**Evidence to inform resource allocation for tuberculosis control in Myanmar: a systematic literature review**

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**Abstract**

Myanmar represents an extreme example of the difficulties in optimally allocating resources for maximum public health benefit, on the basis of limited information. At the recent Myanmar Health Forum ‘Investing in Health’ much of the discussion revolved around what to invest in, how health systems could be strengthened, and what research and capacity building areas the international donor community should prioritise for support. Funding for infectious disease control, particularly HIV and tuberculosis, is being channelled to the country at an unprecedented rate, but very little research has been conducted in recent years, and existing information has not yet been synthesised. This paper presents findings of the first systematic literature review on tuberculosis control and the health system in Myanmar, with the aim of informing the development of optimal research priorities and strategies. Medline and gray literature was searched for relevant papers. Inclusion criteria and analyses were structured to capture data on the Myanmar health system, healthcare delivery, financing, tuberculosis control indicators, and information systems. A total of 77 papers were included in the analysis. Results indicate that there has been a large increase in the number of peer-reviewed articles published on tuberculosis in Myanmar over the past decade, although the absolute number of studies remains small. We identified several areas in which evidence to inform policy and resource allocation decisions is lacking, including research focused on rural and/or vulnerable populations, analyses of risk factors for TB and drug resistance that can inform prevention strategies and economic analyses for optimising resource allocation. The gaps in research to inform policy identified through this study may be relevant to other low resource settings with extremely limited research capacity.

**Introduction**

Myanmar is in the midst of a period of profound socio-political change, and the current situation represents an extreme example of the difficulties in optimally allocating for maximum public health benefit on the basis of limited information. In November 2015, the country will hold its first elections since a nominally civilian government was introduced in 2011, ending nearly 50 years of military rule. Economically, the situation in Myanmar is rapidly improving alongside these political shifts, due in large part to the lifting of international sanctions and a massive influx in aid funding. An estimated USD 750 million to 1 billion in external donor support is anticipated over the coming five years to support health priorities in Myanmar (Morrison *et al*. 2013), including the country's priority infectious diseases of tuberculosis (TB), HIV/AIDS, and malaria (Ministry of Health 2012). These large sums of funding are however flowing in against a background of very limited information about important factors such as the social epidemiology, transmission dynamics and health systems weaknesses. Indeed, at the recent Myanmar Health Forum ‘Investing Health’ much of the discussion revolved around what to invest in, how health systems can be strengthened, and what key priorities the international donor community can best support (Myanmar Health Forum, 2015).

It is clear that investments to improve health in Myanmar are needed, since the country lags behind others in the South-East Asia region on key health indicators (World Health Organization 2013a; World Health Organization 2012). Infectious diseases continue to account for the greatest proportion of the number of years of life lost, with HIV prevalence and malaria incidence nearly double the respective regional averages (World Health Organization 2013a). A nation-wide TB prevalence survey conducted in 2009-2010 revealed that prevalence of the disease in Myanmar is nearly two and a half times higher than previously estimated, with the revised point estimate of all TB cases at 598 per 100,000 (Ministry of Health 2011). According to a recent National TB Control Programme (NTP) update, the current prevalence is now estimated at 489 per 100,000 population (Saw Thein 2014). Drug-resistant TB is a major concern since approximately 9,000 new cases of MDR-TB are generated in the country every year (South East Asia Regional Office, World Health Organization 2012). The most recent national drug-resistance study, conducted in 2012-2013, revealed that the proportion of primary MDR-TB (that is, MDR-TB in new cases of TB) was 5.0%, compared with a regional average of 2.2% and global average of 3.6% (National Committee for MDR-TB Management, Ministry of Health, Myanmar 2014).

It is therefore widely recognized that the growing challenge from TB and MDR-TB in Myanmar must be addressed urgently, within the context of rapidly developing health, economic, and political systems and considerable funding influx. In order to best direct funding monies, an understanding of existing evidence and gaps in evidence about TB epidemiology and control systems in Myanmar is needed urgently. Given this need, we undertook a systematic review which is the first to summarise findings from, and identify evidence gaps in, the literature describing TB epidemiology, prevention, and control in Myanmar.

