Tuberculosis treatment in a refugee and migrant population: 20 years of experience on the Thai-Burmese border

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_____ S U M M A R Y

SETTING: Although tuberculosis (TB) is a curable disease, it remains a major global health problem and an important cause of morbidity and mortality among vulnerable populations, including refugees and migrants.

OBJECTIVE: To describe results and experiences over 20 years at a TB programme in refugee camps on the Thai-Burmese border in Tak Province, Thailand, and to identify risk factors associated with adverse outcomes (e.g., default, failure, death).

DESIGN: Retrospective review of routine records of 2425 patients admitted for TB treatment in the Mae La TB programme between May 1987 and December 2005.

RESULTS: TB cases notified among refugees decreased over 20 years. Among patients treated with a first-, second- or third-line regimen, 77.5% had a successful outcome, 13.5% defaulted, 7.6% died and 1.3% failed treatment. Multivariate analysis for new cases showed higher likelihood of adverse outcomes for patients who were Burmese migrants or Thai villagers, male, aged >15 years or with smear-negative pulmonary TB.

CONCLUSION: These findings suggest that treatment outcomes depend on the programme's capacity to respond to specific patients' constraints. High-risk groups, such as migrant populations, need a patient-centred approach, and specific, innovative strategies have to be developed based on the needs of the most vulnerable and marginalised populations.

KEY WORDS: tuberculosis treatment; refugees; migrants; Thailand

OVER 9 MILLION new tuberculosis (TB) cases and about 2 million deaths are reported yearly.[1] As 85% of refugees and internally displaced persons (IDPs) originate from or settle in high TB prevalence countries, the disease is a particular burden in this population.[2,3] Specific TB programme strategies have been developed for refugee contexts.[2,4] In TB programmes reporting successful results, common favourable circumstances include relative political stability in the country; provision of basic needs for individuals at the start of TB activities; adequately staffed, funded, and available medical services; and close collaboration and coordination between aid agencies and national programmes.[5] However, peer-reviewed evidence assessing these strategies is scarce.[6–8]

Since Myanmar (Burma) gained independence from the United Kingdom in 1948, civil war between the military government and armed opposition groups has resulted in over 1 million deaths and 2 million IDPs, predominantly among ethnic minority civilians. Meanwhile, thousands of people have fled ethnic conflict to find protection in surrounding countries.[9] Since 1984, a large number of people have found refuge in camps in Thailand. The Thai authorities allowed national and international non-governmental organisations (NGOs) to provide food, shelter and medical care for these refugees. Médecins Sans Frontières (MSF) began providing assistance to this population during the same year and started a TB programme in 1985.

Here, we describe TB programme outcomes, with the objective of identifying risk factors associated with poor outcomes.

METHODS

The refugee camps were located in Tak Province, Thailand, 500 km northwest of Bangkok. The estimated refugee population in Tak Province increased from 10 000 in 1984 to 80 000 in 2004.[10] Refugees from Burma were initially resettled in 14 camps along the Thai-Burmese border. As part of the policies of the Thai authorities, resettlements of the refugees progressively resulted in the establishment of three larger camps: Mae La, Umpiem Mai and Nu Po (Figure 1).

