DOTS-based tuberculosis treatment and control during civil conflict and an HIV epidemic, Churachandpur District, India

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Objective To pilot the WHO guidelines on DOTS for tuberculosis (TB) among displaced people affected by conflict in Churachandpur District, Manipur State, north-east India, which has endured an HIV epidemic, injecting drug use, civil unrest, high levels of TB, and poor TB treatment and prevention services for many years.

Methods Prerequisites for TB control programmes were established. WHO guidelines and protocols were adapted for local use. Outreach workers were appointed from each ethnic group involved in the conflict, and training was conducted. Quality control and evaluation processes were introduced.

Findings TB was diagnosed in 178 people between June and December 1998. Of the 170 with pulmonary disease, 85 were smear-positive. Successful outcomes were recorded in 91% of all patients and in 86% of smear-positive cases of pulmonary TB. The default rate and the mortality rate were low at 3% each. HIV positive serostatus was the only factor associated with a poor treatment outcome.

Conclusion TB treatment and control were possible in a conflict setting and WHO targets for cure were attainable. The factors associated with the success of the programme were strong local community support, the selection of outreach workers from each ethnic group to allow access to all areas and patients, the use of directly observed therapy three times a week instead of daily in the interest of increased safety, and the limiting of distances travelled by both outreach workers and patients.

Keywords Tuberculosis, Pulmonary/diagnosis/drug therapy; HIV seropositivity; Substance abuse, Intravenous; Treatment outcome; Refugees; Ethnic groups; War; Risk factors; Guideline adherence; India (*source: MeSH, NLM*).

Mots clés Tuberculose pulmonaire/diagnostic/chimiothérapie; Séropositivité HIV; Toxicomanie intraveineuse; Evaluation résultats traitement; Réfugiés; Groupes ethniques; Guerre; Facteur risque; Adhésion à directives; Inde (*source: MeSH, INSERM*).

Palabras clave Tuberculosis pulmonar/diagnóstico/quimioterapia; Seropositividad para VIH; Abuso de sustancias por vía intravenosa; Resultado del tratamiento; Refugiados; Grupos étnicos; Guerra; Factores de riesgo; Adhesión a directriz; India (*fuente: DeCS, BIREME*).

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Introduction

In 1994 WHO declared that tuberculosis (TB) constituted a global emergency (*1*). It developed a five-point strategy known as DOTS in order to combat the increasing incidence of the disease. The main aims were to detect 70% of smear-positive TB cases and to treat 85% of smear-positive new cases successfully. The strategy has improved worldwide cure rates, but there are situations in which the implementation of DOTS programmes is difficult. This is true among refugee and displaced populations and in areas of civil conflict.

TB is an increasingly important cause of morbidity and mortality in refugee and displaced populations, particularly during the post-acute phase of complex emergencies (*2*). Until recently, little was done to address this problem, principally because of the difficulties of implementing control programmes where patients could not remain at one site long enough to undertake a full course of treatment (*3*). Furthermore, drug supplies are often irregular and donors may prefer to spend limited resources on shorter-term programmes with more immediate benefits. There has also been a lack of concise guidelines on controlling the disease among refugees. In 1997 WHO recognized the special situation of refugees and the lack of published guidelines, and, in conjunction with the Office of the United Nations High Commissioner for Refugees, developed a field manual on TB control in refugee situations (*4*). Strict criteria were indicated for the initiation and management of treatment and control programmes based on DOTS. These guidelines have not previously been piloted outside a refugee-camp setting or in a conflict setting.

The aims of the present project were to evaluate strategies based on WHO guidelines for achieving a cure rate of 85% in smear-positive TB cases in a context of civil conflict, an HIV epidemic and inadequate TB treatment and control services in Churachandpur District, Manipur State, in north-east India. The proportion of HIV-associated TB cases in Manipur State Hospital was 138/1000 in 1992–96, almost nine times the national rate of 16/1000 (*5*, *6*). During the same period there was also an increase in TB cases in the general population that was not associated with HIV. Government

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drug supplies for the district were erratic and the main drug used to treat the disease, isoniazid, was unavailable for periods of several months. Of the patients who began treatment under the Churachandpur District Tuberculosis Programme in 1996, fewer than 6% were documented as completing the full course.

