Title: Tuberculosis outcomes and mortality risk factors in adult migrants at the Thailand-Myanmar border

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SUMMARY

Background: Migrants in high prevalence areas are at higher risk of tuberculosis (TB). We aimed to identify the causes and risk factors for TB mortality at a migrant-focused TB programme on the Thailand-Myanmar border.

Methods: Routinely collected data on TB cases, treatment outcomes and causes of death were analysed for adult TB cases diagnosed between January 2013–April 2017. Mortality in the six months post-diagnosis was calculated and risk factors were identified using multivariable Poisson regression.

Results: 1344 TB cases were diagnosed; 1005 started treatment and 128 died. Case fatality was 9.5% and the TB mortality rate was 2.4/100 pm. Case fatality was highest in TB/human immunodeficiency virus (HIV) coinfected cases not on antiretroviral therapy (ART) (90.3%), compared to those on ART (14.3%) and those with negative or unknown HIV status (9.3%). Mortality risk factors included older age, HIV and missing data. Deaths were mostly due to pulmonary TB in the first month, while comorbidities or HIV-related infections predominated in later months.

Conclusions: Programme mortality was high among those with HIV, although mortality differed vastly depending on receipt of ART. Strategies to extend TB/HIV screening among migrants and safeguard the continuity of TB care should be prioritised to improve outcomes.

Tuberculosis (TB) control across international borders is a challenge. Diagnostic delays and treatment interruption are more common in mobile populations and lead to poor outcomes.[1,2] Thailand and Myanmar, two neighbouring countries in Southeast Asia, are among the thirty high-burden TB countries globally. Both have high triple burdens of TB, TB and human immunodeficiency virus (HIV) coinfection, and multi-drug resistant TB (MDR-TB).[3] HIV prevalence in both countries is high (1.1% and 0.7% among adults respectively), with migrants in Thailand estimated to have up to four times the HIV prevalence found among the general population, amplifying their risk of developing and dying from TB.[4] Decades of conflict and economic stagnation in Myanmar have resulted in increased population mobility at the Thailand-Myanmar border, with migrants seeking better living conditions and healthcare in Thailand. The cross-border population is marginalised, and lack access to TB/HIV services and information.[5] Mobile patients with TB living outside of refugee camps were excluded from provincial and national statistics up until 2016, and there have been no previous studies reporting TB outcomes or case fatality rates among non-encamped migrants. The invisibility of this rural-dwelling population hampers efforts to understand the extent of their health challenges.[5,6,7] In this study, we sought to identify the demographic and clinical predictors of TB mortality in a cohort of adult migrants from the time of TB diagnosis, and to determine the cause of death in a subgroup of patients.

METHODS

Setting

The displaced population size at the Thai-Myanmar border is estimated at between 200,000 and 500,000, including 127,000 people living in refugee camps.[8] The study setting was two TB clinics run by Shoklo Malaria Research Unit (SMRU), a non-governmental organisation and field research unit linked to the Mahidol-Oxford Tropical Network that provides healthcare to Myanmar migrants. Patients presented to the SMRU TB clinics located on either side of the border: Kou Ko clinic (Myanmar), Wang Pha clinic (Thailand), or were referred after TB diagnosis from Mae Tao Clinic (Thailand), which is run by a separate organisation (Figure 1). The SMRU TB clinics provide a comprehensive package of care, with basic accommodation, psychosocial support and TB health education throughout the course of treatment.

Study design

All TB cases were identified from SMRU's pre-existing TB database, where demographic information, treatment details and clinical outcomes of all patients (all ages) were documented (n=1,697). This retrospective cohort study included all adult (≥16 years old) TB cases diagnosed at SMRU either clinically or bacteriologically between January 2013 and April 2017 (n=1,344) (Figure 2). Pulmonary tuberculosis was defined as involvement of the lung parenchyma or the tracheobronchial tree, including cases with evidence of extra-pulmonary spread. Extrapulmonary TB (EPTB) was defined as localisation of disease in organs other than the lungs. TB cases were classified as bacteriologically confirmed when either microscopy (Ziehl-Neelsen smear) or GeneXpert (rapid molecular test) were positive, while clinically-diagnosed cases had typical symptomatology, chest X-ray appearances or histopathological findings (EPTB) with negative or absent bacteriological tests. At

the SMRU TB clinics, samples that were smear and/or Xpert-positive were sent to the International Organisation for Migration TB Laboratory in Mae Sot, Thailand, for confirmatory testing using conventional culture and drug sensitivity testing (DST).[9] HIV tests were done at the start of TB treatment for all patients enrolled.