Patients enrolled in the programme belonged to three specific groups: refugees from Burma living and
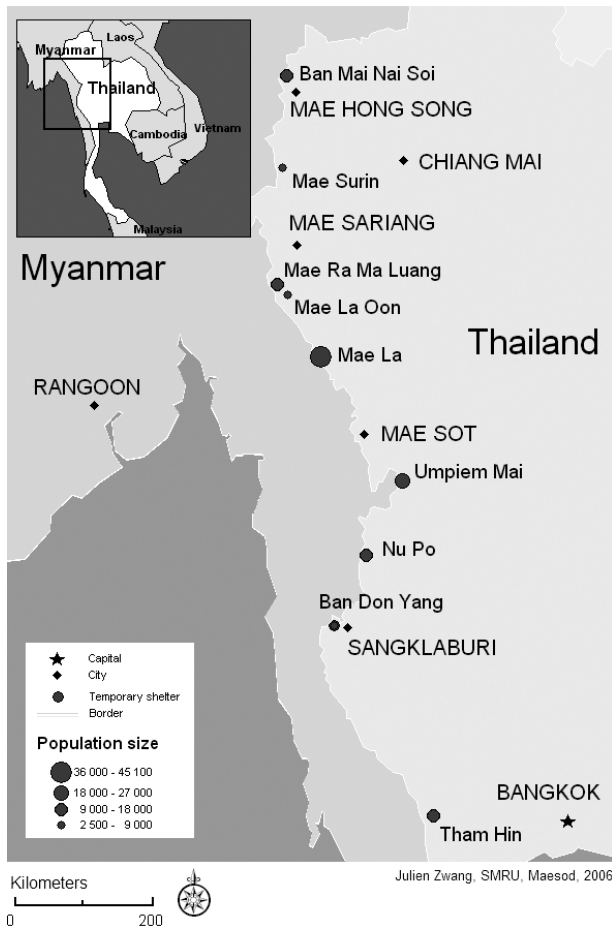
Figure 1 Thai-Burmese border map of Karen refugee camps, 2006. Source: Shoklo Malaria Research Unit, Mae Sot, Tak Province, Thailand.

registered in the camps, illegal Burmese migrants without refugee status, and Thai Karen villagers living near the refugee camps. Patients were ethnic Karen, Bangladeshi Burmese, and ethnic Burmese.

At the start of the programme in 1985, patients with TB were treated in health facilities located in different camps. In 1988, a TB unit was created in Shoklo camp and was relocated in Mae La camp after the transfer of refugees from Shoklo to Mae La camp. This TB unit was the only clinic offering TB treatment to refugees in the region, as the Thai national programme at district hospitals was restricted to Thai citizens.

Definitions of cases, treatment and treatment response

Due to missing data for the first 2 years of the programme (63 patients admitted between 1985 and 1987), only TB cases diagnosed from 14 May 1987 to 31 December 2005 were included. Case definitions were consistent with the World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (The Union) recommendations between 1985 and 2005.[11–17]

TB diagnosis was based on smear microscopy of three sputum specimens collected over 2 days and stained using the hot Ziehl-Neelsen method. X-rays and clinical evidence were used to diagnose smear-negative and extra-pulmonary TB (EPTB). Patients were classified according to the following case definitions: 1) a pulmonary smear-positive patient had two smear-positive results, defined as ≥10 acid-fast bacilli/100 high power fields or one/scanty smear-positive result and TB clinical and radiological presentation suggestive of TB; 2) a pulmonary smear-negative patient had at least three smear-negative results, clinical and radiological signs suggestive of TB, and absence of clinical improvement after two courses of broad-spectrum antibiotics; 3) an EPTB patient had clinical signs corresponding to active EPTB and sputum smear-negative results. A patient with both pulmonary and EPTB was defined as a pulmonary case.

Cases were also defined according to their history of treatment: patients who had never been treated or who had received <1 month of TB treatment in the past were defined as new cases, and patients who had received ≥1 month as retreatment cases. Retreatment cases included relapses, treatment failures and returns after treatment default. As previous treatment was unknown for patients transferring into the programme, transfer patients were classified as retreatment. Patients defined as 'others', cases not fitting the aforementioned definitions, were classified as retreatment cases. Failures of retreatment regimens were defined as chronic cases.

Directly observed treatment (DOT) was administered daily by health workers. All patients, refugees and migrants, were asked to settle within or near the camp. The following drugs were used during the 20 years of the programme: isoniazid (H, INH), rifampicin (R, RMP), pyrazinamide (Z, PZA), ethambutol (E, EMB), streptomycin (S, SM) and kanamycin (K, KM). Treatment regimens were adjusted according to international recommendations over time.

