definitions

TB cases were newly diagnosed patients with new smear positive TB (i.e. patients who were diagnosed with and treated for pulmonary TB for the first time) aged 15 years and over. TB-free controls were persons without TB aged between 15 and 34 years who visited the same DTUs as cases for similar complaints (i.e., persistent cough) but who were diagnosed as not suffering from TB (i.e., three consecutive AFB-negative smears and no abnormalities on CXR).

Those who were currently on TB treatment or who were chronic TB cases were excluded.

Migration was defined as having a so-called KT-3 or KT-4 residential permit or not having a residential permit for Da Nang province. Residential permits in Vietnam contain one of four KT codes. KT-1 citizens are permanent residents living in their native district. KT-2 citizens are permanent residents in their native province, but do not live in the district in which they are registered. KT-3 citizens have a temporary residence permit of 6-12 months, which can be renewed relatively easily after expiration. KT-4 residents have residence permits for 1 to 6 months and are usually residing in guesthouses or temporary dwellings. Only those registered with KT-1 status can freely use all public services. Others must pay for or are excluded from these services [18]. We considered participants with a KT-3 and KT-4 residential permit and participants who were not registered in Da Nang province at all as migrants.

Recent migration was defined as having the reported KT-code for less than 1 year, or, for non-registered participants, having lived in Da Nang province for less than 1 year.

Data Collection

After obtaining written informed consent, all participants were interviewed using pre-structured questionnaires by trained nurses about their medical status (TB-suggestive symptoms, HIV status, chronic diseases), socio-economic status (education, occupation, housing), and life style, such as smoking, and alcohol and drug use. Questions on migration status included questions about the respondent's ethnicity, place of registration, residence permit (KT status) and how long the respondent was registered with this permit code.

Sputum specimens were collected and examined using direct smear microscopy as according to routine procedures at the DTUs. CXRs were taken of cases and controls and were reread at the Da Nang Hospital for Tuberculosis and Lung Disease (DHTLD), which is the provincial TB reference hospital.

Ethical Approval

The study protocol was approved by Da Nang's City's Council and ethical approval of the protocol was obtained from DHTLD.

Data Entry and Analysis

All data were entered in duplicate in EpiData (http://www.epidata.dk); discrepancies were checked against the crude data. Data analysis was done in Stata/SE version 11.1 (Stata Corporation, College Station, Texas, United States of America). Differences in the distribution of risk factors between groups were statistically tested using Chi-square, Fisher's exact, Wilcoxon rank sum test, Cochran-Armitage test for trend or Student's t-test where appropriate. Because frequency matching was applied rather than one-to-one matching, we used unconditional logistic regression models and adjusted all logistic regression models for DTU of enrollment. We focused the analysis on migration. To explore the potential association between migration and TB, bivariable logistic regression was applied to assess which variables were associated with TB and which were associated with migration. The multivariable logistic regression model included DTU of enrollment and the variables associated to TB and migration ($p<0.2$) that changed the odds ratio (OR) for the association between TB and migration with >10%. The model also included a variable for the observed interaction between sex and migration. The second model evaluated the association between migration and young age among TB patients. We calculated ORs and 95% confidence intervals (95%CIs) for the association between potential determinants of TB among young adults compared to TB-positive controls and TB-free controls. A p-value of <0.05 was considered statistically significant.

RESULTS

Per group, 170 participants were enrolled. The DTU staff did not keep statistics of non-responders. However, based on observations during a monitoring visit towards the end of data collection, we could estimate that about 185 young TB patients, 192 older TB patients and 370 TB-free controls had been invited to participate in this study, resulting in estimated response rates of 91.9%, 88.5% and 45.9%, respectively. Young TB-free controls had a low response rate because the interview could often not be done at the time of TB diagnosis and participants had to revisit the DTU or go to DHTLD for an interview. In contrast, TB patients frequently visited the DTU for treatment so that there were opportunities for an interview. Unfortunately, no information was available from non-respondents so that no conclusions can be drawn on their socioeconomic and residential status.

