

Migration histories of multi-drug resistant tuberculosis patients from the Thailand-Myanmar border (2012 – 2014)

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ABSTRACT

Setting: Multi-drug resistant (MDR) tuberculosis (TB) is a growing public health threat in Southeast Asia. TB is typically a disease of poverty and can be spread by infectious humans who migrate from one region to another.

Design: In this research we interviewed 20 MDR-TB patients on the Thailand-Myanmar border with regard to their migration histories. Migration origins and destinations were mapped.

Results: All but one participant had a history of migration and maps of migration ranges revealed wide geographic dispersal. Most described living and work conditions that could contribute to the spread of drug resistant TB, including numerous contacts and close living quarters.

Conclusion: Our results show that at least some migrant workers in the region carry MDR-TB and indicate that this subgroup of the population is important with regard to transmission of MDR-TB throughout the region. Migrants in this region come into contact with high numbers of people and may be able to disperse the disease across wide geographic ranges. Access to diagnosis and treatment and socioeconomic development are at least as important as any TB control measures, meaning that innovative and bold approaches that extend across international borders are needed in order to address these problems.

Background

Myanmar and Thailand have some of the highest tuberculosis (TB) burdens in the world. As of 2015, the estimated TB incidence is 365 (267 - 479) per 100,000 persons in Myanmar and 172 (−102 - 259) per 100,000 in Thailand (1). TB that is resistant to the two most potent first-line anti-TB drugs (i.e. isoniazid and rifampicin), multi-drug resistant (MDR) TB, is also a major public health problem in Southeast (SE) Asia. Myanmar has one of the heaviest MDR-TB burdens in the world, with an estimated 5.1% (3.2-7.0) of new TB cases and 27% (15-39) among previously treated TB cases being MDR-TB. In Thailand an estimated 2.2% (1.5 - 2.9) of new TB cases and 24% (18 - 30) of retreatment TB cases are MDR-TB (1).

Accurate detection and confirmation of MDR cases is challenging, particularly in resource limited settings. Molecular methods can be helpful, but are expensive and do not negate the need for phenotypic drug susceptibility testing (DST) methods which take between six and 16 weeks. Furthermore, treatment of MDR-TB can be costly and requires complicated and lengthy treatment regimens. These problems have led to less-than-satisfactory case detection and treatment enrollment in much of the world, including SE Asia (2).

Some research has indicated that human migration can contribute to the dispersal of TB, including MDR-TB (3,4). Infectious persons from one region who travel to another region may spread the disease in their new destination or at any point along the journey. In 2010 there were an estimated 2 - 2.5 million labour migrants in Thailand, more than half of these migrants were undocumented and the vast majority from Myanmar (5). Furthermore, there are around 105,000 displaced persons living in camps along the Thailand-Myanmar border (6).

Following an observed increase in TB cases presenting at Shoklo Malaria Research Unit (SMRU) clinics along the Thailand-Myanmar border, SMRU established a program

(beginning in 2009) for the detection, diagnosis and treatment of TB cases for migrants and displaced populations residing in the border region. With consultation from the national TB programs of both Myanmar and Thailand, SMRU established two TB clinics, one on each side of the international border. The two clinics have a combined capacity of 198 patients and provide care and directly observed treatment (DOT) for drug sensitive TB, Co TB/HIV, drug resistant TB and MDR-TB, following recommended protocols from the WHO. There was a sharp increase in activity in 2013 following the implementation of an active case detection strategy and use of GeneXpert for all sputum sampled (Table 1). All but one diagnosed MDR-TB patients were enrolled for treatment.

The goal of this pilot research was to document the migration histories of MDR-TB patients at SMRU TB clinics, to analyse spatial patterns in migrations and to initiate an effort to understand the potential links between human migration and the dispersal of MDR-TB within the SE Asian region.

Methods

All patients presenting at SMRU TB clinics with suspected pulmonary TB received microscopy (Ziehl-Neelsen smear) and a GeneXpert test (Xpert® MTB/RIF assay (Cepheid)) for bacteriological confirmation. Diagnostic samples that were smear and/or GeneXpert positive were then sent to the International Organization for Migration (IOM) TB Laboratory in Mae Sot, Thailand for confirmatory testing using conventional culture and drug susceptibility testing (DST) methods.

Once identified, MDR-TB patients are enrolled for treatment in a residential center attached to one of the SMRU TB clinics. At the time of the study, the MDR regimen followed

the current WHO (7) which was based on a 24 month regimen according to the profile of resistance with choices of drugs from group two (injectables), three (fluoroquinolones), and four (oral bacteriostatics) plus pyrazinamide if no resistance was found.