New TB cases had never received treatment for TB or had taken anti-TB drugs for less than one month. Retreatment cases (including relapse cases) had received one month or more of anti-TB drugs in the past.[10] TB treatment was given in accordance with WHO treatment guidelines (2010).[11] New or relapse cases were treated with a Category I regimen (2HRZE/4HR), while other retreated patients received Cat II (2SHRZE/HRZE/5HRE), and patients with drug intolerances, drug resistance, or EPTB received longer courses of non-Category I regimens or specific MDR-TB regimens. Treatment outcomes are defined in line with WHO criteria.[10]

As a second step, additional information was collected from medical records for cases enrolled between January 2015 and April 2017 whose outcome was death (total n=84, total records available n=68). The medical notes and death certificates of 68 patients (written in English) were reviewed. Information on primary and contributing causes of death, test results and co-morbidities was extracted. Deaths were classified into three broad categories: TB-related deaths, AIDS-related deaths, and other medical causes, similar to previous studies.[12,13,14] In cases where the primary cause of death was unclear (n=8, 12.0%), the case was discussed with the team of TB/HIV doctors familiar with local patterns of pathology to determine how to categorise the death.

Analysis

The timing and cause of death were the primary outcomes. Follow-up for each patient began on the day of first smear test and ended six months later, or when death, loss-to-follow-up or transfer preceded this. Date of first smear was used as a proxy for date of diagnosis. The rationale for including pre-treatment cases was that many patients were critically unwell at presentation and died in the intervening period between diagnosis and starting TB treatment. For EPTB patients, date of initiation of TB treatment was used when this preceded the initial smear date as there were often delays in obtaining a sample. Data were censored at six months to understand overall programme mortality during the standard period of treatment, when most deaths occur. Statistical analysis was performed using STATA/IC 14.2.

Kaplan Meier estimates for cumulative case fatality and mortality per 100 TB pm with 95% CI were calculated for each consecutive month after TB diagnosis. This technique was used to provide mortality estimates that take in to account attrition during the six-month follow-up period after enrolment. Cumulative case fatality and mortality were then calculated after stratification by HIV/ART status for two intervals (first and 2nd–6th month).

Incidence rate ratios (IRRs) and corresponding 95% CIs were used to quantify differences in mortality between groups using Poisson regression. The multivariable models included age and gender *apriori*, and a broad inclusion criterion of p≤0.20 in univariable analysis was used for selection of other clinical or programme variables. Interaction terms were used to check for effect modification.

The variable for treatment regimen had significant collinearity with MDR-TB, and was excluded from the multivariable models.

Ethical approval was obtained from the University College London (UCL) Ethics Committee, United Kingdom (13003/001).

RESULTS

Study population and programme outcomes

Between January 2013 and April 2017, 1,344 diagnoses of tuberculosis in adults were made at SMRU, and of these, 1,005 started treatment (Table 1). The median age was 38 years (IQR 30–50). There were approximately equal proportions of Burmese (31.4%) and Karen (32.3%) ethnicity. A further 3.4% were from other Myanmar minority ethnic groups, and 32.9% had undocumented ethnicity.

Most patients had pulmonary TB (91.8%). A high proportion had TB/HIV co-infection (18.5%) and 16.4% of the cohort were already on ART. Among those with HIV, 71.0% were new diagnoses. The cohort consisted of 179 (17.8%) patients who did not receive the Category I treatment regimen. This includes the 100 MDR-TB patients, and a further 79 who had mono or poly-drug resistant TB, or allergies to first line drugs. The overall treatment success rate was 79.8% for all TB cases enrolled. Treatment success rates were lowest among those with MDR-TB (73.3%) and TB/HIV co-infection (70.2%).

