Treatment of Tuberculosis in Complex Emergencies in Developing Countries: A Scoping Review

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Abstract

Almost 172 million people live in complex emergencies globally resulting from political and/or economic instability. The provision and continuity of health care in complex emergencies remain a significant challenge. Health agencies are often hesitant to implement tuberculosis programmes in particular because its treatment requires a longer commitment than most acute diseases. However, not treating tuberculosis promptly increases mortality and untreated tuberculosis further increases the incidence of tuberculosis. Given that complex emergencies are increasing globally, there is an urgent need to analyse the available evidence to improve our understanding of how best to deliver tuberculosis programmes in such settings. Using

a scoping review method, we selected and analysed fifteen studies on tuberculosis programmes in complex emergencies. We found that despite the challenges, tuberculosis programmes have been successful in complex emergencies. We identified seven cross-cutting factors that were found to be important: service providers and treatment regime, training and supervision, donor support, adherence, leadership and coordination, monitoring, and government and community support. In general, programmes showed greater creativity and flexibility to adapt to the local conditions and at times, it also meant diverting from the WHO guidelines. We identify areas of further research including the need to study the effectiveness of programmes that divert from the WHO guidelines and their implication on drug resistance.

Keywords: Tuberculosis, scoping review, complex emergencies, conflict

Introduction

The number of armed conflicts has been increasing globally since 2013 (Dupuy et al. 2017). Although colonial and interstate conflicts have reduced, conflicts internal to countries have increased, but these internal conflicts often have external state actors. These conflicts can be categorised as complex emergencies, defined by the World Health Organisation (WHO) as "situations of disrupted livelihood and threats to life produced by warfare, civil disturbance and large-scale movements of people, in which any emergency response has to be conducted in a difficult political and security environment" (Wisner and Adams 2002). Complex emergencies do not have straightforward transmission between phases, they are characterised by continued political instability, economic instability and chronic conflict that can disrupt countries for long periods of time. There is also a 50% risk of post conflict societies reverting to conflict within the first five years (Collier et al. 2003). Low- and middle-income countries (LMIC) bear the largest burden of complex emergencies. Of the 172 million people affected by complex emergencies globally, the majority live in LMIC (Centre for Research on the Epidemiology of Disasters (CRED) 2013).

The impact of complex emergencies on population health can be devastating. Besides the increased deaths as a direct result of the emergency, there is also an increase in the incidence of diseases. Connolly et al. (2004) estimate that the highest excess morbidity and mortality often occurs during the acute phase of the emergency, and communicable diseases, alone or in combination with malnutrition, account for most of these deaths. Of particular concern is the rise in incidence and mortality from tuberculosis. As seen in several war-struck countries: In Bosnia and Herzegovina, the incidence of newly diagnosed tuberculosis rose to four times the pre-war levels (Toole

et al. 1993), in Guinea-Bissau tuberculosis was associated with a three-fold increase in mortality during the first six months of the war (Gustafson et al. 2001). Congo-Brazzaville experienced a period of war from 1997 to 1999; the annual number of new tuberculosis cases increased from 1,691 in 1994 to 4,218 in 2000 (M'Boussa et al. 2002).

Kimbrough et al. (2012) state that while incidence and mortality from tuberculosis tend to increase during times of complex emergencies, treatment rates decrease with increasing intensity of the emergency. This may be because of disruptions to health services (Biot et al. 2003, M'Boussa et al. 2002) and being an airborne disease, untreated tuberculosis, in turn, increases the transmission rate. Moreover, there is a risk of further spread of infection due to overcrowding, acute malnutrition and poor living conditions (Cegielski and McMurray 2004, Toole et al. 1993).

The treatment of tuberculosis is complex. Tuberculosis affects the lungs in 85% of the cases and 57% of these cases are sputum smear-positive and therefore highly infectious (World Health Organization 2016). The standard regimen for pulmonary tuberculosis, recommended by the WHO, includes a six-month course of antibiotics using directly observed treatment (DOTS) strategy, which involves patients swallowing the medication whilst being directly observed by a health staff, supervised and supported treatment, control the rise of multidrug-resistant tuberculosis (MDR-TB) that emerges due to the inappropriate or incorrect use of drugs, or interruption of treatment (World Health Organization 2010).

In complex emergencies, detection and treatment of TB become even more challenging. Unlike other communicable diseases such as measles, mumps and pneumonia, symptoms of TB are not easily visible. Governments and NGOs are also hesitant to address TB as the treatment requires a longer commitment than most acute diseases and the risk of interruption of treatment due to the conflict can lead to increased resistance to TB medications. In these circumstances, they are unsure whether they can comply with the treatment targets set by the WHO - TB programmes should focus on sputum-positive pulmonary TB patients and they should aim to achieve 85% cure rate with DOTS in six months (Biot et al. 2003). As these high levels of cure rates and the provision of undisrupted treatment are not guaranteed, in many complex emergencies, TB programmes are often postponed until stability is secured. The consequence is delayed, disrupted treatment for a large and highly vulnerable and infectious group of patients.

To reduce the human, social and economic costs of TB, for the first time, the WHO drafted recommendations for TB control specific to emergencies (Kimbrough et al. 2012). However, despite these recommendations, evidence on what works is unclear and fragmented. The aim of this paper is to conduct a scoping review of available evidence and identify factors that contribute to successful implementation of TB programmes in complex emergencies. We specifically focus on LMIC as these countries not only bear the global burden of complex emergencies, they also bear the global burden of TB: 95% of TB cases and 98% of TB deaths occur in LMIC (World Health Organization 2016).

Methodology

Inclusion and exclusion criteria

Studies published between January 1995 and September 2015 that examined the implementation of TB programmes in complex emergencies in LMIC were included in the review. We included all types of studies, including reviews, commentaries and policy reports. Conference proceedings and abstracts were included only if full texts were available. Studies on refugee camps, which have a different set-up as compared to complex emergencies, were excluded. We also excluded studies where TB was discussed as a secondary illness to HIV and studies that focused entirely on MDR-TB.

Search Strategy

A comprehensive strategy was implemented to identify relevant literature. We first conducted the search using several online databases: Embase, Global Health, MedLine with the Ovid search engine, and CINAHL Plus and Health Policy Reference Center using the EBSCOhost search engine. A MeSH thesaurus and the Cochrane Database for reviews were consulted to identify key words to search these databases. The search string included a combination of these words: [“tuberculosis” or “TB”] and [“continuation of care” or “treatment continuation” or “treatment programme” or “directly observed treatment” or “deliver* of treatment”] and [“complex emergency” or “crisis” or “war” or “conflict” or “armed conflict” or “fragile state” or “unstable” or “chronic complex emergency” or “conflict-affected” or “fragile” or “insecurity” or “violence”, or “humanitarian crisis”]. We further used country limiters to capture studies on LMIC only. Secondly, to identify grey literature, we searched OpenGrey and the websites of key organisations that have

technical expertise in delivering health programmes in complex emergencies (WHO and Médecins Sans Frontières (MSF)).