From June 1997 to October 1998 two ethnic groups in Churachandpur District, the majority Paite group and a minority group, the Kuki, originally displaced from the north of the state, were involved in open conflict. Firearms were widely available and sporadic fighting occurred, largely between young men belonging to opposing factions, although random killings and sniper fire were also common. There were 10 ethnic communities in the district, each with its own language. Smaller tribes lacking the strength or influence to remain neutral were drawn into the conflict. Over 50 villages were destroyed and some 13 000 people were displaced. The majority moved to areas surrounding the district capital of Churachandpur, where they were housed in makeshift refugee centres in schools, hospitals, and other buildings; some were given shelter by relatives. Several hundred Indian Army soldiers were moved into Churachandpur early in 1998 with the purpose of restoring order. This was not successful, however, and outbreaks of violence continued until the church brokered a ceasefire in October 1998.

The conflict severely affected the provision of health care: most community health programmes, including TB control, malaria control, and the Expanded Programme on Immunization, were abandoned in rural areas. The district TB centre was closed from June 1997 to June 1998, principally because the staff fled in response to attacks by snipers. The impact of the conflict on TB treatment and control was unclear because there was inadequate record-keeping before the conflict and none during and shortly after it. However, most affected individuals with TB probably remained untreated during this time. It was against this background that our TB study was established in May 1998.

Methods

The following provisos were met before the study was set up, as laid down by WHO (*4*): commitment to TB control; availability of adequate funds; ability to establish and maintain a sputum microscopy service; commitment to use of recording and reporting systems recommended by WHO; reliable source of medications; availability of essential clinical services, basic drugs, and experienced staff.

A local advisory group was formed in May and June 1998. All protocols were based on guidelines issued by the Indian Revised National Tuberculosis Control Programme and WHO (*4*). Locally specific treatment protocols were developed which indicated case definitions, drug regimens in which directly observed therapy (DOT) was used three times a week instead of daily, procedures for follow-up and delivery of treatment including education of patients, incentives for compliance, and definition of non-compliance and default. Laboratory and TB patient registers were obtained from the regional WHO TB officer in Delhi. The forms used by the Revised National Tuberculosis Control Programme to monitor treatment, also based on WHO guidelines, were employed in the project. Protocols for counselling and testing study participants for HIV were developed. Project-specific forms for recording clinical and sociodemographic information on patients were created. Mechanisms were established for laboratory quality control. All drug treatment against TB was free.

Local staffing requirements were identified and a programme of staff training was developed. A part-time local community outreach worker was employed from each ethnic group in Churachandpur District in order to allow access to all affected communities while conflict was continuing. Community elders were asked to recommend two people suitable for each position, one of whom was selected by project staff. A laboratory technician and a TB coordinator were appointed. The outreach workers, the laboratory technician, and the TB coordinator all underwent a formal training programme.

Passive case-finding was performed in accordance with WHO recommendations (*4*). National prevalence figures suggested that 200 patients would be recruited during the first six months of the project. During the active phase of the conflict, when it was difficult to travel freely in town, an alternative to the clinic of the Society for HIV/AIDS Lifeline Operation in Manipur was used to ensure access. When the community moved into a post-conflict phase the alternative facility was no longer needed and all patients attended the Society's clinic.

When patients presented, details were recorded of name, age, sex, address, ethnic group, and people who could be contacted in the event of default. Three sputum specimens, including one taken early in the morning, were obtained from each patient and examined in the laboratory. The coordinator then reviewed all patients and allocated a case definition (new case, relapse, treatment failure, treatment after interruption, transfer from other centres of TB treatment, and other) and treatment category (I: $2\,H_3R_3Z_3E_3$, $4\,H_3R_3$; II: $2\,S_3H_3R_3Z_3E_3$/ $1\,S_3H_3R_3Z_3E_3$, $5\,H_3R_3E_3$; III: $2\,H_3R_3Z_3$, $4\,H_3R_3$).[a] Patients whose sputum gave a negative result or who gave only one positive sample were assessed according to the WHO guidelines (*4*). Sputum-negative pulmonary TB was diagnosed according to the study protocol.

Each patient was then allocated to an outreach worker of her or his ethnic group, who arranged where and when DOT would be carried out. When treatment began the patients were counselled on the need to comply fully with the regimen and all gave a signed undertaking to do so. If a patient was absent at the specified time, which happened only rarely, the outreach worker returned later the same day or the next to perform DOT. The outreach workers lived in the same areas as their patients, and consequently the distance of each round trip for administering DOT was less than six kilometres. Patients had to travel five kilometres at the most in order to attend the Society's clinic for clinical review.