Case fatality and mortality

A total of 831 cases completed six months of follow-up, and 128 died overall. Transfers out (211 cases, 15.7%) and losses to follow-up (121 cases pre-treatment and 48 cases following enrolment, 12.6%) accounted for a large proportion of remaining cases (Table 1).

There were 128 deaths, with an overall case fatality of 9.5% (Table 1). The mortality rate was 2.4 per 100 TB person-months (pm) (Table 2). The cumulative case fatality, which takes into account attrition following enrolment, was 12.3% (Table 2). Mortality was highest in the first month after diagnosis (5.5/100 pm), and declined over the subsequent months. When stratified by HIV and ART status (Table 3), cumulative case fatality was lower among those with negative or unknown HIV status (9.3%) compared to HIV-positive cases on ART (14.3%) and off ART (90.3%).

Factors associated with early and late death

Risk factors for death were analysed overall (Table 4) and separately for the first and 2nd–6th months following TB diagnosis (Supplementary Tables). Death was more likely in those aged over 55 years (IRR 3.29, CI 1.99–5.45), with undocumented ethnicity (IRR 2.87, CI 1.84–4.48) or undocumented TB history (IRR 2.31, CI 1.07–4.98), and those who were HIV-positive (on ART (IRR 1.99, CI 1.23–3.23), off ART (IRR 36.67, CI 19.99–67.28)) when analysed for the whole 6-month period.

When stratified by time since diagnosis, the risk factors differed. Early mortality was associated with smear positive TB and MDR-TB, while retreatment TB cases had a higher risk of death in the later months. Advanced age remained a strong independent predictor of late mortality.

HIV-positive patients off ART had a high risk of death both early (IRR 27.70, CI 12.45-61.62) and late (IRR 55.36, CI 21.11-145.18) after diagnosis compared to HIV-negative patients, while being on ART was associated with late death only (IRR 3.05, CI 1.66-5.59) compared to HIV negative patients. There was no evidence of an association with calendar period in the univariable or multivariable models.

Clinical causes of death

In the subgroup of patients where medical notes were reviewed (Table 5), pulmonary TB was the dominant cause of early death. Other medical conditions that were non-AIDS and non-TB related accounted for second highest number of deaths overall, mostly occurring during the 2nd–6th months. Opportunistic fungal infections (pneumocystis pneumonia, penicilliosis, cryptococcosis) were leading causes of late death among patients with HIV.

DISCUSSION

This retrospective cohort study reports outcomes from a TB programme at the Thailand-Myanmar border from 2013–April 2017. Overall case fatality was high (9.5%), with over a quarter of early deaths among patients who had not started TB treatment (33/128). The high pre-treatment losses to follow-up (121 cases, 9.0%) is concerning and reflects the logistical difficulties of following patients up in this setting. Patients are often uncontactable, with no telephone number or address, and are therefore instructed to return to the clinic to collect their results in person within 2 or 3 days. This may not be economically feasible for highly mobile migrants, who are often employed precariously in seasonal jobs. Among those enrolled in treatment following TB diagnosis, the availability of TB education and psychosocial support early on resulted in better retention.

Overall, 79.8% completed treatment successfully. Although this falls short of the WHO target of 85%, it compares favourably to outcomes reported by studies in similar settings in migrant and refugee populations (74.3%, 77.5%).[15,16] Our results suggest that this programme, with its residential setting and availability of social support, is well adapted to the needs of mobile patients and supports engagement with treatment.[17]

Early mortality was more likely in smear positive and MDR-TB patients, both of which imply clinically severe TB. Deaths among patients presenting with advanced disease were likely unavoidable. Our study lacks information about patient illness severity and duration of symptoms, however the high number of pre-treatment deaths and physiological compromise observed by clinicians at presentation suggest that in many cases there were very long delays before accessing effective medical care. Earlier diagnosis through community engagement and better availability of health information would reduce mortality. There was a high burden of TB/HIV co-infection among this population and these patients had much poorer outcomes. Mortality rates were highest among those not on ART. ART guidelines in Thailand have evolved in recent years, following strong evidence that early initiation of ART reduces mortality and incidence of new OIs among TB/HIV coinfected patients.[18] However, physicians may have still been reluctant to start ART in TB patients with advanced HIV infection due to risk of immune reconstitution inflammatory syndrome (IRIS).[19]

