Field research in humanitarian medical programmes

Treatment of a cohort of tuberculosis patients using the Manyatta regimen in a conflict zone in South Sudan

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Abstract
This is a descriptive report of a pilot project of tuberculosis (TB) treatment in a conflict zone. A TB programme was implemented by Medécins Sans Frontières (MSF)-Holland in a semi-nomadic population in a very insecure and underdeveloped area of Upper Nile Province in South Sudan. Outcome measures were operational feasibility, default rate, and sputum smear conversion at 4 months. A cohort of TB patients was admitted over a 10-week period (July–September 2001). Adherence strategy, project implementation, and contingency planning were adapted to local conditions. The treatment regimen (4 HRZE [4-month daily supervised regimen] followed by 3EH or 3TH [3-month unsupervised regimen]: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and thiacetazone (T)) was a variant on the Manyatta regimen developed for semi-nomads in Kenya. Of 163 patients, 84 (52%) were children aged < 15 years. Lymph node TB comprised 34% and spinal TB 15% of all patients. Among adults, 41% had smear-positive pulmonary disease. Only 1 patient (0.6%) defaulted. All sputum smear-positive patients who completed 4 months of therapy converted to smear-negative although 2 were subsequently found to have relapsed. TB in complex emergency situations is an underrecognized priority. Using an approach adapted specifically to this setting, TB treatment was successfully implemented with minimal risk of promoting drug resistance, in an unstable setting.

Keywords: tuberculosis, extrapulmonary tuberculosis, conflict, humanitarian aid, South Sudan

Introduction

Tuberculosis (TB) is among the top 10 causes of death worldwide (Murray & Lopez, 1997). Despite increasing efforts, it is estimated that only 32% of smear-positive TB cases globally are diagnosed in directly-observed treatment, short-course (DOTS) programmes each year (WHO, 2003).

There is evidence of increased TB morbidity and mortality in populations affected by the adverse conditions of war (Barr & Menzies, 1994). The complex emergencies which commonly accompany wars lead to malnutrition, crowded living conditions, poor hygiene, displacement, disrupted health care services, shortage of medical personnel, and lack of TB drugs, thereby increasing the burden of TB (Toole & Waldman, 1997; Houston, 1998).

Even where the problem of TB is recognized, humanitarian relief agencies have often been hesitant to address it. Because TB requires a longer commitment than most acute medical conditions, it is difficult to determine when to initiate TB treatment under the difficult and unpredictable conditions of complex emergencies. The feasibility, sustainability, security, and quality of the programme, and ultimately the risk of promoting drug resistance, are important concerns. Criteria have been proposed for implementing quality TB programmes under such circumstances (Médecins Sans Frontières, 1995; Global Tuberculosis Programme, WHO and UNHCR, 1997). Some of these preconditions, such as 'relative stability for 6–12 months' are difficult to predict, delaying the provision of TB programmes for this large and highly vulnerable group of patients.

This article describes the implementation of a pilot project to treat TB patients under difficult and insecure conflict conditions in South Sudan. The primary patient outcomes assessed were operational feasibility, default rate, and sputum smear conversion at the end of 4 months of supervised therapy.

Setting

Political situation

The civil war in Sudan is the world's longest running conflict. The ethnically and culturally African people of the South are struggling for self-determination against political and religious domination by the Islamic and Arab North. Conflict over recently developed oil deposits is a further obstacle to peace and has increased military activity in areas of oil development such as Upper Nile Province. In addition, violent conflicts among tribal groups, political factions, and local warlords within South Sudan contribute to a very insecure, unstable environment. The results of 20 years of civil war include more than 2 million deaths, millions of people displaced internally or to neighbouring countries, massive human rights violations including sexual violence and slavery, collapse of the social, economic and health systems, chronic and acute malnutrition, and high morbidity and mortality from infectious diseases such as visceral leishmaniasis (VL; kala-azar) and TB. Infrastructure, roads, shops, and schools are primitive or non-existent. Health care facilities are few, isolated, very basic, and almost totally dependent on international non-governmental organizations (NGO).

Population

Upper Nile Province (Figure) in south-eastern Sudan borders North Sudan. The population consists mainly of Nuer, a semi-nomadic agro-pastoral tribe, subsisting largely through cattle herding, cultivation, and fishing. Most communities migrate during the dry season (October–May) to seek grazing pastures, fishing opportunities and rivers to water their livestock. Lactating women and the elderly tend to stay in the villages. People return to their villages in the wet season (May–October), to cultivate sorghum and maize.