Using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009), all retrieved studies were initially screened using the title and abstract. After removing those that did not meet the inclusion criteria, full texts of the remaining studies were reviewed and only those that met the inclusion criteria were selected. Finally, we screened the bibliographies of all selected studies. A study was selected only if both the authors agreed it was relevant for the review.

We did not follow the methodology like the one suggested by the Cochrane Effective Practice and Organisation of Care Review Group (EPOC) because we were interested in the process and operationalisation of tuberculosis programmes in complex emergencies that have been studied using non-experimental study designs using both qualitative, quantitative and mixed methods (Ridde and Morestin 2011) . EPOC approach is normally applied for synthesizing evidence on effectiveness. Instead, we used the scoping review method, which is recommended for studying the process of implementing complex interventions and it does not discriminate among studies based on methodological criteria (Arksey and O'Malley 2005)

Data extraction and synthesis

Our data extraction and analysis consisted of two parts. First, we extracted data on the study context, methodology, treatment, service delivery, and main organisations

involved in the programme. We used the WHO target to assess treatment success i.e. 85% cure rate for DOTS (Biot et al. 2003). Given that complex emergencies can differ in terms of severity, using Macias (2013) typology, we categorised the emergency for each included study as *acute* (active high-level armed conflict), *chronic* (persistent low-level armed conflict) or *protracted* (high-level armed conflict with diffused violence and persistent instability involving neighbouring states).

Second, we analysed the full text of the included studies to identify factors that contributed to the success of TB programmes. In accordance with the scoping review method, we did not distinguish between studies in terms of the soundness of their design nor did we assign weights dependent on their data (Arksey and O'Malley 2005). However, we have summarised the studies in the results section that provide an indication of the robustness of the designs used.

Results

Description of studies

Fifteen studies met our inclusion criteria and were included in the review: ten quantitative, two qualitative and three mixed-methods studies (Figure 1).

Figure 1

Of the fifteen studies, covering twelve countries, the majority were from Africa (n=6) and Asia (n=6), one each from South America and Europe, and one used data from multiple countries. Together, they included six acute, five chronic, and four protracted emergencies. (Table 1).

Table 1

The majority of the quantitative studies used a longitudinal design (n=7), where they followed patients on TB treatment (Salomao 1991, Keus et al. 2003, Agutu 1997, Doveren 2001, Rodger et al. 2002, Norval et al. 1998). Only Das et al. (2014) include two different approaches of delivering TB treatment in India – DOTS and SAT (self-administered treatment). Five studies used routinely collected patient and administrative data (Ahmadzai et al. 2008, Martins et al. 2006, Heldal et al. 1997, Tigani et al. 2008, Mauch et al. 2010). Among the qualitative and mixed methods studies, three studies were written in a case-study format (Seddiq et al. 2014, Tigani et al. 2008, Mauch et al. 2010) and two included interviews with staff and key informants (Liddle et al. 2013, Seddiq et al. 2014)..

Applying the WHO target of 85% cure rate, only four countries did not meet this target, but three of them achieved 81% cure rate in some years/regions (Figure 2). In Nicaragua, the cure rate of 81% was achieved in the conflict zones in 1988 (Heldal et al. 1997) but it dropped the next two years to 63%. However, it is important to note that the higher rate of 81% was the highest cure rate in the country, even outperforming the regions unaffected by the conflict. In East Timor, the cure rate improved from 50% in 1997 to 81% in 2003 (Martins et al. 2006), similar to the rate reported in Haiti (Mauch et al. 2010). In contrast, in Mozambique, the cure rate did not improve in the five years covered by the study (1985-1989) and remained close to 75% (Salomao 1991).

Figure 2

In Somalia, Agutu et al. (1997) using data from 1998, reported a cure rate of 74% in the Luuq. Although Mauch et al. (2010) and Liddle et al. (2013), studying later periods, reported higher rates, 89% (2000-2005) and 81% (2005-2012): the former figure is the average national rate for the NTP while the latter is an MSF-run programme operating in only two regions.

In India, Das et al. (2014) found that the DOTS regimen performed better than the shortened SAT, 70% vs 53%, although both performed below the WHO threshold. However, the authors still concluded that these programmes were successful. In contrast, a previous study from India (Rodger et al. 2002), different region and time period, did meet the WHO threshold and achieved 86% cure rate with a DOTS-based programme.

Five countries (Afghanistan, Angola, Cambodia, Kosovo, and South Sudan) consistently reported a successful cure rate. From these, Kosovo reported the highest cure rate of 93% which increased from 87% in 2001. Democratic Republic of Congo (DRC) reported 85% cure rate in 2005, slightly higher than 84% reported the previous year. In Afghanistan, cure rate increased from 87% in 2004 to 91% in 2011. The study by Seddiq et al. (2014) on Afghanistan, covered the period from 2006 to 2011 but did not specify the type of TB and therefore, could not be compared to the WHO threshold.

Factors contributing to the success of TB programmes

We identified seven factors that determined the success of TB programmes in complex emergencies.

1. Service providers and treatment format

Service provision and treatment regimens for complex emergencies were not standardised across settings. Service provision reflected the availability of providers and the WHO recommended treatment regimen was adapted based on what was feasible and practical. Modifying the treatment regime and using established service providers were identified as factors of successful TB control programmes.

In South Sudan, the treatment was reduced to four months of daily supervision, instead of WHO recommended six months of DOTS which was found to be unfeasible for a semi-nomadic population (Keus et al. 2003). Further, contingency plans were made and in the event of evacuations of staff and local populations, patients were given "runaway-bags" with a one-month supply of drugs. They were also informed to meet in four weeks at a pre-arranged location to replenish their drug supply if the situation does not improve.

In India, the health workers adopted two different strategies depending on the security situation (Das et al. 2014). When feasible, the standardised DOTS programme was used, otherwise, treatment was delivered through MSF mobile clinics using the Self-administered Tuberculosis Treatment (SAT) strategy. Under SAT, patients were given two months medications and advised to return to a fixed place after six weeks, where the mobile clinic would be with more medication. In another study in Churachandpur, India, the DOTS programme required the staff to meet the patient only three times per week, instead of daily, as it was difficult and dangerous to travel (Rodger et al. 2002). This was reported to have increased adherence.

In Nicaragua, TB treatment was for eight months: two-month intensive treatment, administered in the DOTS format and for the remaining six months, patients were required to attend the health facility only weekly, twice monthly or monthly to receive the supply of TB medications (Heldal et al. 1997).