From 1985 to June 1996, a treatment regimen consisting of an initial phase of 2 months SHRZ followed by 4 months RH was given to new cases.[11–13] During this period, there was no standardised regimen for retreatment cases, who received a 9-month individualised treatment with first-line drugs in combination with KM. Between October 1990 and October 1995, 51 patients were treated as retreatment cases based on medical decision. Exceptionally, for new cases initially treated with SHRZ, the treatment was changed to EHRZ, based on medical decision. From July 1996 to December 2005, a regimen of 2EHRZ/4HR was given to new cases, and 2SEHRZ/1RHZE/5RHE was given to retreatment cases.[16,17] Since 2001, 13 chronic cases have been identified as multidrug-resistant TB (MDR-TB) and have received individualised treatment, including second-line drugs. TB

cultures were performed for particular cases in the Siriraj Hospital, Bangkok.

Treatment response was based on sputum smear microscopy. Treatment outcomes were defined as: 1) cured, for smear-positive patients who completed treatment and were sputum smear-negative in the last month of treatment and on at least one previous occasion; 2) treatment completed, for patients who completed treatment but who did not meet the criteria to be classified as a cure or a failure; 3) failure, for patients who remained sputum smear-positive at 5 months or later during treatment; 4) death, for patients who died during the course of treatment; 5) default, for patients whose treatment was interrupted for ⩾2 consecutive months; and 6) transferred out, for patients who were transferred to another treatment centre and for whom the treatment outcome was not known. Treatment success was defined as a combination of cured and treatment completed.

Statistical analysis

Data were collected through retrospective reviews of patient medical files and single-entered confidentially into an electronic database using EpiData (version 3.1, EpiData Association, Odense, Denmark). Statistical analysis was performed using STATA (version 9.0, STATA Corporation, College Station, TX, USA). The yearly TB case notification rate was calculated for the refugee population using annual population data provided by the Thailand Burma Border Consortium.

Analysis of outcomes was performed per TB case and per patient. For TB case analysis, patients receiving different regimens for the same TB event (e.g., new case and then retreatment case) were counted twice. For patient analysis, a patient failing one regimen and starting a new regimen for the same TB event was counted once. Categorical variables were compared with χ^2 tests and continuous variables using t-tests.

Failure, death and default were considered adverse outcomes. To assess predictors of adverse outcomes for new cases, multivariate analysis was conducted using Cox regression. Results were presented as adjusted hazard ratios (aHRs) with 95% confidence intervals (95%CI), and likelihood ratio tests (LRT) were performed to test the models. $P < 0.05$ was considered statistically significant.

As this retrospective analysis reports on programme monitoring data, ethical committee approval was not sought nor was individual written consent obtained.

RESULTS

Patient characteristics

From January 1985 to December 2005, 2800 patients were admitted to the TB treatment programme. Records were lost for the 63 patients admitted before May 1987, and floods destroyed 170 archives of patients diagnosed between 1 April 1992 and 30 June 1993. A further 140 patient files were lost over the years. Data were thus available for a total of 2425 patients.

Among these patients, 978 (40%) were refugees from Burma living in the camps, 1325 (55%) were Burmese migrants and 122 (5%) were Thai villagers of Karen ethnicity. The majority of the patients were male (68%), and the mean age was 35 years ($\pm$14 standard deviation [SD]). Seventy-eight per cent of patients had smear-positive pulmonary TB, 15% smear-negative pulmonary TB, and 7% EPTB (Table 1). Among the 167 patients with EPTB, 44% ($n = 74$) had lymphatic TB, 22% ($n = 37$) osteoarticular TB, 14% ($n = 23$) meningeal TB and 20% other forms of EPTB (pleural, intestinal, genitourinary, miliary). Patients with EPTB were younger than pulmonary TB patients ($P < 0.001$). Smear-positive pulmonary TB patients were more likely to be male than smear-negative ($P < 0.001$) or EPTB patients ($P < 0.001$). Migrant patients were proportionally more often admitted with smear-positive pulmonary TB than refugee patients ($P < 0.001$).