Sputum was re-examined at the end of the intensive phase of treatment, halfway through the continuation phase, and on completion of treatment. The outcomes were assessed on the basis of the WHO guidelines (*4*). "Cure", i.e. a successful outcome, was only recorded in cases that were smear-positive when treatment began and negative at (or one month prior to) completion of treatment and on at least one other occasion. "Treatment completed" was recorded as a successful outcome in cases of smear-negative and extrapulmonary TB with no

[a] The three categories all consist of an intensive initial phase followed by a continuation phase. I: intensive phase for two months: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E); continuation phase for four months: H, R. II: intensive phase for three months: H, R, Z, E, styreptomycin (S) (S for the first two months only); continuation phase for five months: H, R, E. III: intensive phase for two months: H, R, Z; continuation phase for four months: H, R. "$_3$" denotes that medication was taken three times a week, instead of daily.

evidence of sputum conversion. Death, treatment failure and interrupted treatment, i.e. default, were recorded as unsuccessful outcomes. A record was kept of patients who were transferred to other health facilities for TB care.

All patients were asked for consent to be tested for HIV. The test results were anonymous. Patients who wished to know their HIV serostatus were referred to the Society's confidential HIV counselling and testing service.

Results

From June to December 1998, 1023 patients referred themselves for assessment and 178 were diagnosed with TB. Of these, 85 had smear-positive pulmonary TB, 85 had smear-negative pulmonary TB and eight had extrapulmonary TB (Table 1).

Seventy patients (39%) reported that they were displaced. The average age of diagnosed TB patients was 42 years and 68% of them were male. Very few patients reported formal schooling: the average duration of attendance at school had been only 0.8 years. The average income was less than Rupees 2200 a month (US$ 48). On average there were 4.5 adults per household and 2.2 children per patient. All ethnic groups were represented.

TB had previously been diagnosed in 74% of the patients. The mean previous treatment period with anti-TB drugs was five weeks. Patients with a history of treatment lasting more than a month were classified as retreatment cases requiring a more intensive treatment regime. On entering the study, 61% were classified as new cases, i.e. they had not undergone previous anti-TB treatment lasting more than a month, and 39% were classified as previously treated. About a third of the latter had defaulted from a full course of treatment, most often because of an inability to pay.

Twenty-two patients (13%) were HIV-positive. Of these, 77% were males with a mean age of 37 years. There were no significant differences between the proportions of HIV-seropositive patients who were sputum smear-positive or smear-negative at diagnosis and those of HIV-seronegative patients who were sputum smear-positive or smear-negative. There was a history of injecting drug use in 8% and of commercial sex work in 3% of TB patients. The reporting of current or past commercial sex work was inconsistent. A positive HIV status was not associated with a history of commercial sex work (odds ratio (OR) = 5.1, 95% confidence interval (CI):1.0–27.2, $P = 0.12$). However, injecting drug use was strongly associated with positive HIV status (OR = 17.2, 95% CI: 5.5–54.2, $P<0.0001$).

Overall there was a successful outcome of treatment in 89% of patients. Cure was achieved in 86% of all smear-positive pulmonary TB patients and in 83% of newly detected smear-positive cases. Of the smear-negative patients, 92% completed treatment satisfactorily. The eight patients with extrapulmonary TB all completed treatment. The overall treatment failure rate and the default rate were both 3%. The principal reason given for default was a desire by patients to return to their villages of origin after resolution of the conflict in order to support their families. Whereas 3% of enrolled TB patients died, the mortality rate among the 22 HIV-positive patients was 18%.

Table 2 shows treatment outcomes in all patients, smear-positive patients and those diagnosed as HIV-seropositive. HIV-positive patients were significantly more likely to die during treatment (OR = 28; 95% CI: 3–242, $P<0.0001$). Success rates among those who remained alive at the end of treatment were comparable with those among patients who were HIV-negative: HIV-positive patients were as likely to complete treatment or be cured as HIV-negative patients.