The service provider, as a key factor for success, were emphasised in Cambodia and India. In Cambodia, TB wards were integrated into the general public hospitals, reducing significant delays in starting the treatment (Norval et al. 1998). In India, using an established and trusted clinic gave credibility to the programme (Rodger et al. 2002).

2. Training and supervision

All studies underlined the importance of continuous learning and training opportunities for staff. Training and supervision also helped build strong relationships between team members, who work under stressful circumstances, and created a unified approach to problem-solving.

In Mozambique, training through annual national seminars, strengthened programme supervision (Salomao 1991). In East Timor, staff attended a three-month training workshop (Martins et al. 2006). In Nicaragua, the personal responsible for managing the programme attended regional training before the introduction of the short-course treatment. In addition, doctors and nurses attended annual seminars to refresh practical skills and discuss common problems. This also helped develop problem-solving skills and team-building (Heldal et al. 1997). In Churachandpur, India, outreach workers, TB coordinator and lab technician attended a formal training programme which also facilitated team-building and respect (Rodger et al. 2002). In

South Sudan, educating all staff rather than focusing on only those in the TB programme, improved case findings by reducing delays in diagnosis (Keus et al. 2003).

In Afghanistan, DOTS training was extended to community health workers (CHWs). Besides bridging the gap between the community and health facilities, engaging CHWs in delivering the TB programme also enabled the development of a stronger relationship between the community and the programme and made the programme more responsive. Furthermore, the programme put emphasis on recruiting women CHWs as it also improved access to women's health issues (Ahmadzai et al. 2008, Seddiq et al. 2014). Although not measured, it was hoped that using women CHWs would minimise gender disparities within TB diagnosis and treatment.

In Angola, the staff training was more comprehensive. Besides training in DOTS administration, they also received training on educating patients and defaulter tracing techniques. Furthermore, the lab personnel received training in staining techniques, sunlight microscopy and waste disposal. Three training sessions of one week were conducted in a new province every month (Doveren 2001). Staff willingness to engage and learn made a big difference to the programme performance. As found in other studies, this also helped team-building and developed problem-solving skills.

The Cambodian Programme emphasised continuous training rather than one-off training for staff. Refresher training was regularly held for all levels of staff that also helped to maintain staff interest. For provincial staff at the central level, workshops using a shortened version of the WHO module, quarterly seminars and annual

conferences were organised. In addition, payment of per diem on supervision and training visits greatly enhanced the motivation of staff (Norval et al. 1998).

The Kosovo study emphasised the importance of human resources development within the international framework (Tigani et al. 2008). For example, individualised training was performed throughout the programme by international consultants. Senior staff took part in many regional workshops and international conferences and courses, which also improved staff motivation. Likewise, in Somalia, international staff played an important role in training and supervision (Liddle et al. 2013). Initially, the international staff were based in Somalia but due to safety concerns were later evaluated. They, however, continued to provide support from a neighbouring country, Kenya, and there was no effect on treatment rates (adjusted OR 0.85, p=0.27).

In addition, continuous support and supervision of staff were also identified as key factors in Nicaragua, Somalia, Mozambique and Kosovo. In Somalia (Liddle et al. 2013) and Mozambique (Salomao 1991) this was done either by regular visits or daily communication by the remote management team. In Kosovo, the core team of international consultants were engaged throughout the five-year period, offering assistance in planning, implementation and technical support (Tigani et al. 2008).

3. Donor support

Countries suffering from complex emergencies are fragile states with a weakened government lacking in financial and human resources. In such settings, several studies emphasised the necessity of consistent donor support.

In many countries, donor support for supplies, funds and drugs contributed to the success of the TB programmes. In Somalia, donors provided communication equipment which helped both the field staff and the remote team to communicate and coordinate their activities, as well as made staff, feel supported (Liddle et al. 2013). Further, continuous supply of anti-TB drugs from international suppliers was also critical to avoid disruption to treatment (Agutu 1997). International support for TB drugs was also crucial in South Sudan, East Timor and India (Keus et al. 2003, Martins et al. 2006, Rodger et al. 2002). In India, drugs were stored on site in secure facilities for the 12-month period and treatment was free (Rodger et al. 2002).

In Cambodia, support was provided by several international organisations. The initial supply of drugs was donated by non-governmental organisations. French funds, through WHO, covered the costs of training and supervision, and later the World Bank gave a five-year loan of $8 million that guaranteed the continuous availability of anti-TB drugs (Norval et al. 1998). In East Timor, external donor funds were seen as a key component in accelerating the process of developing and not for the continuous supply of drug they provided (Martins et al. 2006).

In Afghanistan, besides provision of funds, international support in technical assistance was also important. The WHO provided technical assistance in proposal writing and fulfilling grant implementation requirements, helping the programme to secure larger funds (Seddiq et al. 2014). In Kosovo, the NTP, in collaboration with DOW-US, acquired a grant from the GDF, which provided for free TB drugs for three years (Tigani et al. 2008).

4. Adherence

Many programmes devised methods of promoting treatment adherence. These methods can be divided into five types: distance to treatment, incentives, building strong relationships, educating patients, and record keeping.

Reducing the distance travelled by patients to reach clinics encouraged compliance. In Somalia, the programme ensured patients coming from distant locations stayed near the project in "TB Villages" throughout the treatment course (Liddle et al. 2013). This MSF-run programme also provided accommodation for relatives. In addition, "DOTS corners" were set up in towns, which provided treatment near the patient's place of residence. Similar strategies were used in South Sudan, Nicaragua and DRC (Keus et al. 2003, Heldal et al. 1997, Ndongosieme et al. 2007) where severely ill patients were offered accommodation in tents within the treatment centres or were hospitalised if they lived too far away. Likewise, in Angola and East Timor, patients who were unable to walk long distances or who lived too far away, were offered temporary housing for a limited period near the outpatient clinic (Doveren 2001, Martins et al. 2006).

In Churachandpur, India, instead of bringing the patients closer to the treatment, the treatment was brought closer to the patients. Outreach workers providing the DOTS treatment lived in the same area as their patients (Rodger et al. 2002). Each round trip was less than six kilometres. This not only had an effect on adherence; if a patient was absent at the specified time, the outreach worker could return later that day to administer the medication as the distance travelled was not far, but it also reduced hazards and the probability of encountering an unsafe situation. Only for clinical

reviews at the larger clinic, patients had to travel but the distance was less than five kilometres. Reducing patient travel had an added benefit of reducing possible TB transmission. However, Rodger et al. (2002) study had a small cohort of 178 patients, all living in the same region. This method may not be feasible for larger groups of patients, dispersed over larger areas.