More than 85% of invited young TB-free adults who visited the DTUs of Son Tra, Lien Chieu and Ngu Hanh Son participated in the study. We compared the characteristics of young TB-free participants in these districts with characteristics of young TB-free participants in other districts. Compared to DTUs with a low participation rate, TB-free controls from the DTUs with high participation rates included higher proportions of migrants (30% *vs* 9%, p=0.001) and more participants obtained a college or university degree (44% *vs* 18%, p=0.006). Also, the proportion of males was slightly higher than in other districts, though the difference with districts with a lower response rate was not statistically significant (34% *vs* 23%, p=0.12). There were no differences with respect to household expenditure (data not shown).

General characteristics of all three groups are displayed in Table **1**. As expected, the mean age of young TB patients was similar to that among TB-free suspects. Men were overrepresented in all groups, but the TB-free control group consisted of significantly fewer men than TB patient groups. Also, there were more men among young than among older TB patients and this difference almost reached statistical significance (p=0.054).

The most commonly mentioned TB-suggestive symptom in all groups was productive cough lasting for at least two weeks. The duration of productive cough was significantly longer among TB patients than among TB-free suspects. Fever, hemoptysis and weight loss were more often mentioned by TB patients than by TB-free suspects. Symptoms did not differ between young and older TB patients (Table **1**).

Only 8.1% of the study population had a known HIV status at the time of the interview, and of these, 2.4% (one case in TB patients of ≥35 year) was infected with HIV.

TB patients more often had a history of smoking than non-patients. Cigarettes were by far the most consumed type of tobacco in this population. The mean number of cigarettes smoked per day was higher among older TB cases than among young TB cases, and the latter were smoking more cigarettes per day than TB-free controls. There were fewer total alcohol abstainers among TB patients than among TB-free controls (Table **1**). Young TB patients were more frequently unemployed than TB-free controls, but less frequently than older TB cases. Compared to both control groups, young TB patients were more frequently self-employed. Odds ratio's for these characteristics are displayed in Table **2**, comparing young adults with TB to young TB-free adults and young TB patients with older TB patients.

There were 49 migrants participating to this study: 16 (32.7%) of these were young TB cases, 26 (53.1%) were young TB free controls, and 7 (14.3%) were older TB cases. Of these, 23 (46.9%) were students. The study populations recruited at the DTUs of Lien Chieu, the most industrialized district of Da Nang province, and Ngu Hanh Son, the main tourist area on the beach, counted the highest proportion of migrants (22% in each). The Lien Chieu study populations counted significantly more migrants than any other district (OR among all groups combined 3.51, 95%CI 1.81-6.78). The DTU of the only rural district in Da Nang province, Hoa Vang, recruited no migrants. Of 49 migrants, only 9 (18.4%) had migrated to Da Nang in the last year before inclusion into the study. Therefore, all analyses concerned all migrants irrespective of length of stay in their current dwelling.

Table 1. Characteristics of the Study Population Including TB Patients Aged 15 Years and Above and Tuberculosis Suspects Visiting District Tuberculosis Units in Da Nang Province, 2008-2009*