Médecins Sans Frontières (MSF) activities in South Sudan

MSF-Holland has worked in Upper Nile Province since 1989 in the 'transitional zone' between the government militia and local factions, an area of particular instability. Programme activities include provision of basic health care, emergency health responses to outbreaks of meningitis, measles, cholera and malnutrition, and treatment of VL and TB. Over 14 years, more

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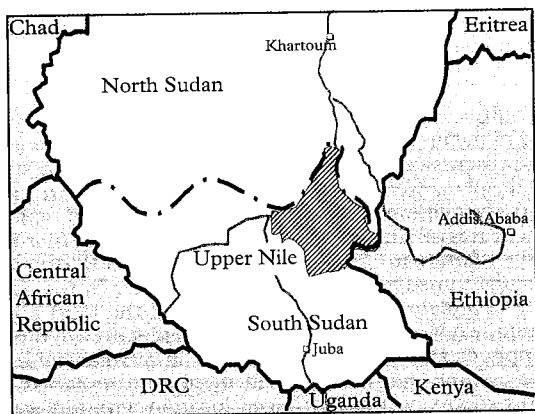
Figure. Map of South Sudan: the hatched area indicates Upper Nile Province.

than 25 000 persons have been treated for VL, an otherwise fatal parasitic disease (Seaman et al., 1996). Some of these patients have had coexisting or subsequent TB.

In the mid-1990s, MSF initiated TB treatment in a less insecure area of Western Upper Nile. Between 1993 and 1998, about 2000 patients received treatment with the Manyatta regimen (2SHRZ/2HRZ/3TH [two 2-month daily supervised regimens followed by a 3-month unsupervised regimen]: streptomycin (S), isoniazid (H), rifampicin (R), pyrazinamide (Z), and thiacetazone (T)). Analysis of 1418 patients treated between 1993 and 1996 showed that 89% completed the 4-month supervised component of treatment, 5% died, 5% defaulted and 1% failed treatment. Among 590 sputum-positive patients, 85% were smear-negative at the end of 4 months; 5% defaulted, 5% died and 4% were still smear-positive. Encroachment of military activity related to oil exploration ended the programme in 1998.

Following this experience and confronted with many TB patients in Lankien, Upper Nile Province where MSF was implementing VL treatment, with strong support from both the local community and expatriate health staff, the decision was made to re-initiate TB treatment in 2001. A TB programme had been operated temporarily in the community by another NGO in the previous year.

Tuberculosis epidemiology in Sudan

Few data exist on TB rates in South Sudan. The Nuer are not only ethnically and culturally distinct from both the Arab and Bantu populations, but probably differ historically in terms of past exposure to TB. Because there has been minimal access to TB therapy in South Sudan recently and no private or other source of TB drugs in the community (except streptomycin which is often found in the local market), the probability of drug resistance was expected to be low. This was supported by the findings on resistance testing of approximately 30 sputum specimens collected during the course of the previous TB programme. HIV prevalence is currently low: only 2 of 231 (0.8%) VL patients aged > 15 years treated in Lankien were seropositive.

Methods of implementation
Planning and organization

The pilot project planned to limit the number of cases admitted to 200, to avoid exceeding staffing capacity. Enrolment was limited to a 10-week period (July–September 2001) commencing in the rainy season. Based on a year's experience in the area it was decided that insecurity was too great to permit the safe, continuous operation of a TB programme during the

dry season when military forces can move freely. Another concern was that adherence might be limited by population movements to dry season pastures.

The project was implemented by 3 Sudanese health workers, assisted by 3 drug dispensers and 1 laboratory assistant who had only low levels of primary education and no previous experience in health care. The national staff were intensively supervised by an expatriate doctor and laboratory technician and trained on the job. Quality control of sputum microscopy was implemented through the WHO reference laboratory in Nairobi, Kenya.

Although local personnel were trained to continue supervising treatment temporarily should expatriates have to evacuate during insecurity, all decisions on admission, discharge, and treatment regimen were made by the expatriate doctor.

Directly-observed treatment, short-course procedures

Prior to programme initiation, to maximize political support and influence stability in the region, community leaders, chiefs, army commanders, and local authorities were informed about the programme, the community risk of drug resistance, and the critical importance of treatment adherence.