**Methods**

*Conceptual approach & search strategy*

A search protocol was developed to identify electronically accessible literature relating to any element of the vertical program components for TB control and prevention described in the SYSRA toolkit developed by Atun *et al*. (2004). These components include:

1. External environment (PLEST = political, legal, economic, socio-demographic, and technologic);
2. Health system structure and organization (TB organizational system, structure and relationships; TB laboratory capacity; TB drug distribution networks);
3. Healthcare delivery (TB control system, service delivery, care processes, patterns of provision and utilization, human resources);
4. Financing (financing arrangements and resource allocation for TB control);
5. TB control indicators/Needs assessment (levels of morbidity/mortality, cure, transfer, loss rates, drug resistance rates); and
6. Information system (infrastructure, flows, use of information for decision-making, content of routine data sets, quality assurance, TB classification systems).

Medline was searched for papers published online in English prior to the search date (30 June 2015). Due to the relatively limited number of peer-reviewed papers discussing TB in Myanmar, the selected free text terms were left intentionally broad. Full Medline search terms were: (Burma OR Myanmar) AND (TB OR tuberculosis); filters: English, Humans. Pilot searches revealed that the inclusion of MeSH terms did not improve the sensitivity or specificity of the search strategy and therefore were omitted.

Online searches of the gray literature were performed by reviewing the publicly accessible repositories of key Myanmar government agencies, bilateral/multilateral agencies, and non-governmental organisations active in the country. These included the Myanmar Ministry of Health (MoH) and National Tuberculosis Programme (NTP); the World Health Organization (WHO), including the South East Asia Regional Office (SEARO) and the Country Office, Myanmar; the United Nations Development Programme (UNDP); Population Services International (PSI); Médecins Sans Frontières (MSF); and the Open Society Institute (OSI). Additional relevant sources of gray literature were identified through snowballing of references.

*Inclusion & exclusion criteria*

Papers meeting the following criteria were included in the review:

* Studies considering any aspect of TB burden, control, and/or prevention, according to the SYSRA vertical programme framework (Atun *et al*. 2004); note that TB did not need to be the primary focus of the study to meet inclusion criteria;

Papers meeting the following criteria were excluded from the analysis:

* Studies focusing exclusively on migrants from Myanmar in a second-country setting, with the exception of research performed in countries immediately bordering Myanmar where there was explicit indication of bidirectional movement of study subjects between Myanmar and the additional country(ies) and
* Inability to access full-text article via PubMed, LSHTM online journal holdings, or Google Scholar.

*Data extraction & analysis*

Medline results from the primary search were screened by title and abstract for potential inclusion, according to the phases of a systematic review recommended in the PRISMA Statement (Moher *et al*. 2009). For studies provisionally meeting inclusion criteria based on the abstract, full text copies were retrieved and screened against the inclusion and exclusion criteria. Additionally, references cited in the included studies were reviewed in detail; for those with titles suggesting potential relevance to the inclusion criteria, the process of abstract screening and retrieval of full texts was repeated (a process referred to in the results as the secondary peer-literature search). A number of gray literature studies were similarly identified from the reference lists of included peer-reviewed studies; these augmented the manual search of targeted websites, as described above.

All eligible studies were reviewed in detail, with full-text analysis supported by a data extraction tool developed to capture elements from the SYSRA framework. Retrieved studies were additionally coded according to publication characteristics (year of publication; publication type; location of research, if reported; and key research focus) in NVivo (see Table 1). Study quality and bias was not explicitly assessed, as the intention of this review was to provide an overview of the range of internationally available literature on TB in Myanmar, rather than to conduct a meta-analysis of a specific research question. Additionally, as retrieved papers represented a spectrum of study types and heterogeneous research questions, attempting a uniform assessment of study quality would not have been appropriate.

To supplement the systematic review already described, we obtained and analysed a hard copy the Annotated Bibliography of Research Findings on Tuberculosis in Myanmar, which compiles TB studies conducted in Myanmar by local authors between 1910 and 2006 (Kyi et al. 2008). Findings from our analysis of this source are summarised in the discussion.

**Results**

*Search results*

The primary Medline search of the peer-reviewed literature identified a total of 77 candidate papers. Twenty-one were excluded on the basis of title. The remaining 56 were reviewed by abstract and full-text, when available. Of these, 34 articles met all criteria for inclusion in the data analysis. Secondary search of the peer-reviewed literature, performed by scanning the reference lists of included articles and retrieving relevant studies, resulted in an additional six papers meeting all criteria for analysis. A total of 37 studies published as gray literature were identified through a combination of targeted searching of relevant organizational databases and reference list review. As the majority of the gray literature retrieved consisted of reports updated at regular intervals (for instance, the WHO’s Global Report on Tuberculosis and NTP annual reports), only the most recent reports were included for recurring publications. Figure 1 presents these results as a flow chart depicting inclusion and exclusion of papers for analysis. Overall, 77 papers were included in the analysis.