Characteristic[#]	TB Patients 15-35y N=170	TB Patients ≥35 y N=170	Adults 15-35y without TB N=170
DTU of enrollment			
Hai Chau	33.5	33.5	33.5
Thanh Khe	18.8	18.8	18.8
Lien Chieu	14.1	14.1	14.1
Son Tra	13.5	13.5	13.5
Cam Le	10.0	10.0	10.0
Hoa Vang	8.2	8.2	8.2
Ngu Hanh Son	1.8	1.8	1.8
Age, mean±SD	25.6±5.5¶	48.0±9.9¶	25.8±5.6¶
Sex, % male	72.4‡,†	81.2‡,†	58.8†
% with TB-suggestive symptom:			
Cough	77.7	79.4	75.9
productive cough (mean duration in wks)	84.1[#] (3.9)	79.4 (4.4)	72.9[#] (2.3)
shortness of breath	14.7	14.7	8.2
Fever	37.7[#]	35.9	21.2[#]
Fatigue	29.4	37.1	28.2
Hemoptysis	15.9†	22.4†	4.1†
chest pain	37.1	42.9[#]	29.4[#]
Night sweats	5.9	3.5	3.5
lost appetite/weight loss	37.7†	32.9†	17.7†
Other	3.5	8.2	3.5
Number of symptoms, median (IQR)	3 (2-4)†	3 (2-4)†	2 (2-3)†
HIV status			
% HIV+	0	0.6	0
% HIV-	12.9†	8.9†	1.8†
% unknown status	87.1†	90.5†	98.2†
White patches/sores in mouth, %	1.2	4.1	4.7
Diabetes mellitus, %	0	2.4	0
Hepatitis B, %	1.2	2.4	0
Ever smoked tobacco, %	42.4[&]	59.4[&]	27.1[&]
Currently smokes tobacco			
% daily	11.8	19.4	19.4
% occasionally	8.2	10.0	3.5
Total %	20.0‡	28.8‡	22.9
Number of cigarettes/day, mean ± SD	5.3±7.7[&]	9.0±10.5[&]	2.7±5.2[&]
Pack-years of smoking, mean ± SD	2.3±4.6[&]	10.0±15.7[&]	1.3±3.4[&]
Consumes alcohol, %	51.2†	59.4†	37.6†
Number of alcoholic cons per month			
% 0	48.8¶	62.4¶	62.4¶
% 1-4	35.3[#]	23.5	23.5[#]
% 5 or more	15.9¶	14.1¶	14.1¶

(Table 1) contd…..

Characteristic[#]	TB Patients 15-35y N=170	TB Patients ≥35 y N=170	Adults 15-35y without TB N=170
Ever used intravenous drugs, %	0.6	1.2	0
Usually spends leisure time in bars, restaurants or taverns, %	13.5	17.1	12.4
Ever stayed in:			
Hospital, %	71.2¶	83.5¶	66.5¶
Prison, %	1.2	4.7[#]	0.6[#]
Boarding school, %	4.7	2.9	1.8
Highest level of education			
% primary school or less	3.5¶	17.1¶	1.2¶
% secondary school	33.5	37.7	37.1
% continued education after secondary school	40.0	33.5	35.9
% college or university	22.9¶	11.8¶	25.9¶
Migrant (KT status 3 or 4), %	9.4‡	4.1[#],‡	15.3[#]
Not registered in Danang or having KT 3 or 4 status for <1 year, %	4.7¶	0.6¶	8.2¶
Work-related migration among recent migrants (n=22), %	37.5 (3 out of 8)	100 (1 out of 1)	38.5 (5 out of 13)
No piped water available in own residence, %	18.8	25.9	23.5
No private flush toilet, %	13.5	15.9	16.5
Roof of house of asbestos, galvanized iron or natural materials, %	70.6	71.4	75.3
Sleeping room has ≤3 walls, %	14.8	11.2	11.2
Household expenditure quartile			
% lowest	20.7	26.5	29.0
% middle lower	30.8	25.3	29.6
% middle higher	22.5	19.9	21.3
% highest	26.0	28.3	20.1
Has no paid job**, %	7.1[&]	16.5[&]	1.8[&]
Self-employed, %	24.7[#]	16.5	15.3[#]
Little to no ventilation at working place, %	20.0‡	31.1[#],‡	16.4[#]
Has job involving contact with many people in closed spaces˜, %	29.4¶	11.8¶	35.3¶

* Abbreviations used in this table: y, year; N, number; DTU, district tuberculosis unit; SD, standard deviation, IQR, inter-quartile range; Tests used are Fisher's exact, Chi-square, t-test or Wilcoxon rank-sum test where appropriate; [&] Statistically significant difference between all groups; [#] Statistically significant difference between these groups; † Statistically significant difference between group 1 and group 3 and group 2 and group 3; ¶ Statistically significant difference between group 1 and group 2 and between group 2 and group 3; ‡borderline statistically significant difference between group 1 and 2 (p<0.06); ** This excludes housewives and retired persons. ˜ This includes the following 'jobs': student, staff at high school (involving contact with students at boarding schools), bus- and taxi driver, policeman/military, health care worker, waiter in restaurant/pub, stewardess, hotel staff, construction workers and hairdresser.