We obtained sufficient supplies of quality-assured antituberculosis drugs from an international supplier, as well as laboratory materials. Because of the unreliability of air transport in the rainy season, a 2-month reserve supply of drugs and materials was maintained in a locked cupboard at the programme site.

Passive case detection by sputum microscopy was initiated. Patients with suspected TB were referred from the basic health care clinic which was operated by another expatriate NGO in the same community or at times, for example during periods when the primary care service was not operating, presented directly to the TB service. Efforts were made to improve case finding by educating the staff of the basic health care centre. Many patients had to travel great distances by foot to reach care. MSF's role in this community, along with TB treatment, included a VL programme and a feeding centre. X-ray facilities were not available.

Smear-positive pulmonary TB was diagnosed by Ziehl–Neelsen staining of sputum. A small number of patients were diagnosed with TB despite repeated negative sputum examinations, if they had persistent symptoms without another apparent diagnosis and without a response to 2 courses of broad spectrum antibiotics. Spinal TB was diagnosed on the basis of a grossly visible angular deformity of the spine. Lymph node TB was diagnosed in the presence of persistently enlarged, usually draining, lymph nodes; TB in children was diagnosed based on a scoring system modified from that of Edwards (Crofton et al., 1992).

Regimen used

Since a longer period of supervision greatly complicates the delivery of the TB programme in unstable situations and there was some concern that 6 months in the treatment centre might be too long for a semi-nomadic population, we selected a modification of the Manyatta regimen which had been used successfully for Kenyan semi-nomadic populations (Idukitta & Bosman, 1989). New patients received a 4-month daily intensive phase in which swallowing of every dose was observed by a health worker, consisting of HRZE (E = ethambutol). For children in the intensive phase, individual drugs were used while adults received fixed-dose combination (FDC) drugs. Adults and children were discharged with 3 months of unsupervised EH or TH, respectively, in an FDC tablet (4HRZE/3EH or 3TH).

A regimen of 2SHRZE/1HRZE/5HRE (similar to the WHO and International Union Against Tuberculosis and Lung Disease [IUATLD] re-treatment schemes

except that treatment was given daily throughout) was given under direct observation throughout, to relapses, returned defaulters and treatment failures.

The final cure and relapse rates with this regimen have not been documented because the regimen was developed specifically for nomadic populations where follow-up for the full duration of the treatment course could not be assured. Studies of 4-month 4-drug regimens have achieved an 85% or more cure rate (East African/British Medical Research Councils Study, 1981; Singapore Tuberculosis Service/British Medical Research Council, 1986). In these studies, no resistance to rifampicin occurred among the relapsed cases and development of resistance to other drugs was uncommon. The 3-month continuation phase (equivalent to half the continuation phase of the IUATLD regimen) is expected to increase the cure rate, perhaps by a further 5–10%. Biot et al. (2003) demonstrated by mathematical modelling (assuming a low prevalence of HIV and a low level of primary drug resistance) that the 4-drug 4-month regimen alone would result in significant benefits to individual TB patients, with minimal risk of contributing to transmission or resistance.

Adherence strategy

The following measures were put in to place to enhance adherence (Volmink et al., 2000). (i) Patients were intensively counselled on the importance of treatment and the need to remain in the treatment centre for 4 months of intensive treatment. Since the man makes family decisions in Nuer tradition, female patients were counselled with their husbands. (ii) Every patient and his/her attendant received an adequate weekly food ration of grain, pulse, oil, corn [maize]–soya blended flour and salt (2200 kcal/d). In addition, patients received daily milk and biscuits (900 kcal/d) with their medicines. Food was an important incentive in this setting of frequent food insecurity. (iii) Health education on the cause, transmission, and treatment of TB, hygiene, etc., was given weekly. Special emphasis was given to the individual and community risks of defaulting treatment. (iv) Sixty-five percent of the patients stayed near the treatment centre with family or friends and attended daily for assessment and observed treatment. Sputum-positive cases and severely ill patients were offered accommodation in tents within the treatment centre. (v) Every day patients were interviewed by staff about medication side effects. A medical doctor was present to examine patients with problems, deal with the side effects or treat other concurrent disease, encouraging a strong doctor–patient relationship. (vi) Patients were divided into 3 groups, each headed by an MSF-trained health worker who knew their patients very well. If a patient did not appear for treatment, he/she was traced the same day. In exceptional individual circumstances, patients were given permission to leave the programme for a few days to attend a funeral or wedding.