The majority of patients in this cohort did not know their HIV status at presentation. Tackling HIV infection through earlier detection and initiation of ART prior to developing TB would save lives. There is no ART coverage for non-Thai migrants without health insurance, which makes it unaffordable for most migrant labourers. Expansion of migrant-friendly health services are urgently needed to support ART coverage among non-Thai populations living in Thailand, particularly those with TB.[20]

Consistent with studies conducted in Thailand and elsewhere, TB mortality was highest in the first month, with pulmonary TB accounting for the majority of early deaths, while AIDS-related deaths and deaths due to other comorbid conditions were more common in later months.[12,14] There was a surprisingly large number of deaths due to non-TB, non-HIV related causes, particularly congestive cardiac failure and lung cancer. Since non-infectious cardio-respiratory conditions often mimic the symptomatology of TB, and in the absence of onward referral options, the TB clinics inadvertently become a site for end of life care in smear negative terminally ill patients.

There was no effect of ethnicity on outcome. This result differs from a study performed at the Thai-Myanmar border during the time of armed conflict, where Burmese migrant patients were more likely to die, become lost to follow-up, or fail treatment compared to encamped Karen refugees.[15] A study conducted in Khartoum, Sudan by Bohler et al (2005) similarly reported better outcomes in encamped patients compared to those living outside the camps. Our study, performed six years after the ceasefire reflects a more heterogenous population of non-encamped migrants, who face more barriers to accessing services (low knowledge about services, travel costs and lost wages, concerns regarding legal status and language barriers).[17,21]

The main strength of this study is that it quantifies TB mortality from the time of TB diagnosis rather than from start of treatment. Only one other study in a high TB incidence setting has quantified pre-treatment deaths, and found that previously recorded programme case fatality rates consistently underestimated true TB mortality.[22] In our study there were, however, large initial losses to follow-up and transfers out with unknown outcomes, which biases our results and likely leads to underestimation of case fatality. Additionally, there were small numbers in some sub-categories and results with wide CIs should be interpreted with caution. Follow-up on patients who were lost-to-follow up was censored on this date, and so were assumed to be non-informative for the outcome of death. The validity and reliability of causes of death relied on the quality of the primary data recorded by certifying physicians, and budget constraints and geographical distance to other facilities restricted access to confirmatory diagnostic tests, potentially resulting in misdiagnosis.

The situation along the Thai-Myanmar border is dynamic. The results of this study show that a residential TB programme can achieve good outcomes in migrant populations, although reducing pre-treatment mortality and losses to follow-up is a challenge. In this low resource setting, effective and sustainable interventions are needed to boost community engagement so that potential TB cases seek care earlier. This work adds to the body of literature demonstrating disproportionately high risk of TB mortality among HIV-positive individuals, particularly those not on ART. Improving migrants' access to HIV testing and ART and strengthening of cross-sectoral and cross-border collaboration is key to improve outcomes.

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Table 1: Patient characteristics for 1344 TB cases diagnosed and 1005 TB cases started on treatment between January 2013 and April 2017

		All TB cases		TB cases started on treatment	
		n	%	n	%
Total		1344	100	1005	100
Gender*	Male	890	66.3	661	65.8
	Female	452	33.7	344	34.2
Age at diagnosis*	<35	501	37.3	374	37.2
	35-54	583	43.4	441	43.9
	>55	255	19.0	190	18.9
Ethnicity	Burmese	422	31.4	398	39.6
	Karen	434	32.3	415	41.3
	Other	46	3.4	44	4.4
	No data	442	32.9	148	14.7
TB site	Pulmonary	1234	91.8	921	91.6
	Extra-pulmonary†	110	8.2	84	8.4
Year of diagnosis	2013-2014	541	40.3	416	41.4
	2015-2017	803	59.7	589	58.6
Smear result	Positive	825	61.4	588	58.5
	Negative	462	34.4	374	37.2
	No data	57	4.2	43	4.3
GeneXpert assay	Positive	916	68.2	642	63.9
	Negative	256	19.0	217	21.6
	No data	172	12.8	146	14.5
Case type	New	888	66.1	863	85.9
	Retreatment	144	10.7	135	13.4
	Unknown	312	23.2	7	0.7
Drug susceptibility	Non-MDR-TB	1244	92.6	930	92.5
	MDR-TB	100	7.4	75	7.5
Treatment regimen	Category I	826	61.5	826	82.2
	Non-Category I	179	13.3	179	17.8
	Not started‡	339	25.2	-	-
HIV/ART status	Negative/unknown	1096	81.5	765	76.1
	Positive: ART	220	16.4	220	21.9
	Positive: no ART	28	2.1	20	2.0
Outcome	Cure/complete	802	59.7	802	79.8§
	Failed	13	1.0	13	1.3
	Lost to follow-up	169	12.6	48	4.8
	Not evaluated§§	232	17.3	47	4.7
	Died	128	9.5	95	9.5