Positive HIV serostatus was the only factor examined that was associated with an unsuccessful treatment outcome (OR = 0.17, 95% CI: 0.61–0.52, $P = 0.002$) (Table 3). Injecting drug use was identified in univariate analysis as a predictor of poor outcome, but after adjustment for HIV infection this was no longer significant (revised OR = 0.96, 95% CI: 0.16–5.81, $P = 0.97$). Outcomes did not vary significantly between TB patients who were displaced and those who were not displaced.

Table 1. **Characteristics of patients by case definition**

Characteristics	No. of cases		
	Pulmonary smear positive *n* = 85	Pulmonary smear negative *n* = 85	Extra-pulmonary *n* = 8
Sociodemographics			
Male	69 (81)[a]	49 (58)	3 (38)
Currently married	13	16 (19)	1 (13)
Mean age in years	42	44	40.3
Mean years of education	1.2	0.4	0.9
Tuberculosis (TB) treatment history			
Previous diagnosis of TB	59 (70)	67 (79)	5 (63)
Mean length of treatment (months)	1.9; *2.5*[b]	1.5; *1.5*	1.2; *0.75*
Case definition on entry			
New case	53 (62)	50 (59)	6 (75)
Relapse	1 (1)	1 (1)	0
Transfer from other TB care facilities	2 (2)	19 (22)	2 (25)
Treatment after default	29 (34)	1 (1)	0
Other	0	13 (15)	0
Risk behaviours for contracting bloodborne viruses			
History of injecting drug use	5 (6)	10 (12)	0
History of commercial sex work	5 (6)	0	0
HIV-seropositive	10 (12)	12 (14)	0
Treatment outcome			
Successful outcome: cured (smear positive cases) or treatment completed (smear negative or extrapulmonary)	73 (86)	78 (92)	8 (100)
Died	2 (2)	3 (4)	0
Failure	6 (7)	0	0
Default	3 (4)	2 (2)	0
Transfer to other TB care facility	1 (1)	2 (2)	0

[a] Figures in parentheses are percentages.
[b] Figures in italic are standard deviations.

Discussion

Refugees and displaced people are at increased risk of developing active TB as a consequence of nutritional deficiency, crowded living conditions, and lack of access to TB treatment services. It is estimated that 50% of refugees are infected with

Table 2. **Treatment outcome in all cases, sputum smear-positive cases (new and retreatment) and HIV-seropositive cases**

Outcome	No. of cases			
		Smear-positive		
	All *n* = 178	New *n* = 53	Retreatment *n* = 30	HIV-positive *n* = 22
Successful[a]	159 (89)[b]	44 (83)	28 (93)	15 (68)
				< 0.001[c]
Died	5 (3)	2 (3.5)	0 (0)	4 (18)
				< 0.001
Failure	6 (3)	4 (8)	1 (3.5)	0 (0)
Default	5 (3)	2 (3.5)	1 (3.5)	1 (5)
Transfer	3 (2)	1 (2)	0 (0)	2 (9)

[a] In smear-negative cases: treatment completed with no evidence of sputum conversion. In smear-positive cases: smear-negative at (or one month prior to) the end of treatment and on at least one other occasion.
[b] Figures in parentheses are percentages.
[c] Figures in italic are *P*-values.

Table 3. **Univariate analysis of factors associated with unsuccessful treatment outcome**

Factor	Odds ratio of successful outcome	95% confidence interval	*P*-value
HIV-positive	0.17	0.61–0.52	0.002
Current injecting drug user	0.05	0.005–0.44	0.001
Male	0.36	0.10–1.30	0.12
Displaced	0.88	0.34–2.24	0.79
Sputum smear-positive	0.50	0.19–1.32	0.16
History of tuberculosis infection	1.42	0.52–3.88	0.51

TB. In 1966 the number of refugees and displaced people was estimated to exceed 26 million globally (*3*, *7*).

The control of TB should be given low priority in the immediate emergency phase of a refugee situation, when precedence should be given to the provision of food, water, shelter, sanitation, and basic drugs. The WHO guidelines suggest that a control programme should commence in refugee settings when the death rate is below 1 per 10 000 per day, basic needs are met, and essential services are available (*4*). The principal aim is to cure at least 85% of detected smear-positive patients.

There have been few studies examining the feasibility and effectiveness of DOT-based TB control programmes in conflict settings. Despite poverty and civil war, successful treatment rates of 70% were achieved in Nicaragua during the 1980s (*8*). DOT was employed only during the intensive phase of treatment. The major factors identified as essential for the success of the programme were government commitment and good programme management. In Somalia an overall cure/treatment completed rate of 70% was achieved by a short-course regimen (*9*).