Contingency planning

Following an extensive analysis of possible scenarios and discussion with patients and national staff, contingency plans were made to deal with potential insecurity and evacuation, balancing the interests of patients under treatment with the risks of causing drug (particularly rifampicin) resistance by allowing TB drugs to circulate unsupervised in the community. In the event of a complete evacuation of MSF and the local population, each patient would be provided with a 1-month supply of HE or HT FDC tablets in a 'runaway-bag'. We assume that MSF would be able to re-access the TB patients at a pre-arranged location within 4 weeks in most circumstances

Results

This first cohort consisted of 163 patients, 84 (52%) children aged < 15 years and 79 adults (Table 1). Among adults, 32 (41%) had smear-positive and 4 (5%) smear-negative pulmonary disease. Twenty-seven (34%) of the adults and 28 (33%) of the children had lymphatic disease, while 9 (11%) and 15 (18%) respectively had spinal TB. Almost one-third of the patients were aged 5–14 years, which was unexpected since this age group usually has a relatively low TB incidence (Doege, 1965; Comstock et al., 1974).

Among initially smear-positive patients, the sputum smear conversion rate after 2 months was only 70%, perhaps reflecting the advanced state of disease in many patients. Of 33 sputum-positive patients, 3 (9%) died during the intensive phase but all 30 completing 4 months of supervised therapy became smear-negative (Table 2). No smear-positive patient defaulted during the supervised component of therapy.

Although the treatment programme was predicated on the assumption that many patients would not be able to return to the treatment centre after completion of the unsupervised second phase of treatment, all were actively encouraged to attend for a final follow-up visit if possible. Twenty-five initially smear-positive patients provided sputum samples at 7 or 8 months, of whom 2 (8%) had failed treatment (a 30-year-old women thought to be immunosuppressed due to metastatic disease from probable breast cancer and a frail 75-year-old man), reducing the number of initially smear-positive patients with an overall successful outcome to 28 (85%). Five smear-positive patients (15%) did not return for sputum examination after completion of their continuation phase. Among 130 extrapulmonary and smear-negative patients, 125 completed therapy, 4 died and 1 defaulted.

Anonymous unlinked HIV testing of all adult pa-

Table 1. Distribution of tuberculosis patients by age and type of disease, Upper Nile Province, South Sudan, July–September 2001

Type of tuberculosis	Age (years)						Total (%)
	0–4	5–14	15–24	25–34	35–44	≥ 45	
Smear-positive	0	1	6	5	7	14	33 (20)
Smear-negative	0	4	1	2	1	0	8 (5)
Nodal	5	23	7	6	10	4	55 (34)
Spinal	7	8	3	1	3	2	24 (15)
Paediatric[a]	21	9	0	0	0	0	30 (18)
Other[b]	1	5	1	2	2	2	13 (8)
Total (%)	34 (21)	50 (31)	18 (11)	16 (10)	23 (14)	22 (13)	163 (100)

[a]Diagnosed using a modification of Edwards' paediatric diagnostic scoring system (Crofton et al., 1992).
[b]Eight abdominal, 1 skin, 1 TB meningitis, 3 bone/joint TB.

Table 2. Treatment outcomes at four months among smear-positive tuberculosis patients, Upper Nile Province, South Sudan, July–September 2001

Type of tuberculosis	Acid-fast bacilli negative *n* (%)	Died *n* (%)	Defaulted *n* (%)	Total *n* (%)
New smear-positive	24 (89)	3 (11)	0	27 (100)
Re-treatment smear-positive	6 (100)	0	0	6 (100)
Total	30 (91)	3 (9)	0	33 (100)

tients in this cohort of TB patients revealed no positives.

Discussion

This study indicates that TB treatment is operationally feasible and that very high levels of treatment adherence can be maintained under extremely difficult conditions. Although there are several reports of TB treatment in the relatively confined setting of refugee camps, published experience of TB treatment in war zones is limited. However, national TB programmes were developed and successfully implemented in Mozambique and Nicaragua during periods of civil war (Salomao, 1991; Heldal et al., 1997).