Strong relationships between health workers and patients contributed to improving compliance. This is particularly important in conflict regions where suspicion and mistrust are common and most programmes incorporated special arrangements to strengthen this aspect. In the MSF-run programme in South Sudan, patients were divided into three distinctive groups, supervised by a specific MSF-trained health worker who understood the personal needs and situation of the patients (Keus et al. 2003). In addition, medical staff spent extra time with patients and showed interest in their daily life and regularly inquired about any treatment side effects affecting their lifestyle. This helped develop a strong doctor-patient relationship. In Churachandpur, India, part-time local community outreach workers were employed for each ethnic group, extending access to all affected communities. Community elders acted as advisors to the outreach workers, which helped the workers to understand and take account of ethnic sensitivities (Rodger et al. 2002). In East Timor, community-based treatment observers, known as "motivators" were engaged in the programme to promote adherence (Martins et al. 2006). During the conflict in Kosovo (Tigani et al. 2008) health workers were carefully selected: who can safely cooperate with both dominant and minority populations. In the TB programme a "Minorities Coordinator" was also appointed to particularly assist services in the minority regions.

Incentives were effective in improving adherence in seven countries. This is contrary to the WHO field manual for TB treatment in refugee populations which states that incentives are not routinely necessary for successful TB treatment (Connolly et al. 2007). Given the food supply insecurity in complex emergencies, food rations were successful. In Somalia, besides patients, their guarantors, who signed a written agreement stating the patient must complete the full course of the treatment, were also given a dry food ration as an incentive to support the patient (Liddle et al. 2013). Similarly, treatment guarantors were also given rations in South Sudan. In India, distributing eggs to patients on a weekly basis was an incentive for patients to remain in the area (Rodger et al. 2002). In Cambodia and Afghanistan, food support was provided in collaboration with the World Food Programme (Norval et al. 1998, Seddiq et al. 2014). In East Timor, besides supplementary food, the programme also covered transport costs for some patients (Martins et al. 2006). Only in Angola patients were given non-ration incentives (Doveren 2001). They were awarded a certificate on completing the initial phase. The patients valued this certificate greatly as this meant they were no longer excluded from work.

Educating patients on TB treatment and transmission was another method to promote adherence, however, this is not unique to complex emergencies. In Somalia, education activities with patients were carried out regularly in the DOTS centres (Liddle et al. 2013) and the patients have explained the importance of completing their anti-TB medication in the outpatient clinics (Agutu 1997). In South Sudan, before starting the treatment every patient was counselled to avoid defaulting (Keus et al. 2003). The programme approach to overcoming certain traditions in the Nuer culture was to counsel female patients along with their husbands, as the man traditionally makes

family decisions. By having the husband present during these sessions, he too understood the importance of adherence. In Churachandpur, India, patients were not only counselled on the need to comply but signed a declaration stating they will complete the full treatment (Rodger et al. 2002). In Angola, weekly education sessions for the patients waiting in the outpatient clinic were given both in Portuguese and the local dialect. Further, time was allocated for medical consultation and patient counselling daily (Doveren 2001). In India, default patients were given additional supportive counselling (Das et al. 2014).

Keeping up-to-date patient records, including their contact details, in the clinics helped the staff to follow-up. In Somalia, mobile numbers were taken from patients in case they needed to be contacted (Liddle et al. 2013). In South Sudan, health workers were able to trace their patients the same day they defaulted (Keus et al. 2003). In India, the project also maintained records of other people who could be contacted if the patient did not attend an appointment (Rodger et al. 2002).

5. Leadership and coordination

Strong, stable and flexible management, was found to be important in seven countries. In Afghanistan, visible leadership taken by one agency was crucial in avoiding confusion, diffused implementation and duplication of efforts (Seddiq et al. 2014). Effective coordination among stakeholders was achieved through regular meetings and e-sharing. The programme further engaged patients, their families and communities through social mobilisation activities, for example by involving religious scholars and priests. No other study created partnerships at the community level as part of their coordination strategy. In Nicaragua, a manager was appointed for each area, who coordinated with the laboratory and patients, oversaw adherence and

ordered supplies (Heldal et al. 1997). Strong and stable partnerships and coordination were also identified as important in Afghanistan, DRC, Haiti and Somalia, which was achieved by using a common framework for TB control with the DOTS programme (Mauch et al. 2010). In the DRC, effective coordination between non-government organisations and the Ministry of Health was achieved by creating a memorandum of understanding signed by all parties involved. This memorandum described the rights and responsibilities of each partner, ensuring all partners understood their role (Ndongosieme et al. 2007). In East Timor, duplication of efforts was avoided by clearly discussing individual responsibilities of each agency involved in the implementation of the TB programme and coordination was improved by holding weekly meetings (Martins et al. 2006). In Kosovo, an authoritative agency was identified to provide oversight and keep track of goals and objectives (Tigani et al. 2008). For example, the WHO assumed responsibility, in the absence of a Ministry of Health, for TB control and considered various organisations on the ground to identify as lead partner. As mentioned in other countries, this approach helped avoid duplicating efforts.

6. Monitoring

Effective monitoring was identified as an essential factor for implementing TB programmes in most countries. Countries used different mechanisms of monitoring but all programmes emphasised the importance of data and communication. In Somalia, patient data and pharmacy consumption data was reviewed weekly to avoid stock outs (Liddle et al. 2013). Random checking of the TB registration book and of patient medical records was conducted. Weekly monitoring calls were held with international staff based in Nairobi and when safe, the international staff came to meet the in-country team and visit field sites. In India, up-to-date patient records, including

treatment and laboratory data, were maintained and reviewed regularly (Das et al. 2014). In Churachandpur, India, recording and reporting systems, recommended by the WHO plus RNTCP, were found to be useful in monitoring (Rodger et al. 2002). The programme also created project-specific forms used for recording clinical and sociodemographic information of patients. In Nicaragua and Kosovo, quarterly supervisory visits were conducted to review records, verify reporting and discuss operational problems (Heldal et al. 1997, Tigani et al. 2008). These visits were continued in Nicaragua even when the region was unsafe due to the on-going conflict.

Programmes in Afghanistan, East Timor, Cambodia, and Mozambique established national monitoring systems. The Afghanistan NTP introduced uniform training systems and quality assurance guidelines, and monthly service reports were submitted by more than 90% of the health care facilities (Ahmadzai et al. 2008, Seddiq et al. 2014). In East Timor, the Caritas Tuberculosis Programme (CTP) and the NTP conducted regular laboratory quality-assurance checks using the WHO standard methods (Martins et al. 2006). In Cambodia, quarterly reports and cohort analysis were done for each TB unit and these reports were sent to the CENAT and the Ministry of Health for monitoring (Norval et al. 1998). In Mozambique, besides regular monitoring, the central staff participated in yearly national seminars where case-findings, treatment and quality control system were discussed across regions (Salomao 1991).