TB case notification

Overall, the 2425 patients in the programme accounted for 2564 TB registered cases: 87% ($n = 2231$) were new cases, 11% ($n = 286$) retreatment cases and 2% ($n = 47$) chronic cases. Migrant admissions increased

Table 1 Characteristics of patients by type of TB disease, Mae La TB programme, 1985–2005

	Pulmonary smear-positive TB disease ($n = 1904$) n (%)	Pulmonary smear-negative TB disease ($n = 354$) n (%)	Extra-pulmonary TB disease ($n = 167$) n (%)	Total ($N = 2425$) n (%)
Age, years, mean $\pm$ SD	37.3 $\pm$ 13	29.8 $\pm$ 16.7	22.6 $\pm$ 15.8	35.2 $\pm$ 14.5
Male sex	1344 (70.6)	215 (60.7)	87 (52.1)	1646 (67.9)
Origin				
Refugees	696 (36.5)	194 (54.8)	88 (52.7)	978 (40.3)
Migrants	1113 (58.4)	139 (39.3)	73 (43.7)	1325 (54.7)
Thai Karen	95 (5.0)	21 (5.9)	6 (3.6)	122 (5.0)

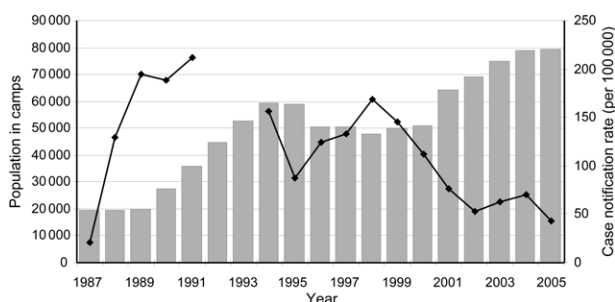TB = tuberculosis; SD = standard deviation.

Figure 2 Trend of tuberculosis case notification rate (black line) and population in refugee camps (grey bars), Tak Province, Thailand, 1985–2005. Patient records are missing for the period April 1992–June 1993.

Table 3 Overall patient treatment outcomes by residency status, Mae La TB programme, 1985–2005 (*n* = 2425)

Treatment outcome	Refugees (*n* = 978) *n* (%)	Migrants* (*n* = 1325) *n* (%)	Thai Karen (*n* = 122) *n* (%)
Cured	591 (60.3)	742 (56.1)	68 (55.7)
Treatment completed	253 (25.8)	214 (16.2)	14 (11.5)
Died	57 (5.8)	112 (8.5)	14 (11.5)
Failed treatment	6 (0.6)	24 (1.8)	1 (0.8)
Defaulted	73 (7.5)	230 (17.4)	25 (20.5)

* Two patients transferred among migrants.
TB = tuberculosis.

from 10 in 1987 to 178 in 2004 (mean 70/year), and remained relatively stable for refugees (mean 51/year) and Thai Karens (mean 6/year).

The average annual TB case notification rate among the refugee population was estimated at 122 cases per 100 000 population. TB cases reported in the camps increased sharply from the start of the programme until 1991 (212/100 000), and then progressively decreased to 43/100 000 in 2005 (test for linear trend *P* < 0.001; Figure 2). Notification rates for 1992 and 1993 could not be calculated, as patient files were missing during parts of this period.

Treatment outcomes

Of the 2231 new cases, 75.5% had a successful outcome (Table 2). A total of 121 patients (6.9% of smear-positive new cases) were considered treatment failures and were therefore proposed retreatment regimens. Among the 286 retreatment cases, 62.9% had a successful outcome. Of the 47 chronic cases, 13 were MDR-TB.

Refugees had lower death and defaulter rates than migrants (*P* = 0.022 and *P* < 0.001) and Thai Karen villagers (*P* = 0.016 and *P* < 0.001), respectively

(Table 3). The relative proportion of negative outcomes increased with the increase in admission of migrant patients to the programme (Figure 3).