*Dates, geographic scope and types of publication*

There has been a sharp increase in the number of studies and other articles on TB in Myanmar published in peer-reviewed journals over the past decade (see Supplementary Data). The earliest study retrieved was published in 1974; between 1974 and 1999, only three additional studies were published in the peer-reviewed literature available through Medline. The pace of publication began to accelerate between 2000 and 2004, with one to three articles published annually. A total of nine articles were published in peer-reviewed journals in 2005-2006 alone, four of which responded directly to the withdrawal of the Global Fund to Fight AIDS, Tuberculosis & Malaria (GFATM) funding from Myanmar in 2005. An additional nineteen studies retrieved have been published since that time.

Although the location of research could not be determined or was not applicable in seven (17%) of the 40 retrieved peer-reviewed papers, 22 (55%) reported on research performed within Myanmar. Of these, most of the studies (n=13; 59% of studies in Myanmar, or 33% of total) explicitly included Yangon as a study site, and four studies were conducted at multiple sites countrywide. Other research locations cited included Mandalay (n=1), Shan State (n=2), and Kachin and Rakhine States (n=1). Regionally, three studies were performed at the Thai-Myanmar border, one was performed at the Indo-Myanmar border, and one study included data from multiple sites around the South East Asia region. Six desk-based studies reported on research performed from outside of Myanmar (five in Geneva and one in the United States).

The types of research reported in the peer-reviewed literature varied substantially, with clinical research (n=7, 18%), narrative reviews (n=5; 13%), secondary data analyses (n=4; 10%), and reports of drug-resistance studies (n=4; 10%) the most frequently represented. Other types of research captured in the peer-reviewed literature search included qualitative research focusing on patient and provider perspectives on TB (n=3; 8%), epidemiologic surveys (n=2; 5%), program evaluations/operational research (n=2; 5%), an equity study (3%), and a retrospective cohort study (3%).

While not exhaustive, the body of gray literature retrieved in this search revealed a relatively small number of research studies (n=6; 16%), including narrative reviews (n=3), a case study, one instance of operational research, and a comprehensive needs assessment of health in Myanmar, perhaps the most complete overview of tuberculosis in Myanmar currently available internationally (Stover *et al*. 2007).

*Thematic analysis*

Of the five key health systems components incorporated from the SYSRA toolkit, TB control indicators/needs assessment – that is, research relating to TB morbidity, mortality and/or rates of cure, transfer, default, or drug resistance (Atun *et al.* 2004) – was the domain most commonly addressed, with the majority of peer-reviewed studies (n=28; 70%) including some discussion of TB epidemiology or programmatic outcome assessment in Myanmar. The most notable study in this regard is the National Tuberculosis Prevalence Survey 2009-2010 (Ministry of Health 2011). This landmark report summarizes a nation-wide prevalence survey conducted by the NTP, encompassing 70 clusters and more than 50,000 participants. The results of the survey have been far-reaching, as they demonstrated a prevalence of TB in Myanmar nearly two and a half times higher than previous estimates; following the publication of this report, most of the key indicators capturing the burden of TB in Myanmar had to be revised to reflect this higher prevalence rate. Important studies documenting the scale of the MDR-TB challenge in Myanmar (Yangon) and initial investigations of risk factors include those conducted by Phyu, Ti *et al*. (2003), Phyu (2005) and Aung *et al*. (2007). Ti *et al* (2006) conducted the first national drug-resistance survey in 30 townships nation-wide, and established that the prevalence of MDR-TB was higher than previously estimated, at 4% and 15.5% in new and previously treated patients, respectively. The findings of this study have only recently been updated in a follow-up national drug-resistance survey, conducted 2012-2013 (National Committee for MDR-TB Management 2014; full results not yet published).

Twenty-five (63%) studies considered at least one element of healthcare delivery for TB in Myanmar, including aspects of the TB control system, delivery of services, clinical care processes, utilization patterns, and human resources. Eighteen (45%) studies discussed health system structures for TB management in Myanmar, including the TB organizational system, laboratory capacity, and/or networks for drug distribution. Fifteen (38%) studies addressed TB financing and resource allocation, while sixteen (40%) studies discussed various aspects of the external environment impacting TB prevention and management in Myanmar, with the majority of these papers focusing on political (n=9), economic (n=10), and/or socio-demographic aspects (n=8); no studies included discussion of technologic aspects of the external environment. A minority (n=6; 15%) of papers included some consideration of health information systems relevant to TB. It is important to note that, as these conceptual domains are not mutually exclusive, a single study might include discussion of more than one key component, as reflected in the total numbers presented here.