Participants were interviewed using a set of semi-structured questionnaires. Questions addressed participants' place of origin and destination; retrospective migration histories, including the timing of movements and durations of stay; the number of people with which they housed during migrations; their history of symptoms and history of TB contacts.

Migrations were mapped using ArcGIS 10.2 and Euclidian (straight line) distances were calculated between the points of origin and destination. Actual travel pathways were not recorded, however, these pathways will always be at least as far as the Euclidian distance between a point of origin and a point of destination.

Results

During the study period (April 2012 – March 2014), a total of 21 patients were enrolled for treatment for MDR-TB at SMRU clinics, 20 of which participated in this study (one was too ill to be interviewed and died).

Quantitative:

In addition to isoniazid and rifampicin resistance nine of the 20 MDR-TB participants had resistance to other first-line anti-TB drugs (Table 2): three presented with *Mycobacterium tuberculosis* that was resistant to Pyrazinamide, four to Ethambutol and nine to Streptomycin. Six of them also had active TB with strains that were resistant to second line anti-TB drugs, including one patient whose strain showed resistance to six anti-TB drugs. Two had strains resistant to Levofloxacin, five to Ethionamide, none showed resistance to Kanamycin, one to Cycloserine and one to Para-aminosalicylic acid.

The majority of participants were adults, with a median age of 36.5 years, ranging from 15 to 50 years old (Table 3). Over half (13/20: 65%) were male. All participants were originally from Myanmar, 35% (7/20) considered themselves to be migrants, 15% (3/20) were refugees, and 50% (10/20) were non-Thai nationals (from Myanmar) who were now residing in a clinic on the Thai side of the border for the purpose of receiving care. Around half of all participants (11/20: 55%) reported multiple migrations and three (15%) reported having migrated both in Myanmar and Thailand (Table 3).

The majority of interviewed patients cited work as the main reason for movement, both within Myanmar and to Thailand. The average duration of a stay in a migration destination was 56.4 months (approximately 4 ½ years), with a median duration of stay of 24 months (range one to 276 months [23 years]). Nine of the participants had travelled to Thailand more than once and five participants had travelled to Thailand three times (Table 3). Twelve participants had visited Thailand during the last two years (a period of time in which they may have been contagious (8)), prior to presenting with symptomatic MDR-TB at the clinic. The median duration from the onset of likely TB symptoms to diagnosis was 6 months and 17 of the cases were retreatment cases (participant had previously been taking TB medication more than one month and experienced either a treatment failure or a relapse with subsequent TB infection).

Of the 15 participants who had ever travelled to Thailand, 14 had worked in indoor settings such as plywood factories, rice mills, a non-governmental organisation (NGO) clinic, as housemaids, waiters, students or as monks during at least one of their stays (most participants had migrated multiple times, with different jobs during different migrations). Twelve of those 14 who had worked in indoor settings in Thailand had done so in the two years leading up to their diagnosis. The remaining seven had always worked in outdoor settings such as cattle ranches,

prawn farms, in casual labor, or as a vender. Of the seven who had migrated within Myanmar, five also worked in indoor settings in at least one migration.

Almost all participants (19/20) had shared accommodation with other co-workers or family members. Seven out of 12 who worked in indoor settings in Thailand in the last two years had shared working spaces with co-workers, with reported numbers of co-workers ranging from one to almost 50.

Spatial:

Maps were created with points indicating places of origin, destinations and durations of stay in those destinations (Figure 1). The spatial extent of migrations was relatively broad and dispersed. For example, one individual travelled over 1000 km, from Rakhine State, Myanmar to Tak Province, Thailand (Figure 1). Most individuals travelled shorter distances, with a median distance between points of origin and destination of around 300 km. Most movements were toward larger urban centers and over half (55%) of all migrations to Thailand were into central provinces, deep within Thailand. At least two of the migrations within Thailand are likely to have occurred while participants were infectious.

Discussion

Migration and movement among persons with active TB, particularly MDR-TB, is important for several reasons, both at individual and population levels.

MDR-TB patients must undergo expensive, long-term treatment. Even when funding for treatment is available (and it frequently is not) difficulties in accessing such treatment remain. MDR-TB therapy can take about two years from beginning to end, with regular check-ups and treatments. This means that an individual with active MDR-TB must either remain in a given

area where treatment is available, must frequently return (including paying travel costs) to the treatment centre, or must be able to receive adequate follow-up treatments in different regions.