In Table **3**, characteristics of the study population in relation to migration are given. Migrants were younger than Da Nang province long-term residents participating in the study. Also, compared to the long-term resident population, they more often reported having suffered from white patches in the mouth the month before the interview (which is regarded as a sign immunosuppression). Besides, their household expenditure level was lower, but their education level was higher, they were less often unemployed or self-employed, but more often had a job involving contacts with many people in a closed environment (such as taxi driver; Table **3**). Although there was no difference in the proportion of smokers, migrants tended to smoke less cigarettes daily than the long-term residents (p=0.053, Table **3**).

Among young adults, migrating men had a 0.14 times lower risk of TB than others (women and long-term resident men; Table **4**, first column). Vice versa, only men among the long-term resident population had a significantly increased risk of TB if compared with others (women and migrating men; aOR 7.0; 95%CI 1.6-31.3).

There were more migrants among young TB patients than among older patients (9.4% *vs* 4.1%, respectively). In the naive model including migration and district of enrolment only, the association between young age group and migration was almost statistically significant (OR 2.47, 95%CI 0.98-6.22). This near-to-significant association disappeared after adjusting for all confounders (aOR 1.72, 95%CI 0.64-4.62, p=0.28; Table **4**, second column).

Table 2. Bivariable Analyses for the Association of Tuberculosis Among Young Adults and Several Characteristics of the Study Population, Da Nang Province, 2008-2009*

Characteristic	Adults 15-35y with TB Versus Adults 15-35y without TB OR (95% CI)‡	TB Patients 15-35y Versus TB Patients -≥35y OR (95% CI)‡
Age, per year increase	1.00 (0.96-1.03)	NA (no overlap)
Male sex	1.89 (1.18-3.00)	0.59 (0.35-1.00)
TB-suggestive symptoms		
Cough	1.14 (0.64-2.01)	0.87 (0.48-1.58)
productive cough	2.03 (1.17-3.49)	1.39 (0.79-2.43)
Hemoptysis	4.56 (1.91-10.9)	0.65 (0.37-1.13)
shortness of breath	1.95 (0.97-3.93)	1.00 (0.54-1.85)
Fever	2.28 (1.40-3.71)	1.08 (0.69-1.68)
Fatigue	1.06 (0.67-1.74)	0.69 (0.43-1.10)
chest pain	1.46 (0.91-2.36)	0.79 (0.50-1.21)
Night sweats	1.72 (0.61-4.90)	1.73 (0.61-4.93)
lost appetite/weight loss	2.95 (1.76-4.93)	1.24 (0.79-1.95)
Other	1.00 (0.31-3.26)	1.56 (0.53-4.58)
White patches/sores in mouth	0.23 (0.05-1.13)	0.27 (0.06-1.35)
Ever smoked tobacco	2.13 (1.32-3.44)	0.47 (0.30-0.75)
Currently smokes tobacco (p=0.052)	0.82 (0.47-1.43)	0.60 (0.35-1.00)
Cigarettes smoked per day, per cigarette increase	1.92 (1.32-2.79)	0.61 (0.45-0.80)
Consumes alcohol	1.82 (1.16-2.85)	0.70 (0.45-1.09)
Number of alcoholic cons per month		
0	1 (REF)	1 (REF)
1-4	1.97 (1.19-3.26)	1.07 (0.64-1.80)
5 or more	1.51 (0.77-2.96)	0.39 (0.22-0.69)
Usually spends leisure time in bars, restaurants or taverns	1.13 (0.57-2.22)	0.75 (0.41-1.38)
Ever stayed in:		
Hospital	1.31 (0.81-2.12)	0.46 (0.27-0.81)
Prison	2.03 (0.18-23.0)	0.23 (0.05-1.13)
Boarding school	2.80 (0.72-10.9)	1.64 (0.52-5.15)
Highest level of education		
Primary school or less	1 (REF)	1 (REF)
Secondary school	0.29 (0.06-1.54)	4.56 (1.74-11.9)
Cont'd education after secondary school	0.37 (0.07-1.90)	6.26 (2.38-16.5)
College or university	0.29 (0.05-1.52)	10.3 (3.59-29.3)
Migrant (KT status 3/4, or not registered in Danang)	0.56 (0.28-1.10)	2.47 (0.98-6.22)
Not registered in Danang or KT 3/4 status for <1y	0.54 (0.22-1.34)	8.56 (1.05-69.7)
No piped water available in own residence (p=0.056)	0.64 (0.33-1.24)	0.53 (0.28-1.02)
No private flush toilet	0.66 (0.30-1.48)	0.79 (0.40-1.56)
Roof of house of asbestos, galvanized iron or natural materials	0.80 (0.47-1.27)	0.95 (0.59-1.54)
Sleeping room has ≤3 walls	1.42 (0.72-2.79)	1.42 (0.72-2.78)