Risk factor analysis

Of the 2231 new cases, we excluded 54 patients incorrectly treated with the retreatment regimen. Therefore, the analysis was performed on 2177 patients. Multivariate analysis showed that female sex, age <15 years, refugee status and smear-positive pulmonary TB were
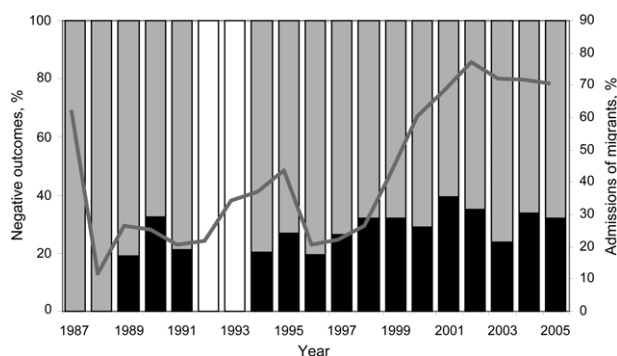

Figure 3 Trend of negative outcomes (failure, death or default) over time (grey bars) and admission of migrant patients (grey line), Mae La Tuberculosis Programme, 1985–2005. Patient records are missing for the period April 1992–June 1993.

Table 2 Treatment outcomes for new, retreatment and chronic cases by case definition, Mae La TB programme, 1985–2005

TB type (*N* =2564)	Cured *n* (%)	Treatment completed *n* (%)	Failed *n* (%)	Died *n* (%)	Defaulted *n* (%)	Transfer *n* (%)
New cases (*n* = 2231)						
Pulmonary smear-positive (*n* = 1765)	1257 (71.2)	72 (4.1)	121 (6.9)	127 (7.2)	188 (10.6)	0
Pulmonary smear-negative (*n* = 311)	0	237 (76.2)	0	26 (8.4)	47 (15.1)	1 (0.3)
Extra-pulmonary (*n* = 155)	0	120 (77.4)	0	10 (6.5)	25 (16.1)	0
Total	1257 (56.3)	429 (19.2)	121 (5.4)	163 (7.3)	260 (11.7)	1 (0.1)
Retreatment cases (*n* = 286)						
Pulmonary smear-positive (*n* = 230)	129 (56.1)	8 (3.5)	23 (10.0)	12 (5.2)	58 (25.2)	0
Pulmonary smear-negative (*n* = 44)	0	33 (75.0)	0	4 (9.1)	7 (15.9)	0
Extra-pulmonary (*n* = 12)	0	10 (83.3)	0	0	2 (16.7)	0
Total	129 (45.1)	51 (17.8)	23 (8.1)	16 (5.6)	67 (23.4)	0
Chronic cases (*n* = 47)						
Pulmonary smear-positive (*n* = 47)	23 (48.9)	2 (4.3)	5 (10.6)	4 (8.5)	13 (27.7)	0

TB = tuberculosis.

Table 4 Risk factors associated with adverse outcome for new cases, Mae La TB programme, 1985–2005 (n = 2177)

Risk factor	n	Univariate analysis			Multivariate analysis		
		HR	95%CI	P value	aHR	95%CI	P value
Age, years							
<15	147	Reference			Reference		
15–39	1204	1.84	1.15–2.94	0.011	1.82	1.10–3.01	0.019
40–59	684	2.09	1.30–3.37	0.002	2.01	1.20–3.36	0.008
⩾60	142	2.21	1.28–3.84	0.005	2.15	1.20–3.84	0.010
Sex							
Female	701	Reference			Reference		
Male	1476	1.45	1.19–1.76	<0.001	1.33	1.09–1.62	0.005
Residency status							
Refugee	928	Reference			Reference		
Migrant	1137	1.86	1.52–2.28	<0.001	1.80	1.46–2.21	<0.001
Thai Karen	112	2.45	1.71–3.52	<0.001	2.34	1.63–3.36	<0.001
TB type							
Smear-positive	1712	Reference			Reference		
Smear-negative	310	1.08	0.84–1.39	0.54	1.38	1.06–1.80	0.017
Extra-pulmonary	155	0.82	0.58–1.17	0.27	1.20	0.83–1.73	0.34
Regimen							
SHRZ	577	Reference					
EHRZ	1477	0.78	0.48–1.28	0.33			

TB = tuberculosis; HR = hazard ratio; CI = confidence interval; aHR = adjusted HR; S = streptomycin; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol.

predictors of favourable outcomes (Table 4). Excluding age, similar associations were found for smear-positive pulmonary cases (n = 1712; data not shown).