Furthermore, some individuals with MDR-TB will initially be so ill that they are unable to continue to work or engage in normal household activities like cooking and cleaning and may be unable to even wash and feed themselves, or to take care of their family. Migrants with MDR-TB may therefore represent a vulnerable position where social networks are of heightened importance yet are frequently unavailable. Public health policies should take note of this potentially widespread problem.

At a population level, MDR-TB positive migrants who are infectious can spread the disease across wide geographic ranges. Migrants, as demonstrated in this study, frequently live and work in settings that are optimal for the spread of this disease (i.e. close quarters, poor ventilation). The maps illustrating migration ranges from this study indicate an extensive landscape through which MDR-TB could have been distributed. A more extensive study would likely result in maps indicating even more expansive geographic ranges and more dense connections between major cities for migrants, including those with MDR-TB. The potential existence of TB and MDR-TB hotspots in this region needs to be explored through a spatial epidemiologic approach.

Twelve of the twenty participants in this study reported having visited Thailand within the two years prior to being diagnosed with MDR-TB. Movements, as well as living and working arrangements, during this period of time could have contributed to the spread of MDR-TB. At least one study has suggested conservative estimates for the reproductive number (specifically for MDR-TB) of 1.60, ranging from 1.02 to 2.67 (9). Applying this figure to the twelve participants who had visited Thailand within the last several years, we might expect anywhere

from twelve to 32 secondary MDR-TB infections. The number of people with whom an MDR-TB migrant patient comes in contact may be higher than non-migrant members of a population, as a direct result of the living and working conditions, and frequent changes in places of residence and work.

Despite the importance of MDR-TB diagnosis and treatment services, scaling-up of such services in both Thailand and Myanmar has been relatively slow. In 2011, only 13% and 23% of the total estimated MDR-TB cases, in Thailand and Myanmar respectively, were diagnosed, and only 6% and 3% of diagnosed cases were enrolled in the MDR-TB treatment (10).

In addition to financial constraints, human resources, technical and infrastructure constraints are also impediments towards achieving universal coverage of MDR-TB diagnosis and treatment. While Myanmar's health services are developing, and the National Tuberculosis program has recently made significant improvement related to TB control services, access to general health care services for border populations is almost solely achieved through border hospitals, private clinics, NGOs and International NGOs clinics on Thailand side (11).

Shorter courses of treatment for MDR-TB have recently shown promise and a regimen lasting less than 12 months is now recommended by the WHO under some specific criteria (12–15). This shorter and cheaper regimen would increase patient adherence but it should be used carefully and only in situations that meet very specific criteria which exclude patients with: documented or suspected resistance to second line drugs, previous exposure to any of the second line regimen drugs, or with known or suspected resistance to any of the drug used in the shorter regimen. In those situations, it is recommended to use the conventional longer protocol (16,17). Had this shorter regimen been available, more than half of the participants (12/20) in this study would have been eligible and would have benefited from the shorter treatment duration.

Conversely, while we do not have resistance profiles for the latest drugs from D2 and D3 groups (especially bedaquiline, delamanid, meropenem), the results that we do have from drug susceptibility testing show high profile of resistance for 8 patients (table 2). These results show the necessity of a qualified environment before introduction of these regimens, as well as the need for developing programmatic management of drug resistant TB and for better adherence of patients.

There are several limitations to this study. It was a small study, with only 20 participants who were selected by their MDR-TB status and willingness to participate. It may not be fully representative of the total population in either places of origin or destination. A small sample size and non-random sampling mean that more sophisticated statistical approaches aren't appropriate. Furthermore, maps indicate rough geographic ranges while the actual route of travel and locations of infection remain unknown. Regardless of these limitations, the information gained through this work is important, points toward the need for further research along these lines, and highlights the need for improving diagnostic and treatment services.

Conclusions

Myanmar has recently undergone many political reforms. With increasing cross-border cooperation expected through the beginning of ASEAN (Association of Southeast Asian Nations) (18), as well as the establishment of special economic zones in the region, this pattern of migration from neighbouring countries into Thailand, and vice versa, is likely to increase (5).

Several key steps are therefore warranted. At a regional level, cross-border collaborations and facilitation of referrals between health care providers are necessary to address the problems associated with TB and MDR-TB diagnosis and treatment among migrants. Furthermore,

interventions that are better suited to migrant lifestyles and circumstances, and resource poor settings, should be widely implemented. Cost effective and accurate rapid diagnostics (19) are necessary in order to identify MDR-TB cases in a timely manner. Ideally, the new shorter treatment regimen should be implemented when all necessary conditions of assessment and monitoring are met. Active screening in workplaces, in contacts of MDR-TB patients, using comprehensive tools for diagnosing MDR-TB could also help identify patients in a timely and cost effective manner.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SST and FN conceived the research. SST conducted the interviews and collected the data. KA analysed the laboratory data and SST, DMP, LLS, SP, MVD and CLL analysed the interview data. SST and DMP wrote the paper. All authors critiqued and helped in rewriting the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the Oxford Tropical Research Ethics Committee (OXTREC 525-14). All participants gave oral and written consent to participate in this project.