(Table 2) contd…..

Characteristic	Adults 15-35y with TB Versus Adults 15-35y without TB OR (95% CI)‡	TB Patients 15-35y Versus TB Patients -≥35y OR (95% CI)‡
Household expenditure quartile		
Lowest	1 (REF)	1 (REF)
Middle lower	1.51 (0.82-2.78)	1.61 (0.87-3.01)
Middle higher	1.52 (0.80-2.91)	1.50 (0.77-2.92)
Highest	1.90 (0.99-3.63)	1.20 (0.65-2.24)
Has no paid job**	4.30 (1.18-15.6)	0.38 (0.19-0.78)
Self-employed	1.86 (1.07-3.24)	1.68 (0.98-2.89)
Little to no ventilation at working place	1.29 (0.68-2.44)	0.52 (0.28-0.97)
Has job involving contact with many people in closed spaces†	0.75 (0.47-1.20)	3.18 (1.79-5.65)

*Abbreviations used in this table: TB, tuberculosis; OR, odds ratio; 95%CI, 95% confidence interval; cont'd, continued; REF, reference group; ‡ all odds ratios in this column are adjusted for district TB unit of enrollment; ** this excludes house wifes and retired persons; † This includes the following 'jobs': student, staff at high school (involving contact with students at boarding schools), bus- and taxi driver, policeman/military, health care worker, waiter in restaurant/pub, stewardess, hotel staff, construction workers and hairdresser.

Compared to older TB patients, younger TB patients were more likely to be female, have a higher education level and a job involving indoor contacts with other people.

DISCUSSION

In this case-control study among TB suspects visiting DTUs with TB suggestive symptoms, young male TB patients compared to young TB-free suspects less often had a history of internal migration. Also, among TB patients, a history of migration was not associated to being aged between 15-34 years. Thus, it is unlikely that the recent increases in TB case notification rates among young adults (mainly young men) are explained by increasing rural-to-urban migration.

The bivariable analysis showed associations between TB and male gender, tobacco smoking, and alcohol consumption (Table **2**), in accordance with those reported by many other studies [8,19], or as expected in this Vietnamese population (the male to female ratio among notified TB cases in Vietnam is about 3:1 [20]). However, the association between TB and higher household expenditure level is opposite of what is frequently found, also in Vietnam [21,22]. This inverse association remained borderline statistically significant after controlling for migrant status (Table **4**). Possibly, this is because the poorest patients only seek care for tuberculosis suggestive complaints at a very late stage or not at all since many have to pay for (part of) the public services and are thus not captured in this study [23].