DISCUSSION

This retrospective study shows a reduction in TB cases notified over 20 years in a refugee setting. The sharp increase in TB cases reported from 1987 to 1992 was probably due to increased TB case detection at the beginning of the programme. The TB case notification rate among refugees subsequently decreased continuously between 1992 and 2005. Offering appropriate TB care to a refugee population likely contributed to this reduction. The overall improvement in living conditions and nutritional status of the refugees also probably contributed to the decrease.

The overall treatment success rate of 77.5% is consistent with other studies in refugee settings.[6–8] The low failure rate of 1.3% might have been underestimated, as defaulters may also have failed treatment. Despite the absence of systematic TB culture, there was no factor suggesting a problem of drug resistance in this population at that time.

It is important to note that the TB targets suggested by Kessler et al.[5] were achieved in the refugee population, with the exception of the default rate, which remained above the target. The programme was less effective in reaching the targets in the migrant and Thai villager populations, who experienced high mortality and default rates. Although the overall failure rate among new cases was worrisome, these cases were retreated and the few failures that remained were concentrated in the migrant group.

Few studies have reported predictors of adverse TB treatment outcomes in displaced populations.[18,19] The high death rate of smear-negative patients (around 9%) could be explained by the existence of human immunodeficiency virus co-infection.[20,21] It may also be the consequence of misdiagnosis, as little capacity was available in this programme to diagnose smear-negative pulmonary TB.

As reported elsewhere, we observed a higher proportion of male patients admitted to the programme.[1] The worse outcomes in males is consistent with previous studies reporting better treatment adherence in women.[22] Men were more likely than women to work outside the camp, thus potentially hindering treatment adherence.

Burmese migrant patients were more likely to be male (P < 0.001) and older (P < 0.001), as mainly male adults crossed the border seeking employment in Thai factories. They were also more likely to have smear-positive pulmonary TB. Compared with refugees, they generally reached health services at more advanced stages of the disease, which could also explain their worse outcomes. The risk of defaulting was increased for Burmese migrants, who were illegal in Thailand and, if arrested, were sent back to Myanmar where tracing was not possible.

As this programme was developed initially for refugees living in a closed camp, it was not well adapted to the migrant population. Patients were required to remain in the camp for the duration of their DOT-based treatment, which was not compatible with the migratory patterns of temporary workers.[23] Previous studies have reported that treatment adherence was worse among patients separated from their families[24]

and among non-refugee patients engaged in working activities, compared with refugees living in a camp under assistance.[5]

Patients living in villages around the camps were essentially from the Karen ethnic group. Absence of regular Thai identification papers, language and health costs were barriers to accessing mainstream health services. In this programme, however, they could communicate in their own language and had free access to health care. Nevertheless, they had worse TB treatment outcomes than refugees. A previous study in Khartoum, Sudan, reported worse outcomes in patients living outside an IDP camp compared with patients living in the camp.[25] Unlike refugees, villagers have to rely on their own work for survival, as they receive only partial support from aid agencies.

A number of limitations should be mentioned. The quality of retrospectively collected data was inconsistent over time. Some patients may have concealed previous TB treatment at admission and thus have been misclassified as new cases, which could explain some poor outcomes of new cases. Also, several sociological factors that might predispose groups of patients to an adverse outcome were not addressed. Prospective qualitative studies should continue to investigate sociological and behavioural aspects such as family support, literacy, and drinking or smoking habits, which may influence patient outcomes.