Manipur has a population of 1.8 million and is one of seven states in India not fully covered by the Indian Revised National Tuberculosis Control Programme. In Churachandpur District, with a population 180 000, the combination of civil conflict, population displacement, limited TB treatment and control services, and a high incidence of HIV infection contributed to an escalating TB problem.

Manipur has less than 0.2% of India's population but 17% of its HIV cases (*10*). Injecting drug use began to increase dramatically in the early 1980s as heroin became readily available from the neighbouring country of Myanmar. Unsafe injecting practices resulted in great vulnerability to HIV transmission (*11*). In Manipur the majority of persons infected with HIV are injecting drug users. Unsafe sexual practices among injecting drug users and their partners have led to the heterosexual spread of HIV (*12*). In order to develop a comprehensive indigenous response to the HIV epidemic in Churachandpur District, the Society for HIV/AIDS Lifeline Operation in Manipur was established in 1994 through collaboration between the Macfarlane Burnet Centre for Medical Research and an Indian nongovernmental organization, the Emmanuel Hospital Association.

Our results have demonstrated that the control and treatment of TB were possible during conflict and its aftermath where WHO guidelines were adapted for local use. A successful treatment outcome was achieved in 89% of the recruited patients. Of the cases of smear-positive pulmonary TB, 86% were cured. Among new smear-positive cases, 83% were cured, this being only slightly below the WHO target of 85% in stable environments. The default rate was only 3%. The success of the programme was all the more remarkable when viewed against the effects of the conflict, i.e. destruction of health facilities, danger to personnel, limitation of access to facilities, and displacement of populations.

A number of factors appeared to account for this success. The prerequisites for TB control were met, i.e. adequate funding, clear objectives, experienced staff, a working laboratory with quality control mechanisms, a regular supply of drugs, and good management structures (*4*). The availability of adequate funding made it possible to procure sufficient drugs at the outset to give an uninterrupted supply, stored on site in secure facilities, for the twelve-month period. In addition, all protocols and drug treatment regimens were based on current WHO best practice guidelines and the guidelines of the Revised National Tuberculosis Control Programme, which are DOTS-based and ensure continuity if programme funding ceases.

The main factors that were specific to the success of the programme were the commitment of the local community and the efforts and commitment of the local staff. Also vital was the recognition by local leaders that TB was a major problem in their communities. Furthermore, the Society for HIV/AIDS Lifeline Operation in Manipur had been established for a number of years in the area and the directors were well known and respected locally. The involvement of the Society played a large part in ensuring community acceptance of and support for the programme, which might not have been so readily forthcoming had reliance been placed exclusively on an unknown international body.

The selection of the outreach workers by their local communities and ethnic leaders lent a degree of empowerment and ownership of the programme to the ethnic groups and allowed internal regulation of the performance of these workers by the communities. The use of outreach workers from each ethnic group was particularly important in facilitating free access to all areas and patients. Ethnic sensitivities should always be taken into account when the staffing of a project such as the present one is being planned, in

order to maximize compliance and ensure the safety of personnel.

The use of combination medications three times a week instead of daily allowed increased compliance because this meant that both the outreach workers and the patients were required to dedicate less time to the programme than would otherwise have been the case. This was particularly significant in a conflict situation in which travel on a daily basis was not advisable. That the thrice-weekly schedule was as efficacious as daily therapy was demonstrated by the overall cure rates. Moreover, compliance was encouraged by minimizing the distances that had to be travelled by patients attending clinics and by outreach workers performing DOT, as this reduced the hazards to which both groups were exposed.

The most important factor limiting the success of any TB programme is the default rate. In the present study it was only 3% and the principal causative factor was that patients from remote areas wished to return home once the conflict was over. They had no means of generating income or supporting their families in the area to which they had been displaced. In order to encourage subjects to remain in a TB treatment programme area following conflict there should be an income-generation component so that patients can work and provide for their families while undergoing therapy. Eggs were given to patients weekly as an incentive to remain in the area. Financial incentives were not used, although this was an option.