In their paper about trends in TB case notification rates in Da Nang province between 1999 and 2004, Duc and colleagues observed annual increases in case notification rates among young men specially in Lien Chieu (industrial with large factories, but also housing universities, colleges and student dormitories), Son Tra (harbor) and Ngu Hanh Son (main tourist area). They speculated that these increases may be due to new TB among migrants [6]. In our study, the greatest proportions of migrants among the study population were enrolled in Lien Chieu and Ngu Hanh Son (22% of the study population). In contrast to what we expected based on the previous paper [6], in the current study, young male migrants were less likely to get a TB diagnosis than residents. Many of the young male migrants were studying at college or university.

We included TB suspects visiting DTUs since we wanted to test the hypothesis that increasing notifications of young adult TB patients by DTUs might be the result of migration [6]. Possibly, these DTUs only receive a selection of migrants who are relatively well-to-do or have families that can pay the cost of TB treatment. According to national law, migrants are not entitled to free use of public services, including health services, and are either denied access or charged for the services [18]. A small-scale 2003 study conducted in Ha Noi, Ho Chi Minh City and Da Nang focusing on migrants with temporary or no registration found that only 36% of migrants had labour contracts and 99% of respondents had neither social insurance nor work-related accident insurance [24]. In addition, Duong *et al*. reported that migrants usually do not seek care at public (9%) or private (1%) health facilities but rather go for self-treatment (81%) when being ill. Of those seeking care at public facilities, 67% had to pay out of pocket for the services [18].

Indeed, data of the General Statistics Office (GSO) suggest that DTUs do not capture the total migrant population. We enrolled 49 participants with no registration status, KT-3 or KT-4 status (9.6% of the total study population), only 9 (1.8%) of whom immigrated in the past year. In contrast, Da Nang province had a net migration rate of 15.3% in 2009, corresponding to 77 migrants per 1000 inhabitants (7.7%; [11]).

We found a statistically significant interaction between migration and sex (p=0.01; Table **4**). TB-free men more often had a history of migration than male TB patients. Among females, a history of migration was more frequently reported by TB patients than by TB-free controls, although the latter was far from statistically significant. Although the differences in education and expenditure level between migrants and long-term residents were more extreme among men than among women, our data offer no clear explanation for this interaction.

Our study has limitations. First, as explained above, we selected TB suspects visiting DTUs for this study. However,

Table 3. Association Between Characteristics of the Study Population and Migration in Danang Province, 2008-2009*

Characteristic	Migrant** N=49	Not a Migrant N=461	p-Value¶
DTU of enrollment			
Hai Chau	26.5	34.3	0.28
Thanh Khe	12.2	19.5	0.22
Lien Chieu	32.7	12.2	<0.001
Son Tra	12.2	13.7	0.78
Cam Le	12.2	9.8	0.58
Hoa Vang	0	9.1	0.03
Ngu Hang Son	4.1	1.5	0.20
Age, mean±SD	28.9±9.6	33.7±13.0	0.005
Sex, % male	71.4	70.7	0.92
% with TB-suggestive symptom:			
Cough	79.6	77.4	0.73
productive cough	69.4	79.9	0.09
shortness of breath	14.3	12.4	0.70
Fever	28.6	31.9	0.64
Fatigue	40.8	30.6	0.14
Hemoptysis	18.4	13.7†	0.37
Night sweats	4.1	4.3	0.93
chest pain	30.6	37.1	0.37
lost appetite/weight loss	28.6	29.5	0.89
Other	4.1	4.1	0.99
Unknown HIV status, %	100	91.1	0.09
White patches/sores in mouth, %	8.2	2.8	0.048
Ever smoked tobacco, %	34.7	43.8	0.22
Currently smokes tobacco,%	18.4	24.5	0.34
Mean number of cigarettes/day ±SD	3.4±6.0	5.9±8.7	0.053
Consumes alcohol, %	55.1	50.1	0.51
Usually spends leisure time in bars, restaurants or taverns, %	18.4	13.9	0.39
% ever stayed in:			
Hospital	65.3	74.8	0.15
Prison	0	2.4	0.27
Boarding school	4.1	3.0	0.69
Highest level of education			<0.001
Primary school or less	4.1	7.6	
Secondary school	16.3	38.2	
Continued education after secondary school	22.5	38.0	
College or university	57.1	16.3	
No piped water in own residence, %	28.6	22.1	0.31
No private flush toilet, %	22.5	14.5	0.14
Roof of house of asbestos, galvanized iron or natural materials, %	69.3	72.8	0.62