* Gender: data missing for 2 cases. Age at diagnosis: data missing for 5 cases.

† Extra-pulmonary TB cases were at the following sites: 28 meningeal, 15 pleural, 26 lymph node, 18 abdomen, 9 spine, 2 renal, 1 bone, 1 skin, 1 joint, 1 eye and 9 undocumented sites.

‡ Treatment not started in 33 TB cases dying before starting treatment, 168 cases that were transferred to other care providers prior to initiating treatment, 17 cases that had no recorded treatment outcome and 121 cases that were lost to follow-up.

§ Treatment success rates were 70.2% for TB/HIV co-infection and 73.3% for MDR-TB.

§§ Not evaluated: includes 211 (15.7%) TB cases that were transferred to other care providers either before or after starting treatment, and 21 (1.6%) that had no recorded treatment outcome.

TB = tuberculosis; MDR-TB = multi-drug resistant TB; HIV = human-immunodeficiency virus; ART = antiretroviral therapy; IRR = incidence rate ratio; CI = confidence interval.

299 Table 2: Case fatality, mortality rate and risk of death by month since TB diagnosis

Time since diagnosis	Number at risk	Number of deaths	Cumulative case fatality (%)*	Person months	Rate per 100pm (monthly) (95% CI)	IRR (95% CI)	p value
1st month	1344	56	5.0	1024	5.5 (4.2-7.1)	1.00	-
2nd month	953	32	8.2	934	3.4 (2.4-4.8)	0.63 (0.41-0.97)	0.03
3rd month	915	19	10.1	898	2.1 (1.3-3.3)	0.39 (0.23-0.65)	<0.001
4th month	887	9	11.0	875	1.0 (0.5-2.0)	0.19 (0.09-0.38)	<0.001
5th month	867	4	11.4	857	0.5 (0.2-1.2)	0.09 (0.03-0.24)	<0.001
6th month	850	8	12.3	842	1.0 (0.5-1.9)	0.17 (0.08-0.36)	<0.001
Overall	1344	128	-	5430	2.4 (2.0-2.8)	-	-

300 * Kaplan Meier estimates used to take into account attrition and differing lengths of follow-up.

301 TB = tuberculosis; IRR = incidence rate ratio; CI = confidence interval; pm = person months.

Table 3: Case fatality, mortality rate and risk of death by month since TB diagnosis, by HIV and ART status

HIV status	Time since diagnosis	Number at risk	Number of deaths	Cumulative case fatality (%)*	Person months	Rate per 100pm (monthly) (95% CI)	IRR (95% CI)	p value
Negative /unknown	1st month	1096	39	4.3	790	4.9 (3.6-6.8)	1.0	-
	2nd-6th month	729	37	9.3	3440	1.1 (0.8-1.5)	0.22 (0.14-0.34)	<0.001
	Overall	1096	76	-	4230	1.8 (1.4-2.2)	-	-
Positive ART	1st month	220	4	1.8	218	1.8 (0.7-4.9)	1.0	-
	2nd-6th month	214	27	14.3	950	2.8 (1.9-4.1)	1.55 (0.54-4.42)	0.42
	Overall	220	31	-	1168	2.7 (1.9-3.8)	-	-
Positive No ART	1st month	28	13	51.5	16	80.3 (46.7-138.4)	1.0	-
	2nd-6th month	10	8	90.3	16	50.9 (25.5-101.8)	0.63 (0.26-1.53)	0.31
	Overall	28	21	-	32	65.9 (42.9-101.0)	-	-

* Kaplan Meier estimates used to take into account attrition and differing lengths of follow-up.