The only factor associated with poor outcome was HIV seropositivity. HIV-positive patients were more likely than others to die before the end of treatment, but outcomes among those who survived were comparable to those of HIV-negative patients. However, HIV testing should not be offered to TB patients unless adequate confidential testing and counselling facilities are available. ■

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Résumé

Traitement de la tuberculose basé sur le DOTS et lutte antituberculeuse dans un contexte de conflits et d'épidémie de VIH dans le district de Churachandpur (Inde)

Objectif Expérimenter les directives DOTS pour le traitement de la tuberculose chez des personnes déplacées victimes de conflits dans le district de Churachandpur (Etat de Manipur) dans le nord-est de l'Inde, où l'on observe depuis de nombreuses années une épidémie de VIH, l'usage de drogues injectables, des troubles civils, des taux élevés de tuberculose et une insuffisance des services de prévention et de traitement de la tuberculose.

Méthodes Les conditions préalables aux programmes de lutte antituberculeuse ont été définies. Les directives et protocoles de l'OMS ont été adaptés à la situation locale. Des agents de santé périphériques ont été recrutés dans chacun des groupes ethniques impliqués dans le conflit et ont reçu une formation. Des procédures de contrôle de la qualité et d'évaluation ont été introduites.

Résultats La tuberculose a été diagnostiquée chez 178 personnes entre juin et décembre 1998. Sur les 170 malades atteints de tuberculose pulmonaire, 85 étaient à frottis positif. Une issue favorable a été enregistrée chez 91 % de l'ensemble des malades et chez 86 % des cas de tuberculose pulmonaire à frottis positif. Le taux d'abandon et le taux de mortalité étaient tous les deux faibles (3 %). La séropositivité vis-à-vis du VIH était le seul facteur associé à une issue défavorable du traitement.

Conclusion Le traitement de la tuberculose et la lutte antituberculeuse étaient possibles dans un contexte de conflits, et les cibles établies par l'OMS pour les taux de guérison étaient atteignables. Les facteurs associés à la réussite du programme étaient un fort soutien de la communauté locale, le recrutement d'agents de santé parmi les groupes ethniques impliqués dans le conflit de façon à assurer l'accès à tous les secteurs et tous les malades, l'administration du traitement sous observation directe trois fois par semaine au lieu d'une fois par jour pour assurer une meilleure sécurité, et la réduction des distances devant être parcourues par les agents de santé périphériques et par les malades.

Resumen

Tratamiento y control de la tuberculosis mediante DOTS en un contexto de disturbios y epidemia de VIH en el distrito de Churachandpur (India)

Objetivo Ensayar las directrices de la OMS sobre el tratamiento DOTS para la tuberculosis entre las personas desplazadas afectadas por los conflictos habidos en el distrito de Churachandpur —Estado de Manipur, noreste de la India —, que durante muchos años ha tenido que afrontar toda una serie de problemas: una epidemia de VIH, uso de drogas inyectables, agitación social, altos niveles de tuberculosis y deficiencias de los servicios de tratamiento y prevención de la tuberculosis.

Métodos Se establecieron requisitos para los programas de control de la tuberculosis. Las directrices y los protocolos de la OMS se adaptaron para uso local; se designaron agentes de extensión a partir de cada grupo étnico implicado en el conflicto, procediéndose a su adiestramiento, y se implantaron procedimientos de control de la calidad y de evaluación.

Resultados Se diagnosticó tuberculosis en 178 usuarios de drogas inyectables entre junio y diciembre de 1998. De los 170 con enfermedad pulmonar, 85 presentaban frotis positivo. Evolucionaron favorablemente el 91% de todos los pacientes y el 86% de los casos de tuberculosis pulmonar con frotis positivo. La tasa de inobservancia y la tasa de mortalidad fueron bajas, de un 3% cada una. La seropositividad para el VIH fue el único factor asociado a un mal resultado del tratamiento.

Conclusión Fue posible tratar y controlar la tuberculosis en un entorno de conflictos, y se pudieron alcanzar las metas de curación

de la OMS. Los factores asociados al éxito del programa fueron un enérgico apoyo de la comunidad local, la selección de agentes de extensión de los distintos grupos étnicos para poder acceder a todas las zonas y todos los pacientes, el uso de la terapia administrada bajo observación directa tres veces a la semana en lugar de diariamente para mayor seguridad, y la limitación de las distancias viajadas tanto por los agentes de extensión como por los pacientes.

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