(Table 3) contd…..

Characteristic	Migrant** N=49	Not a Migrant N=461	p-Value¶
Sleeping room has ≤3 walls, %	16.3	11.9	0.38
Household expenditure quartile			<0.001
Lowest	62.5	21.5	
Middle lower	16.7	29.8	
Middle higher	6.3	22.8	
Highest	14.6	25.9	
Has no paid job, %†	4.1	16.7	0.02
Self-employed, %	6.1	20.2	0.02
Little to no ventilation at working place	19.5	22.0	0.71
Has job involving contact with many people in closed spaces‡	55.1	22.3	<0.001

* Abbreviations used in this table: N, number; SD, standard deviation; DTU, district tuberculosis unit; ** A migrant either had KT3 or KT4 status, or was not registered in Danang province at the time of enrollment in the study; ¶ p-values were calculated using Chi-square, T-test or Cochran-Armitage test for trend where appropriate; † This excludes house wives and retired persons. ‡ This includes the following 'jobs': student, staff at high school (involving contact with students at boarding schools), bus- and taxi driver, policeman/military, health care worker, waiter in restaurant/pub, stewardess, hotel staff, construction workers and hairdresser.

Table 4. Multivariate Models for the Association Between TB Among Young Adults and Migration Adjusted for All Other Factors in the Table for which an Odds Ratio (OR) is Presented*

Risk Factor	Among Young Adults (15-34y): TB Patients *vs* TB-Free Controls OR (95% CI)	Among TB Patients: Patients 15-34y *vs* Patients ≥35 y OR (95% CI)
Migrant	2.72 (0.76-9.70)	1.72 (0.64-4.62)
Male	2.51 (1.50-4.17)	0.54 (0.30-0.96)
Male migrants	0.14 (0.03-0.64)	--
All others	1 (REF)	--
Household expenditure quartile		
Lowest	1 (REF)	--
Middle lower	1.39 (0.72-2.66)	--
Middle higher	1.59 (0.79-3.19)	--
Highest	1.85 (0.93-3.67)	--
Education level		
Primary school or less	--	1 (REF)
Secondary school	--	4.54 (1.72-12.0)
Continued education after secondary school	--	5.61 (2.11-15.0)
College or university	--	7.01 (2.37-20.7)
Job involving contacts with many people indoors†	--	2.47 (1.34-4.56)

* Multivariate models also included district TB unit (DTU) of enrollment because frequency matching was applied by DTU. However, odds ratios are not shown in this table since these were around 1 and far from statistically significant. Abbreviations in this table: TB, tuberculosis; y, year; *vs* versus; OR, odds ratio; 95% CI, 95% confidence interval; † This includes the following 'jobs': student, staff at high school (involving contact with students at boarding schools), bus- and taxi driver, policeman/military, health care worker, waiter in restaurant/pub, stewardess, hotel staff, construction workers and hairdresser.

migrants often do not seek care with public health facilities as was shown in studies conducted in China (which has a similar TB control program and residential registration system as Vietnam). These reported that migrants are less likely to seek care for TB suggestive symptoms than permanent residents [23,25], even after at least 3 months of suffering from these symptoms [25]. Migrants have a lower income and level of education, lack health insurance and social support, and face intensive working schedules [23,24]. Recruiting the control group from DTUs was done a) because we sought explanations for the increase in TB case notification rates reported by DTUs among young adults [6], and b) because controls should arise from the same base population as the cases come from [26]. While our study found no association between TB and migration among people seeking care at DTUs, it probably underestimated the risk of TB among migrants, since especially the most vulnerable groups do not seek care at DTUs (see also above).