TB = tuberculosis; HIV = human-immunodeficiency virus; ART = antiretroviral therapy; IRR = incidence rate ratio; CI = confidence interval; pm = person months.

309 Table 4: Risk factors for death in 1339 TB cases
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	Category	Total (n)	Deaths (n)	Unadjusted IRR (95% CI)	p value	Adjusted IRR* (95% CI)	p value
Gender	Male	887	83	1.0	0.85	1.0	0.33
	Female	452	44	1.03 (0.72-1.49)		1.21 (0.83-1.76)	
Age category	16-34	501	36	1.0	<0.001	1.0	<0.001
	35-54	583	55	1.35 (0.89-2.06)		1.28 (0.82-1.98)	
	>55	255	36	2.06 (1.30-3.27)		3.29 (1.99-5.45)	
Ethnicity	Burmese	422	44	1.0	<0.001	1.0	<0.001
	Karen	434	32	0.66 (0.42-1.05)		0.91 (0.55-1.50)	
	Other	46	4	0.78 (0.28-2.18)		1.00 (0.36-2.82)	
	Unknown	437	47	2.80 (1.86-4.22)		2.87 (1.84-4.48)	
TB site	Pulmonary	1230	112	1.0	0.15	1.0	0.16
	Extra-pulmonary	109	15	1.52 (0.89-2.61)		1.60 (0.85-3.03)	
TB history	New	888	96	1.0	<0.001	1.0	0.14
	Retreat	143	22	1.50 (0.95-2.39)		1.10 (0.64-1.89)	
	No data	308	9	7.51 (3.91-14.40)		2.31 (1.07-4.98)	
Smear result	Negative	460	47	1.0	<0.001	1.0	0.54
	Positive	822	67	0.86 (0.60-1.25)		1.21 (0.80-1.86)	
	No data	57	13	2.79 (1.51-5.15)		1.34 (0.66-2.75)	
Year diagnosed	2013-2014	537	43	1.0	0.11	1.0	0.44
	2015-2017	802	84	1.34 (0.93-1.93)		1.16 (0.79-1.72)	
HIV status	Negative/unknown	1091	75	1.0	<0.01	1.0	<0.001
	Positive: ART	220	31	1.48 (0.97-2.24)		1.99 (1.23-3.23)	
	Positive: no ART	28	21	36.65 (22.60-59.41)		36.67 (19.99-67.28)	
MDR-TB	No	1242	113	1.0	0.16	1.0	0.31
	Yes	97	14	1.52 (0.87-2.65)		1.40 (0.70-2.79)	

311 * All variables displayed in the table were included in the adjusted model.
312 TB = tuberculosis; MDR-TB = multi-drug resistant TB; HIV = human-immunodeficiency virus; ART = antiretroviral therapy; IRR
313 = incidence rate ratio; CI = confidence interval

Table 5: Clinical causes of death by month since TB diagnosis for 68 deaths occurring between January 2015 and April 2017

		1st month (n)	2nd-6th month (n)	Total (n, %)
Clinical cause of death (n, %)		36 (52.9)	32 (47.1)	68 (100)
TB-related	Pulmonary TB	22	8	35 (51.5)
	CNS TB	3	1	
	TB spine	1		
AIDS-related	Pneumocystis pneumonia	1	2	14 (20.6)
	Disseminated fungal infection*		3	
	Cryptococcal meningitis		2	
	Other†	3	3	
Other medical	Congestive cardiac failure	2	3	19 (27.9)
	Lung cancer	1	3	
	Hepatic disorder	2		
	Other cancer	1	1	
	Other‡		6	

* Disseminated fungal infection: penicilliosis (n=2) and one with unknown opportunistic fungal pathogen.

† Other 1st month: *M. Avian* complex, chronic diarrhoea, cytomegalovirus pancreatitis; other 2nd-6th month: HIV encephalopathy, *M. Avian* complex, atypical pneumonia.