In addition to coding articles according to toolkit health systems components, a single key theme or research focus was identified for each study. The largest proportion of peer-reviewed papers (n=8; 20%) focused primarily on the epidemiology of TB. Of these, three studies were international in scope, three reported on the burden of TB in Myanmar, and two focused on major health challenges in Myanmar. In the same vein, five (13%) papers focused on MDR-TB, including a global overview of MDR-TB and reports from several drug-resistance surveys in Myanmar. As mentioned previously, the allocation and subsequent withdrawal of GFATM funding in 2005 prompted publication of five articles (four news reports and one letter; 13%) during 2005-2006. Four papers (10%) each focused on (1) public-private mix (PPM) for TB management and (2) TB prevention and/or management. Key themes for the remainder of the studies included genomics (with a particular focus on MDR-TB; n=3 or 8%); HIV/TB co-infection (n=3; 8%); tuberculin conversion (n=2; 5%); a Knowledge, Attitude and Practice (KAP) assessment of workers’ understanding of TB and care-seeking behaviours (n=1; 3%); TB diagnostics (n=1; 3%); socioeconomic profiles of TB patients (n=1; 3%); and miscellaneous clinical papers in which TB was considered as a risk factor and/or comorbid condition (n=3; 8%).

The gray literature retrieved through this review largely consists of reports produced by government and non-governmental organizations, including national and international steering documents, fact sheets, workshop reports, program evaluations, and survey reports. Two particularly useful papers identified through the gray literature search which provide a comprehensive overview of the burden of infectious diseases in Myanmar over the past decade and the relationship between the TB epidemic and the external environment are reports by Beyrer, Suwanvanichkij *et al*. (2006) and Stover *et al.* (2007). Key themes addressed in the gray literature research reports included the interaction between human rights abuses and infectious diseases in Myanmar; vulnerable populations (particularly internally displaced persons and refugees); health policy recommendations for Myanmar during the current period of political transition; operational research of a social franchise chain, with focus on Public-Private Mix (PPM); regional MDR-TB burden and management; and key infectious diseases (TB, HIV/AIDS, malaria, and emerging infectious diseases) in Myanmar.

**Discussion**

*Gaps in the evidence base*

As increasing international attention and funding flows are focused on Myanmar, identifying critical gaps in knowledge on TB is essential to ensure that research priorities are rationally and efficiently set. A key finding of this review is the overall paucity of research on TB in Myanmar available internationally via traditional online sources. Despite applying very broad search parameters, only 77 peer-reviewed papers were identified of which 40 met all criteria for analysis. An analogous Medline search, substituting the term “Thailand” for “(Myanmar OR Burma)”, yields over 800 entries. While not exhaustive, the targeted gray literature search revealed that the majority of readily retrievable reports (i.e. those from internationally-respected organizations not requiring membership or subscription fees) consisted of routine summary reports at the national and international levels. This relative lack of research on TB in Myanmar has important implications for funding: first, it highlights the need for allocation of additional resources for TB research in Myanmar and, second, it implicitly underscores the fact that emerging resource allocation plans for optimal TB control will likely draw on an incomplete evidence base.

The pronounced increase in the number of research studies published in the internationally-available peer-reviewed literature since 2000 is encouraging, and can reasonably be expected to continue rising in the coming years.

Analysis of the geographic scope of research highlights two key issues. First, a significant proportion of both the peer-reviewed and gray literature available online is comprised of research performed outside of Myanmar. This trend is particularly pronounced in the gray literature, much of which is produced in Geneva or the USA. Second, the research performed in country is focused heavily on Yangon Region, with only a handful of studies performed elsewhere in the country. Limited research has successfully been conducted and reported from the States, with Shan State being the most commonly studied, but many research activities are supported along border regions from neighbouring countries where access is less restricted.

Given the small number of studies meeting criteria for analysis in this review, combined with the heterogeneity of study types represented, it is not possible to draw any significant conclusions about the distribution of publication types. However, it is clear that reviews, secondary data analyses, drug-resistance studies, and clinical research are most represented in the peer-reviewed literature, while research studies retrieved from the gray literature are dominated by narrative reviews. Notably underrepresented in the international peer-reviewed literature on TB in Myanmar are equity studies, research focused on vulnerable populations, economic analyses, epidemiological studies on risk factors for development of drug-resistance, investigations of TB transmission dynamics using genomic approaches, health system analyses and operational research.