Second, less than half of the TB suspects that were not diagnosed with TB agreed to participate in the study, versus

>90% in the other two groups. Non-response analysis showed that the participation rate did vary by DTU. Unfortunately, of the non-responders, no data were available on sex and socio-economic status. We conducted a sensitivity analysis only including the three DTUs that achieved a participation rate in all three groups of >85% (n=150 participants; 50 in each group): Son Tra, Lien Chieu and Ngu Hanh Son. Except for a higher proportion of migrants recruited in these DTUs compared to other DTUs, no other differences were foun. Migration was inversely associated with TB (OR adjusted for DTU of recruitment 0.24, 95%CI 0.08-0.75). Although we cannot estimate the impact of higher participation rates among TB-free controls on the association between TB and a history of migration, it seems unlikely that migration would have become a risk factor for TB in this setting.

Third, we interviewed the participants to assess risk factors for TB. Known challenges of collecting data by interview are recall bias, withholding sensitive information and lack of specificity for some of the answers. To limit the risk of recall bias, all participants were recruited at the time of diagnosis an interviewed as soon as possible after obtaining informed consent. Migration was self reported. As migrants in Vietnam have little status, migrants may feel stigmatized and this may have lead them not to reveal their status.

Fourth, HIV status was not known for most participants (91.9%) at the time of the interview, although TB patients should be tested for HIV according to the national TB guidelines [27]. HIV status was significantly more often unknown among young adults without TB than among TB cases. Hairy leukoplakia is an important indicator of HIV infection, and also oral candidiasis frequently occurs among persons living with HIV [28]. Therefore, we asked participants if they had observed white patches in their mouth during the past 2 months. However, though white patches can be caused by HIV infection, other common causes are smoking, alcohol consumption, and cancer [29], all of which are prevalent in Vietnam [30]. A history of oral white patches was not associated with TB or with smoking or drinking, but it was associated with two out of four typical TB symptoms among HIV-positives: night sweats and weight loss (OR and 95% CI 8.10 (2.40-27.3) and 2.82 (1.07-7.48), respectively).

Fifth, the study was conducted in Da Nang province, which has the second highest net migration rate in Vietnam, but is not comparable to the largest urban center Ho Chi Minh City that attracts many more migrants [11] and has a much higher HIV prevalence than Da Nang [14]. The population in Da Nang city is well educated compared to most other urban centers in Vietnam. In 2009, it had the highest net enrollment rate at college and university at 50.6% and after Hanoi, it had the highest proportion of population with a college or university degree (41.6 *vs* 38.4%) [31]. Other (urban) provinces may show different risk profiles. To provide the Vietnamese NTP with a representative picture of TB in migration in Vietnam, a study in more (types) of provinces is needed.

CONCLUSIONS AND RECOMMENDATIONS

Among TB suspects visiting DTUs because of complaints, migration was not a risk factor for TB, and this study does not provide evidence for a contribution of migration to increased case notification rates among young adults. However, other types of studies need to be done, including surveys among migrant populations using active case finding strategies, to sort out the association between migration and TB in Vietnam.

ABBREVIATIONS

95% CI = 95% confidence interval

CXR = Chest X-ray

DHTLD = Da Nang Hospital for Tuberculosis and Lung Disease

DOTS = Directly observed treatment, short course

DTU = District tuberculosis unit

KNCV = KNCV tuberculosis foundation (KNCV is a Dutch abbreviation standing for Royal Dutch Central Association)

NTP = National tuberculosis (control) program

OR = Odds ratio

TB = Tuberculosis

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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