‡ Other: deaths due to sepsis (n=2), stroke, renal disorder, transverse myelitis and aspiration of vomitus.

TB = tuberculosis; HIV = human-immunodeficiency virus; AIDS = acquired immune deficiency syndrome; CNS = central nervous system.

Supplementary Table 1: Risk factors for death during the first month after TB diagnosis

	Category	Deaths (n)	Unadjusted IRR (95% CI)	p value	Adjusted IRR* (95% CI)	p value
Gender	Male	40	1.00	0.84	1.00	0.56
	Female	15	1.02 (0.71-1.47)		0.84 (0.46-1.53)	
Age category	16-34	20	1.00	0.01	1.00	0.04
	35-54	20	1.31 (0.86-2.0)		0.65 (0.34-1.24)	
	>55	15	1.97 (1.24-3.13)		1.76 (0.86-3.58)	
Ethnicity	Burmese	11	1.00	<0.01	1.00	<0.01
	Karen	13	0.70 (0.44-1.10)		1.48 (0.63-3.49)	
	Other	2	0.84 (0.30-2.34)		1.52 (0.33-6.98)	
	Unknown	29	2.30 (1.53-3.47)		4.51 (2.19-9.29)	
TB site	Pulmonary	49	1.00	0.16	1.00	0.44
	Extra-pulmonary	6	1.5 (0.87-2.57)		1.65 (0.47-5.72)	
TB history	New	43	1.00	0.08	1.00	0.07
	Retreat	4	1.43 (0.90-2.28)		0.37 (0.12-1.15)	
	No data	8	1.96 (1.02-3.75)		1.65 (0.73-3.72)	
Smear result	Negative	11	1.00	<0.01	1.00	<0.01
	Positive	38	0.87 (0.60-1.26)		2.82 (1.36-5.85)	
	No data	6	2.49 (1.35-4.60)		2.27 (0.62-8.28)	
Year diagnosed	2013-2014	12	1.00	0.13	1.00	0.04
	2015-2017	43	1.32 (0.91-1.90)		1.96 (0.99-3.83)	
HIV status	Negative/unknown	38	1.00	<0.01	1.00	<0.01
	Positive: ART	4	1.48 (0.97-2.25)		0.71 (0.24-2.11)	
	Positive: no ART	13	13.49 (8.32-21.87)		27.70 (12.45-61.62)	
MDR-TB	No	48	1.00	0.16	1.00	0.05
	Yes	7	1.52 (0.87-2.64)		2.59 (1.05-6.38)	

* All variables displayed in the table were included in the adjusted model.

TB = tuberculosis; MDR-TB = multi-drug resistant TB; HIV = human-immunodeficiency virus; ART = antiretroviral therapy; IRR = incidence rate ratio; CI = confidence interval.

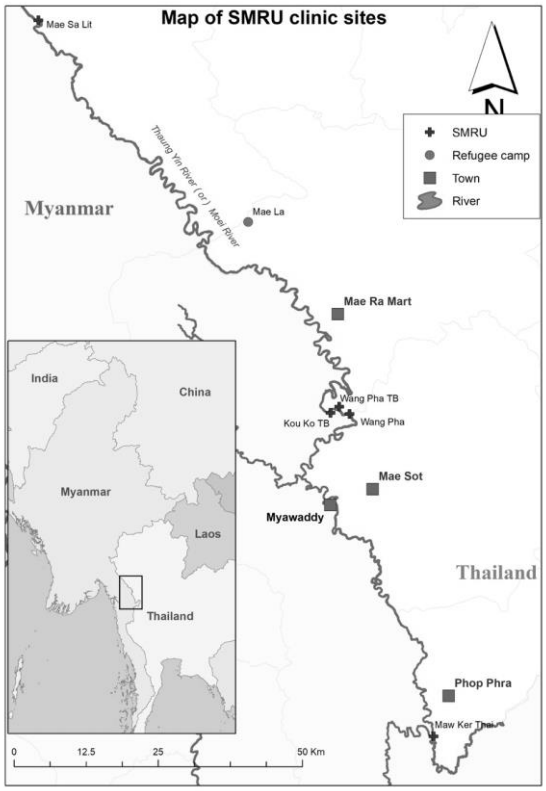
Supplementary Table 2: Risk factors for death during the 2nd to 6th month after TB diagnosis