7. Government and community support

TB programmes in conflict regions required political sanction from community leaders and government. Strong endorsements from the government provided high-level of authority and credibility to the programme team (Norval et al. 1998). In

Somalia and India, acceptance, trust and support from local leaders were essential for programme sustainability (Liddle et al. 2013, Rodger et al. 2002). In India, running the programme from a trusted and established clinic gave it credibility. Besides government and community leaders, the programme in South Sudan also had strong political support from army commanders (Keus et al. 2003). In Afghanistan, the government declared controlling TB as a national priority, which increased commitment from international donors (Seddiq et al. 2014). This was also true for the Nicaraguan programme where health authorities acknowledged TB as a serious threat and helped reserve hospital beds for TB patients (Heldal et al. 1997). In East Timor, the commitment of the local authorities helped vulnerable TB patients - homeless and children orphaned by the armed conflict - receive accommodation during their treatment (Martins et al. 2006).

Discussion

Delivering TB programmes in complex emergencies is challenging. Acute staff shortages, disruption of supplies and funds, destruction of health facilities, and displacement of people are common problems. However, our review found that in spite of these challenges, programmes have been successful in delivering TB programmes in several LMIC countries. We identified several factors that have contributed to this success, however, importance of these factors to a particular programme depended on the nature of the complex emergency and the local context.

Creative solutions were used to promote completion of treatment and reduce noncompliance. Contingency plans were set in place in South Sudan which included giving ‘runaway bags’ of TB drugs to patients when the crisis deteriorated (Keus et al.

2003). In Angola, patients were awarded certificates after completion of the initial phase and in Somalia, patients were made to sign a written agreement to complete the treatment (Doveren 2001, Liddle et al. 2013). These are straightforward solutions, yet produced high adherence rates as the patients greatly valued the certificate and the agreement. In Somalia and South Sudan, guarantors were also identified from the community who supported and encouraged the patients (Keus et al. 2003, Liddle et al. 2013).

Our analysis revealed that many TB programmes diverted from the WHO guidelines. In South Sudan, Somalia, India and Nicaragua, the WHO recommended six-month DOTS programme was modified (Keus et al. 2003, Liddle et al. 2013, Das et al. 2014, Heldal et al. 1997). The directly supervised phase was reduced to four months in South Sudan and to two months in Somalia and Nicaragua, while the remaining treatment was self-administered by the patients. In the SAT programme in India, treatment was unsupervised throughout – patients were given a six-week supply of TB drugs at a time. Despite not following the WHO recommendations, the programmes in South Sudan and Somalia achieved a cure rate of at least 85%. However, in Nicaragua, the programme achieved much lower cure rate (66% on an average). In India, the SAT programme also performed poorly (53%) but DOTS, which was based on the WHO recommendations, did slightly better (69%). However, another study from India, where the frequency of the directly supervised treatment was reduced to three times a week, did achieve a cure rate of 86% (Rodger et al. 2002).

Biot et al. (2003) throw some light into whether "sub-optimal" programmes that do not follow the WHO recommendation of six-month treatment with 85% cure rate,

should be considered in complex emergencies. Using mathematical models, they estimated the benefits and risks of different treatment scenarios and concluded that although TB programmes should aim at 85% cure rate, in complex emergencies, 4-month treatment for 75% of patients is beneficial to a situation of no treatment at all. This raises questions on whether the WHO guidelines need to be relaxed for complex emergencies and begs further empirical research.

It is possible to argue that the complex emergency framework itself is not practical and a better method is needed to identify the variety of crises – as one guideline does not fit all. Furthermore, with the different types of crises, guidelines could be more context-specific. This could imply setting different thresholds for considering cure rates as successful (as suggested by Biot et al. (2003)) and prioritising different strategies depending on the type and scope of crisis. For example, the programme in South Sudan was established during the "acute phase" of a complex emergency, in an unstable and hostile environment. It achieved a cure rate of 85% during the crisis. Factors such as reducing the daily supervision treatment to four months and providing "runaway bags" of medication could be "context-specific" strategies for an acute unstable crisis where an NGO (like MSF in this case) is capable to coordinate such an effort without the support of the local government. Without the support of an NGO, WHO recommendation to postpone TB programmes until stability is restored would be advisable. Conversely, programmes in a longer, more established "chronic complex emergency", such as in Cambodia which was also successful in achieving 85% cure rate, benefited from making sure TB wards were well integrated with the public hospitals as this reduced delays in treatment, and ensured continuous training of staff, regular monitoring and food support for patients and relatives. Therefore, settings in which there is less disruption in the functioning of the existing public health system, and

where NGOs can help fill gaps in coverage, would benefit from strengthening the already established national programmes to deliver TB treatment.

Greater collaboration between the local and external stakeholders was another important factor for implementing successful TB programmes in complex emergencies. Our review found that programmes with strong political support from the national government and the community were able to deliver TB programmes (Liddle et al. 2013, Rodger et al. 2002, Norval et al. 1998). Many programmes obtained political endorsements from local stakeholders - community leaders, army commanders and local authorities. Particularly essential in conflict regions where suspicion and distrust are high. Many programmes used existing public health providers to deliver TB programmes (Norval et al. 1998, Rodger et al. 2002). Where government infrastructure was destroyed, programmes were often operated by NGOs (e.g. MSF). The role of international donors was also crucial in maintaining a continuous supply of drugs and supplies and providing technical assistance, training, and monitoring in many countries (Keus et al. 2003, Rodger et al. 2002, Norval et al. 1998, Tigani et al. 2008). However, the presence of multiple agencies can also lead to duplication of efforts and inefficiencies in implementation. Not only must the diverse agencies interact with people, roles and areas of expertise that they are unfamiliar with, they have to do so under high-risk and high-stress conditions. Start Network offers a refreshing solution; it offers a platform for NGOs to make decisions collectively and respond quickly to "under the radar" emergencies around the world. However, further research is needed to evaluate this and similar initiatives (Start Network).

Adapting to the local socio-political context is important for the success of a programme in any setting. However, in complex emergencies, the need to maintain neutrality was identified as critical in Kosovo and India. This was particularly reflected in the selection of health workers. In Kosovo, healthcare workers were carefully selected from those who could safely cooperate with both the dominant and minority populations (Tigani et al. 2008) and in India, patients were assigned outreach worker from their own ethnic group (Rodger et al. 2002).

Other factors such as trained staff and effective monitoring are not unique to complex emergencies but they are certainly more difficult to realise. In all programmes achieving a cure rate of 85% or over, training and supervision were essential for success. Further, the emphasis was laid on *continued* training and *regular* supervision. Developing staff not only helped maintain quality but also improved staff motivation, team-building and problem-solving skills – qualities needed when working in an emotionally and physically challenging situation.