Abbreviations

TB: Tuberculosis; **MDR:** Multi-drug resistant tuberculosis; **ASEAN:** Association of Southeast Asian Nations; **NGO:** Non-governmental organisation; **WHO:** World Health Organization; **DST:** Drug sensitivity testing; **XDR:** extensively drug resistant; **SMRU:** Shoklo Malaria Research Unit.

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Figure 1: Map representing migrations among all interviewed patients. Migrations are indicated with lines; points of origin (blue box); destinations (orange circle); and the relative duration at each destination (circle size).

Table 1: Shoklo Malaria Research Unit (SMRU) TB program activity

	2010	2011	2012	2013	2014
number of patients diagnosed with TB	63	86	71	212	389
number of patients diagnosed with MDR TB	NA	4	2	20 (2 new patients, 18 retreated cases)	24 (8 new patients, 16 retreated cases)
number of MDR TB patients enrolled for treatment at SMRU	NA	4	2	20	24

Table 2: Drug resistant patterns and case types of study participants (RTM: retreatment case; New: no previous treatment). Coloured boxes indicate resistance.

Case No	Case Type*	1st line anti-TB drugs					2nd line anti-TB drugs				
		Isoniazid	Rifampicin	Pyrazinamide	Ethambutol	Streptomycin	Levofloxacin	Ethionamide	Kanamycin	Cycloserine	Para-amin
		H	R	Z	E	S	Lfx	Eto	Km	Cs	PAS
1	RTM	H	R								
2	New	H	R	Z	E	S					
3	RTM	H	R	Z	E	S		Eto			PAS
4	RTM	H	R					Eto			
5	RTM	H	R								
6	RTM	H	R				Lfx	Eto		Cs	
7	RTM	H	R								
8	RTM	H	R			S					
9	New	H	R		E	S		Eto			
10	RTM	H	R								
11	RTM	H	R			S					
12	RTM	H	R	Z	E	S					
13	RTM	H	R					Eto			

14	RTM	H	R	S	Lfx
15	RTM	H	R		
16	RTM	H	R		
17	RTM	H	R	S	
18	RTM	H	R		
19	RTM	H	R		
20	New	H	R	S	

Table 3: Summary demographic and migration attributes of interview participants. Duration of illness indicates self-reported length of illness prior to diagnosis.

Case no.	age	sex	migrant status at diagnosis	number of current household members	occupation	ever migrated in Myanmar?	ever migrated in Thailand?	number of migrations	duration of treatment at time of interview (months)	duration of illness at diagnosis (months)
1	35	male	Cross Border	6	farmer	No	Yes	3	11	24
2	41	male	Migrant	2	janitor	No	Yes	3	8	3
3	24	male	Cross Border	5	teacher	Yes	No	2	8	1
4	37	male	Local resident	9	taxi driver	Yes	Yes	2	4	10 days
5	40	male	Migrant	5	fisherman	Yes	Yes	2	2	7
6	41	male	Cross Border	2	laborer	Yes	No	1	4	36
7	45	male	Refugee	3	farm worker	No	Yes	1	12	24
8	49	female	Cross Border	6	housekeeper	No	No	0	7	5
9	31	female	Migrant	3	housekeeper	No	Yes	1	9	15 days
10	28	male	Local resident	7	soldier	No	Yes	1	4	12
11	39	male	Cross Border	4	monk	No	Yes	1	9	6
12	15	female	Cross Border	7	student	Yes	No	2	10	5
13	25	female	Refugee	6	NGO staff	Yes	Yes	2	2	3
14	50	female	Cross Border	7	vendor	Yes	No	1	2	12
15	42	male	Migrants	4	ranch hand	No	Yes	3	8	5
16	44	female	Migrants	8	laborer	No	Yes	2	9	9
17	36	female	Refugee	8	vendor	No	Yes	3	16	12
18	17	male	Migrant	5	waiter	No	Yes	1	8	6
19	29	male	Cross Border	7	farmer	No	Yes	1	7	24
20	29	male	Migrant	7	medic	No	Yes	3	6	12