CONCLUSIONS

This retrospective cohort study shows a reduction of TB cases reported over 20 years in a refugee population, in a programme providing adequate quality of care and relief aid, adapted to the specific needs of a resettled refugee population. Nevertheless, the programme was less effective in adequately treating migrants and Thai Karen villagers, with specificities not directly addressed by the programme. These populations would better benefit from a patient-centred approach with TB care delivery adapted to their needs. More flexible strategies, such as self-administered treatment or community-based models, can be effective if strong counselling and support are provided, as well as home-based follow-up. New drugs to shorten the length of treatment are urgently needed to improve adherence, especially for vulnerable populations living in unstable contexts.

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RÉSUMÉ

CONTEXTE : Malgré le fait qu'elle soit une maladie curable, la tuberculose (TB) reste un problème de santé publique majeur et une cause importante de morbidité et de mortalité chez les populations les plus vulnérables, incluant les réfugiés et les migrants.

OBJECTIF : Décrire les résultats de plus de 20 ans d'expérience d'un programme de TB dans des camps de réfugiés à la frontière thaï-birmane dans la Province de Tak en Thaïlande et identifier les facteurs de risque associés à un résultat défavorable (perdu de vue, échec, décès).

MÉTHODE : Revue rétrospective des dossiers individuels de 2425 patients admis pour le traitement de la TB dans le programme TB de Mae La, entre mai 1987 et décembre 2005.

RÉSULTATS : Les cas de TB notifiés parmi les réfugiés ont diminué au cours des 20 ans. Parmi les patients traités avec un régime de première, seconde ou troisième ligne, 77,5% ont eu un résultat positif, 13,5% ont été perdus de vue, 7,6% sont morts et 1,3% ont échoué. L'analyse multivariée des nouveaux cas a montré une plus haute probabilité de résultats défavorables chez les migrants birmans ou les villageois thaïs, les patients de sexe masculin, les patients âgés de plus de 15 ans, ou ceux avec une TB pulmonaire à frottis négatif.

CONCLUSION : Ces résultats suggèrent que le succès du traitement dépend de la capacité du programme à répondre aux contraintes spécifiques des patients. Les groupes à haut risque, comme les populations de migrants, doivent bénéficier d'une approche centrée sur le patient. Des nouvelles stratégies innovatrices doivent être développées spécifiquement en considérant les besoins des populations les plus vulnérables et marginalisées.

RESUMEN

MARCO DE REFERENCIA: La tuberculosis (TB), pese a que es una enfermedad curable, representa todavía un problema considerable de salud pública y una causa importante de morbilidad y mortalidad en las poblaciones vulnerables, que incluyen a los refugiados y a los inmigrantes.

OBJETIVO: Describir los resultados y la experiencia adquirida en más de 20 años de ejecución de un programa de atención de la TB en un campo de refugiados en la frontera entre Tailandia y Myanmar en la provincia Tak de Tailandia y definir los factores de riesgo de desenlaces desfavorables (es decir, abandono, fracaso y muerte).

MÉTODO: Se llevó a cabo un estudio retrospectivo de los registros sistemáticos de 2425 pacientes inscritos al programa de atención de la TB del campo Mae La entre mayo de 1987 y diciembre del 2005.

RESULTADOS: La notificación de casos de TB en los refugiados disminuyó en los 20 años. De los pacientes tratados con una pauta de primera, segunda o tercera línea, 77,5% alcanzaron un desenlace clínico exitoso; 13,5% abandonaron; 7,6% fallecieron; y 1,3% tuvieron un fracaso terapéutico. El análisis multifactorial de los casos nuevos puso en evidencia una probabilidad mayor de desenlaces desfavorables en los pacientes migrantes de Myanmar y los habitantes tailandeses de la población, los hombres, los mayores de 15 años y los casos de TB pulmonar con baciloscopia negativa.

CONCLUSIÓN: Estos resultados indican que los desenlaces terapéuticos dependen de la capacidad del programa a responder a las dificultades específicas de los pacientes. Los grupos de mayor riesgo, como las poblaciones migrantes, exigen un enfoque centrado en el paciente y se precisa establecer estrategias específicas e innovadoras con base en las necesidades de los grupos más vulnerables y marginadas.