Furthermore, a major theme to be explored in complex emergencies, which has not been discussed in our included papers, is a unified system to allow tracking of patients. Technological innovations are currently being developed for resource-poor settings and if used correctly could be highly effective in complex emergencies. For example, mHealth services (healthcare using mobile communication technologies) have been found useful in improving adherence to treatment by sending voice-based reminders to patients to take their medications on time (Narasimhan et al. 2014). Another example is from Operation Asha an NGO, which has developed a system known as “eCompliance” to track every dose a patient takes by scanning their

fingerprints. Patients' medical and TB history is also electronically saved, and if doses are missed, the system issues an SMS alert to the patient and supervisor. This has shown to increase compliance and cure rates (Snidal et al. 2015). These technological innovations can help monitor treatment compliance and reduce visits to the health facility, which can be immensely beneficial in complex emergency settings.

Finally, our review does not include refugee settings however there are similarities and contrasting conclusions. Similar to our findings, close coordination and collaboration between the local health agencies and the NTP of the host country was found to be essential for a successful TB programme in refugee populations (Bam et al. 2007). Although TB prevalence tends to be higher among refugees as compared to host country or country of origin (which could be because of better detection of TB in refugee camps), treatment outcomes are often better because of shorter distances needed to travel and health education campaigns (Bohler et al. 2005, Kimbrough et al. 2012) – distance and education were identified as important in our review as well. An interesting factor that was not found by our review relates to stigma. According to Cookson et al. (2015) in the Syrian refugee camps in Jordan, stigma associated with TB was higher inside the camp than outside because of the overcrowded living conditions, which can reduce diagnosis and compliance to medications.

Limitations of the review and of the literature analysed

To the best of our knowledge, this is the first study that has synthesised information on factors that contribute to successful implementation of TB programmes in complex emergencies. However, our results should be used with caution. In spite of using a broad search strategy, we found only fifteen studies that met our inclusion criteria.

These fifteen studies used varied study designs. Since the context was challenging, understandably none of the studies adopted a randomised control or case-control study design to test different TB programmes. The number of included studies would have been even smaller if we used the EPOC methodology, specifically reducing the studies on the implementation process. The data collected from the studies ranged from 1985 to 2012. In this time period, guidelines for TB treatment have been amended and the humanitarian response to emergencies is constantly changing, making it hard to compare study outcomes over time. Some studies are not recent and do not highlight the current state of complex crises. A recent study on the Ebola outbreak in West Africa used computational models to estimate TB deaths due to a reduction in TB treatment coverage. It estimated that TB deaths increased by 51% in Guinea, 59% in Liberia and 62% in Sierra Leone (i.e. 1281, 592 and 841 additional deaths respectively) during the crisis (Parpia et al. 2016). This was contrary to what Ortuno-Gutierrez et al. (2016) found in ten health facilities in the Conakry region of Guinea i.e. TB programmes and services were sustained during the crisis and there was no drop in diagnosis and cure rates. But, this study was in collaboration with the Damian Foundation which supported and gave additional funds and technical assistance to the ten health facilities under study. However, as in these studies, in depth understanding of the actual implementation of TB programmes is however limited. Studies were also hard to compare in terms of the type and severity of complex emergencies. Publication bias can be an issue in any review. By searching and including grey literature and programme reports we were able to minimise this to some extent. We might have also missed relevant studies written in languages other than English. However, in spite of these limitations, taken together, the studies

provided rich data on the operation and management of TB programmes in complex emergencies.

Future research

The aspect which is largely missing from current research is patients' perspective. We lack an understanding of people experience of accessing TB programmes in complex emergencies. Further, more robust research is needed to assess the effectiveness of sub-optimal programmes that do not follow the WHO guidelines and their implication on drug resistance. In addition, further research must be centred on developing a better framework to identify the variety of crises; as this will enable the development of specific guidelines for the type of crises involved. Finally, it would be beneficial to know the long-term implications and effects of the reported projects to be able to further advocate for the inclusion of TB treatment in complex emergencies.

Conclusion

In conclusion, in spite of the challenges, many TB programmes were successful in complex emergencies. We have highlighted some aspects that contributed to this success. Further research is needed to understand how people in complex emergencies cope with TB and their experience of accessing TB programmes. As more evidence becomes available, WHO guidelines on TB programmes may need to be revisited and probably revised for complex emergencies.