*Unpublished research available locally in Myanmar*

In 2008, the Department of Medical Research (Lower Myanmar), on behalf of the Ministry of Health of the Union of Myanmar and in collaboration with the Myanmar Country Office for the World Health Organization, published the *Annotated Bibliography of Research Findings on Tuberculosis in Myanmar*, which includes a total of 270 citations, most of which are accompanied by short abstracts summarizing research methods and findings. This publication, consisting largely of university theses and conference presentations, is available only in hard copy within Myanmar, and represents a unique, invaluable source of data on the current and historical state of TB research in the country.

We recognize that a key limitation of this study was the inability to include the many abstracts and monographs published locally within Myanmar in the systematic review, as these are not accessible in their entirety online. Since the majority of the research has not been peer-reviewed, the quality of studies is unclear. A brief analysis of the annotated bibliography indicates that the research that has been produced in country has been both more prolific and more varied than that reported in the international peer-reviewed or gray literature. In terms of key research themes, the locally produced literature on TB reveals different emphases than the body of peer-reviewed literature. The most commonly studied themes, in descending order, are: TB treatment (n=52; 19%), extra-pulmonary TB (n=35; 13%), TB diagnostics and screening (n=32; 12%), MDR-TB (n=22; 8%), paediatric TB (n=19; 7%), HIV/TB co-infection (n=18; 7%), indigenous medications (n=17; 6%), knowledge of disease (n=16; 6%), TB control programming (n=16; 6%), and TB epidemiology (n=13; 5%). There were a number of other key themes receiving less attention, including treatment-seeking behaviours, treatment default, TB risk factors, gender, treatment cost, cost-effectiveness analysis, and socio-economic status, among others.

While a limited number of these abstracts and full-text articles are available on ResearchGate and the Online Burma Library, devising ways of making them more broadly accessible to an international audience will be invaluable for guiding future international research collaborations on TB in Myanmar and promoting the work done by local researchers.

*Recommendations for future research to inform policy and resource allocation*

Much of the existing literature on TB in Myanmar available outside the country, whether in peer-reviewed sources or the gray literature, focuses on establishing the burden of TB and MDR-TB. Funding for TB and other priority infectious diseases is the focus of a number of additional studies, while only a small minority of research papers focuses on problems of TB management and prevention, the socioeconomic burden of TB infection and treatment, and care-seeking behaviours. These gaps are all the more significant when contrasted with the research priorities demonstrated by the selection of research topics in the literature on TB conducted locally. In this body of literature, TB treatment, including indigenous medications, accounts for the largest percentage of research papers, with specific issues related to TB management (screening and diagnostics; extra-pulmonary TB; HIV/TB co-infection) also frequently studied. HIV/TB co-infection represents a key health challenge in Myanmar, as reflected in the number of local publications on the topic; despite this, however, concomitant infection with both HIV and TB has been less frequently addressed in the peer-reviewed and gray literature. Finally, although anti-tuberculosis drug resistance has been well documented and is one of the most pressing issues facing the Myanmar health system today, risk factors for the development of MDR-TB have received relatively little attention.

The NTP’s Five Year Strategic Plan for Tuberculosis 2011-2015 (NTP 2010) outlines a strategy for enabling and promoting TB research in Myanmar, with an explicit emphasis on program-based operational research. The Strategic Plan sets out an ambitious program of multiple nation-wide surveys, including a national drug-resistance survey (completed); a knowledge, attitude, and practice survey; and a repeat national TB prevalence survey, to be completed in 2015. Additional suggested topics for operational research activities, to be carried out as funding permits, include (among others) health-seeking behaviours, social determinants of TB, causal factors leading to the development of MDR-TB, and PPM. It is challenging, however, for the NTP, donors and researchers working in Myanmar to rationally design research plans without information on existing research and evidence gaps, which this review is the first to provide. Our analysis highlights the urgent need for targeted, well-designed research to inform new policies and resource allocation strategies in Myanmar. The specific gaps in research to inform policy identified through this study may be relevant to other low resource settings with limited research capacity. Important areas that may be neglected when funding, technical skills and infrastructure for conducting research is low include: studies focused on rural and/or vulnerable populations, analyses of risk factors that can inform prevention strategies, studies of transmission dynamics involving genomic analyses, interventional studies and economic analyses for optimizing resource allocation.

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