Spectrum of disease

This pilot project encountered an unusual spectrum of TB disease. Seventy-five percent of the cases treated were extrapulmonary TB. This is consistent with experience in the Nuer population in the previous MSF programme in Upper Nile Province in the 1990s (a total of 55% extrapulmonary TB, of whom 15% were spinal, 13% nodal, and 22% paediatric). Extrapulmonary TB is more common in certain populations such as Asian immigrants to western countries (Cowie & Sharpe, 1997). Several other possible explanations, either general or site-of-disease-specific, for the high number of extrapulmonary cases are considered below.

Spinal TB was diagnosed only in the presence of a grossly visible gibbus deformity, a finding generally considered to be highly specific (although relatively insensitive) for TB in a high prevalence population. Reliance on this finding would be expected to result in underdiagnosis rather than overdiagnosis of spinal TB.

Lymph node TB was diagnosed clinically, based strictly on spontaneous drainage of chronic lymph nodes. Lymph node biopsy, particularly in children, could not be safely performed under the prevailing conditions. A subsequent cohort of lymph node TB patients was individually reviewed by a clinical TB consultant (S.H.) and TB was confirmed as the most likely diagnosis in most cases under treatment at that time. A treatment response in most cases further supported the diagnosis. While a small number of individual cases may have been misdiagnosed, we think it unlikely that any other infectious or non-infectious disease could account for a large proportion of these cases.

TB is notoriously difficult to diagnose in children under optimal conditions. We have modified a widely recommended paediatric scoring system (Crofton et al., 1992) to make it more stringent, in part by making the weight criteria stricter. Most children also received nutritional support and treatment for other possible conditions before considering a TB diagnosis. Moreover, the existence of high rates of TB in young children is supported by the finding of high rates of skin test positivity in young children in the area (J. Seaman, personal communication).

If extrapulmonary TB patients survive longer, extrapulmonary cases would be overrepresented in a population which lacked access to treatment, the situation that prevailed prior to the implementation of this programme. HIV cannot account for the high proportion of extrapulmonary disease, as no HIV positives were identified.

An alternative explanation for high rates of extrapulmonary disease in a population living in close contact with their cattle, and not boiling or pasteurizing the milk which forms their staple food, might be the impact of *Mycobacterium bovis*, historically associated with higher rates of extrapulmonary disease.

Finally, because of the extremely limited access to TB diagnosis and treatment in South Sudan it is likely that only a small proportion of all TB cases are diagnosed. Care seeking beliefs and behaviour in the local population could substantially bias the types of TB patient presenting for care.

Outcome and evaluation

The observed default rate of 0.6% from the supervised 4-month intensive phase of therapy demonstrates that it is possible to treat patients successfully, with negligible risk of promoting drug resistance, under the difficult prevailing conditions. The high death rate among sputum-positive patients is probably due to treatment delay and very advanced disease at presentation.

Seasonal tuberculosis treatment cohorts

This highly unconventional approach involving seasonal provision of TB treatment was initially thought to be the only safe and feasible mechanism for providing treatment under the unique chronic conflict conditions prevailing in this area of South Sudan. Perhaps not surprisingly, this strategy proved fraught with problems. It caused intolerable professional/ethical difficulties for staff who were expected to turn patients away after the closure of the recruitment period. It also led to tension between MSF expatriates and the community, at one point even fostering insecurity, when a chief and patient threatened the medical doctor. Moreover, since TB is not a seasonal disease and patients continue to present for treatment even when the admission period is closed, the community credibility of the programme, essential to the function of passive case finding, is seriously compromised. Because of these difficulties, the programme was opened to year-round admission about 6 months after closure of the initial cohort. This experience reinforces the position that year-round treatment remains the default position of any TB programme.

Conclusions

TB in complex emergencies and conflict settings is an underrecognized priority.

New ideas and innovative strategies applying established principles of TB treatment to unique and difficult situations are needed to give people living in settings such as Sudan access to this lifesaving care. Based on the experience of this pilot project, 2 more sites for TB treatment have been opened in Upper Nile and the Nuba mountains.

One expected outcome of a TB programme—reducing TB transmission in the community—requires the detection of 70% of all patients. This may not be achievable under conditions of conflict and insecurity.

We believe that the humanitarian benefit of TB treatment provides sufficient justification for a TB programme, even if the impact on transmission may be less than would be anticipated in more stable settings.

Finally, approaches that worked well in South Sudan may not guarantee success in other contexts or conflicts. The decision to start TB treatment should be based on a thorough analysis of the individual situation and careful consideration of benefits and risks. Extensive consultation with the community and insight into the cultural, economic and political situation is essential.

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