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Figure 1. Search results

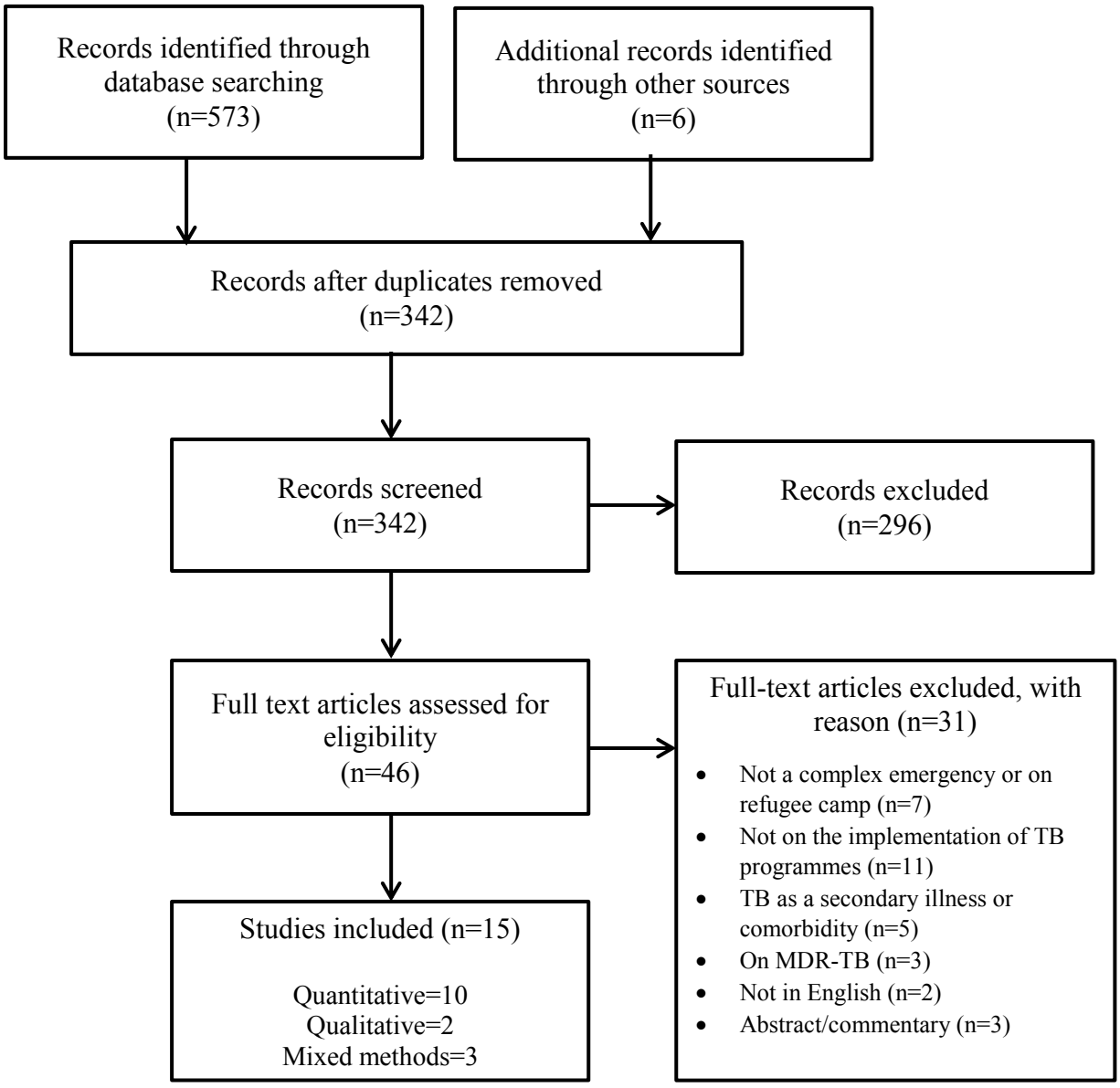
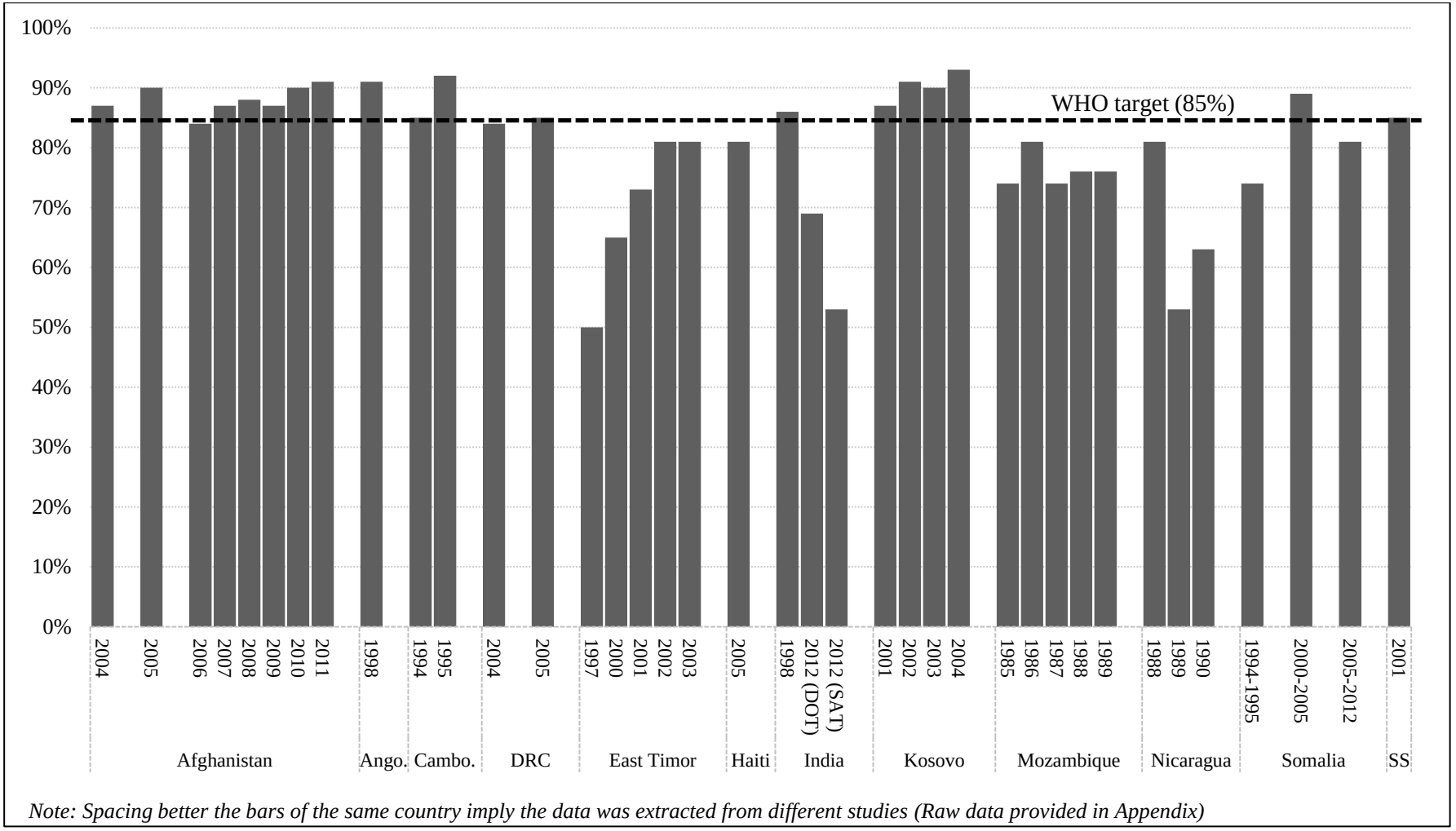


Figure 2. Treatment Success Rates



Note: Spacing better the bars of the same country imply the data was extracted from different studies (Raw data provided in Appendix)

Table 1: Description of Studies (N=15)