	Category	Deaths (n)	Unadjusted IRR (95% CI)	p value	Adjusted IRR* (95% CI)	p value
Gender	Male	43	1.00	0.23	1.00	0.10
	Female	29	1.34 (0.83-2.14)		1.51 (0.93-2.48)	
Age category	16-34	16	1.00	<0.01	1.00	<0.01
	35-54	35	1.95 (1.08-3.52)		2.23 (1.21-4.13)	
	>55	21	2.73 (1.42-5.22)		6.17 (2.97-12.83)	
Ethnicity	Burmese	33	1.00	<0.01	1.00	0.28
	Karen	19	0.52 (0.30-0.91)		0.65 (0.35-1.22)	
	Other	2	0.52 (0.12-2.15)		0.77 (0.18-3.28)	
	Unknown	18	1.48 (0.83-2.62)		1.29 (0.68-2.43)	
TB site	Pulmonary	63	1.00	0.19	1.00	0.78
	Extra-pulmonary	9	1.64 (0.82-3.30)		1.13 (0.51-2.52)	
TB history	New	53	1.00	0.01	1.00	0.09
	Retreat	18	2.25 (1.32-3.84)		1.96 (1.03-3.72)	
	No data	1	3.66 (0.51-26.50)		0.54 (0.06-4.90)	
Smear result	Negative	36	1.00	<0.01	1.00	0.37
	Positive	29	0.50 (0.31-0.81)		0.69 (0.40-1.20)	
	No data	7	2.06 (0.92-4.63)		1.15 (0.44-3.0)	
Year diagnosed	2013-2014	31	1.00	0.77	1.00	0.48
	2015-2017	41	0.93 (0.59-1.49)		0.84 (0.51-1.37)	
HIV status	Negative/unknown	37	1.00	<0.01	1.00	<0.01
	Positive: ART	27	2.64 (1.61-4.34)		3.05 (1.66-5.59)	
	Positive: no ART	8	47.34 (22.05-101.65)		55.36 (21.11-145.18)	
MDR-TB	No	65	1.00	0.48	1.00	0.86
	Yes	7	1.34 (0.61-2.92)		1.09 (0.40-2.96)	

* All variables displayed in the table were included in the adjusted model.

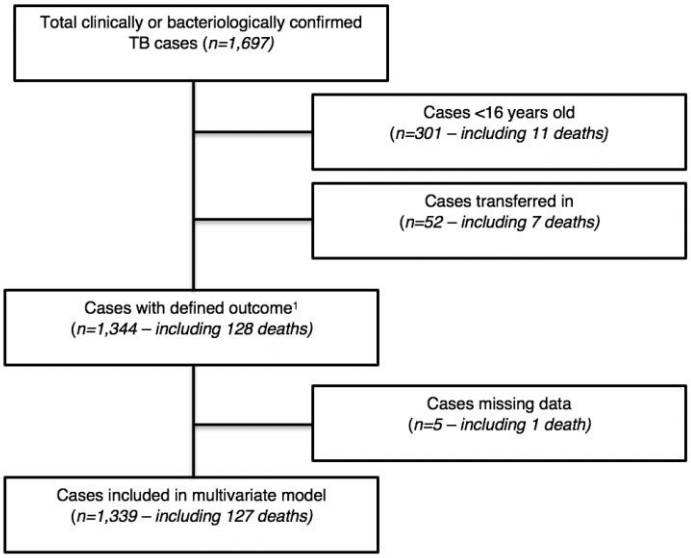
TB = tuberculosis; MDR-TB = multi-drug resistant TB; HIV = human-immunodeficiency virus; ART = antiretroviral therapy; IRR = incidence rate ratio; CI = confidence interval.

Figure 1: Map of the border region displaying the location of the Shoklo Malaria Research Unit clinics (TB clinics: Kou Ko TB and Wang Pha TB)



TB = Tuberculosis.

334 Figure 2: Study population for cohort January 2013 to April 2017



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336 * Includes seven patients continuing treatment for MDR-TB that had completed >6 months anti-tubercular treatment.

337 TB = tuberculosis.