Study	Country	Complex Emergency	Data Period	Programme Period	Type of Study	Study Design*	Service Providers	Treatment Format	Programme Lead
	Africa								
Salomao 1991	Mozambique	Armed conflict (Acute)	1985-1990	1985-1990	Quantitative	Longitudinal study	Health Centres	supervised daily	NTP
Ndongosieme et al. 2007	DRC	Armed conflict (Chronic)	2004-2005	Prior to 2004 (dates not mentioned)	Qualitative	Case Study type (Programme Report)	Health Centres	supervised daily	National Tuberculosis and Leprosy Control Programme
Keus et al. 2003	South Sudan	Civil war (Acute)	2001	2001	Quantitative	Longitudinal pilot study	MSF Outpatient Clinic and TB Clinics	4 months (supervised daily) + 3 months (self-administered)	MSF
Liddle et al. 2013	Somalia	Armed conflict (Protracted)	2005-2012	2005-2012	Mixed methods	Mixed methods (routinely collected patient data and staff interviews)	MSF Outpatient Clinic, Therapeutic Feeding Centre, TB Clinics	2 months (supervised daily) + 4 months (self-administered only for those that have shown good adherence and can attend clinics monthly, for others daily supervision)	MSF
Agutu et al. 1997	Somalia	Civil war (Protracted)	1994-1995	1994-1995	Quantitative	Longitudinal study	District Hospital and TB Outpatient Clinic	supervised daily	District TB Control Programme
Doveren 2001	Angola	Armed conflict (Acute)	1998	Prior to1998 (dates not mentioned)	Quantitative	Longitudinal pilot study (Field report)	MSF	supervised daily	MSF
	Asia								
Ahmadzai et al. 2007	Afghanistan	Conflict setting (Chronic)	2000-2005	2000-2005	Quantitative	Observational study using routinely collected patient data	REACH Facilities	supervised daily	NTP and REACH
Seddiq et al. 2014	Afghanistan	Conflict setting (Chronic)	2001-2011	2001-2011	Qualitative	Case study (literature review and key informant interviews)	Health facilities	supervised daily	NTP
Rodger et al. 2002	India	Civil conflict (Acute)	1998	Prior to 1998 (dates not mentioned)	Quantitative	Longitudinal study	Clinic of the Society for HIV/AIDS Lifeline Operation	supervised thrice-weekly	Local advisory group
Das et al. 2014	India	Conflict setting (Chronic)	2012	2012	Quantitative	Longitudinal study	MSF Mobile Clinics (SAT), Government Community Health Centre (DOTS)	DOTS (supervised daily) and SAT (six-week supply at a time)	MSF
Martins et al. 2006	East Timor	Civil conflict (Acute)	1997 - 2004	1995-2004	Quantitative	Observational study using routine administrative data	Catholic Outpatient Clinics, Community Health Centres and Private Clinics	supervised daily	NTP and Local NGO (Caritas Dili) TB Program operated by Caritas East Timor (Catholic Church)
Norval et al. 1998	Cambodia	Civil war (Chronic)	1993-1996	1994-1996	Quantitative	Longitudinal study	TB units in public hospitals	supervised daily	NTP and WHO
	America								
Heldal et al. 1997	Nicaragua	Civil war (Acute)	1982-1983, 1988-1990	1988-1990	Quantitative	Before-after observational study using routine patient and administrative data	NTP Outpatients Health Posts or Centres	2 months (supervised daily) + 6 months (self-administered, patient visits weekly, twice-monthly or monthly)	NTP
	Europe								
Tigani et al. 2008	Kosovo	Conflict (Protracted)	2001-2004	2001-2004	Mixed methods	Case study (Programme implementation, routine patient and administrative data)	Health Centres	supervised daily	NTP and international partners (WHO, DOW-USA FIC-NIH)
	Multiple regions								
Mauch et al. 2010	Somalia, DRC, Haiti, Afghanistan	Fragile state (Protracted)	2000-2006	2000-2006	Mixed methods	Case study (Programme implementation, routine patient and administrative data)	Health Centres except Outpatient Clinic in Somalia	supervised daily	NTP

* Longitudinal studies

Abbreviations: DRC (Democratic Republic of Congo), MSF (Médecins Sans Frontières), TB (Tuberculosis), NTP (National Tuberculosis Programme), DOTS (Directly Observed Treatment, Short course), SAT (Self-Administered Therapy), WHO (World Health Organisation), DOW-USA (Doctors of the World, USA), FIC-NIH (Fogarty International Center/National Institute of Health USA)

Supplementary File

Table A. Treatment Cure Rates

Country	Year	Treatment Success Rate (%)	Type of Tuberculosis
Afghanistan	2004	87%	Pulmonary Smear Positive only. Available data from 2000-2003 show important inconsistencies. Data from 2004 onward are considered to be reliable.
	2005	90%	Pulmonary Smear Positive only. Data extracted from Mauch et al (2010).
	2006	84%	Does not specify.
	2007	87%	
	2008	88%	
	2009	87%	
	2010	90%	
	2011	91%	
Angola	1998	91%	Pulmonary Smear Positive only.
Cambodia	1994	85%	Pulmonary Smear Positive only.
	1995	92%	
DRC	2004	84%	Pulmonary Smear Positive only
	2005	85%	Pulmonary Smear Positive only. Data extracted from Mauch et al. (2010)
East Timor	1997	50%	Pulmonary Smear Positive only
	2000	65%	
	2001	73%	
	2002	81%	
	2003	81%	
Haiti	2005	81%	Pulmonary Smear Positive only. Data extracted from Mauch et al. (2010)
India	1998	86%	Pulmonary Smear Positive only.
	2012 (DOT)	69%	Using DOTS. All cases (Pulmonary smear-positive, Pulmonary smear negative and Extra pulmonary).
	2012 (SAT)	53%	Using SAT All cases (Pulmonary smear-positive, Pulmonary smear negative and Extra pulmonary).
Kosovo	2001	87%	Pulmonary Smear Positive only.
	2002	91%	
	2003	90%	
	2004	93%	
Mozambique	1985	74%	Pulmonary Smear Positive only using the Short-course Regimen (2SHRZ/6HT).
	1986	81%	
	1987	74%	
	1988	76%	
	1989	76%	
Nicaragua	1988	81%	Pulmonary Smear Positive only in Region I, Region V, and Region VI. The regions affected by conflict.

	1989	53%	
	1990	63%	
	1994-1995	74%	Pulmonary Smear Positive only.
Somalia	2000-2005	89%	Pulmonary Smear Positive only. Data extracted from Mauch et al (2010)
	2005-2012	81%	Pulmonary Smear Positive only.
South Sudan	2001	85%	Pulmonary Smear Positive only.

Table B. Scope of studies (N=15)

Study	Treatment Cure Rates	Adherence	Training & Support	Management, Monitoring, & Organization	Service Delivery	Coordination of Donors & NGOs	Logistics (supplies/ funding)	Government/ Community Support
Mauch et al.	✓			✓	✓	✓	✓	
Salomao	✓		✓	✓				
Ndongosieme et al.	✓	✓	✓	✓		✓		
Keus et al.	✓	✓	✓	✓			✓	✓
Doveren	✓	✓	✓					
Ahmadzai et al.	✓		✓		✓	✓		
Seddiq et al.	✓		✓			✓	✓	✓
Liddle et al.	✓	✓	✓	✓		✓	✓	✓
Agutu et al.	✓	✓	✓					
Rodger et al.	✓	✓	✓		✓		✓	✓
Martins et al.	✓	✓	✓	✓		✓	✓	✓
Das et al.	✓							
Norval et al.	✓	✓	✓	✓	✓		✓	✓
Heldal et al.	✓		✓	✓	✓		✓	✓
Tigani et al.	✓		✓	✓		✓	✓	
Number of issues	15	8	13	9	5	7	9	7
Percentage of Studies	100%	53%	87%	60%	33%	47%	60%	47%