Tuberculosis treatment in complex emergencies: are risks outweighing benefits?

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Tuberculosis treatment in complex emergencies: are risks outweighing benefits?

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Summary Tuberculosis (TB) is a major public health problem in complex emergencies. Humanitarian agencies usually postpone the decision to offer TB treatment and opportunities to treat TB patients are often missed. This paper looks at the problem of tuberculosis treatment in these emergencies and questions whether treatment guidelines could be more flexible than international recommendations. A mathematical model is used to calculate the risks and benefits of different treatment scenarios with increasing default rates. Model outcomes are compared to a situation without treatment. An economic analysis further discusses the findings in a trade-off between the extra costs of treating relapses and failures and the savings in future treatment costs. In complex emergencies, if a TB programme could offer 4-month treatment for 75% of its patients, it could still be considered beneficial in terms of public health. In addition, the proportion of patients following at least 4 months of treatment can be used as an indicator to help evaluate the public health harm and benefit of the TB programme.

keywords tuberculosis, complex emergencies, compliance rate, early treatment result, modelling, drug resistance, economic analysis

Introduction

Measuring the effect of war on the incidence of tuberculosis is fraught with methodological problems and the scarce information available is difficult to interpret. For instance, the doubling of the incidence of tuberculosis (TB) from 50 to 109/100 000 observed in the post-war period in Vietnam (1975–1982) was explained by better case detection systems rather than an increase in transmission (Shimao 1986; Barr & Menzies 1994). However, in a review of the literature in 1994, Barr and Menzies estimated that the incidence of sputum smear-positive pulmonary tuberculosis (PTB (+)) was three times higher among displaced Salvadorians than the national rate in El Salvador. In England and Wales, notifications of tuberculosis increased by 16–19% between 1939 and 1944. A similar increase in the incidence of TB was also observed in Japan during the Second World War.

The concept "complex emergencies" characterises today's armed conflicts and resulting humanitarian disasters. These emergencies represent the ultimate pathway of state disruption. The complexity refers to the multifaceted responses by the international community, which are further complicated by the lack of protection normally afforded by international treaties, covenants and the United National Charter during conventional wars (Burkle 1999). The situations in Afghanistan and Somalia are probably typical examples of such protracted conflicts and never-ending humanitarian disasters. In contrast to natural disasters, where national governments attempt to provide emergency assistance to the victims, in complex emergencies they often deny the means to mitigate the effect of conflicts or manipulate the human misery (Buchanan & Maxwell 1994; Macrae & Zwi 1994). Typically, humanitarian agencies take over from the Ministry of Health the provision of health care in addition to other relief efforts.

Several small-scale TB programmes have been implemented by humanitarian agencies in complex emergencies, with varying levels of success. In Southern Sudan in 1997, nine TB programmes reported a cure rate between 68 and 94.5% among 867 patients (Van Ham, 1998). In Kismayu, Somalia, Médecins Sans Frontières (MSF) reported a cure and completion rate of 80% on 593 patients, from March 1995 to September 1997 (Van Herp, 1998). The African Medical Research Foundation (AMREF) reported similar results in South West Somalia from July 1994 through December 1996 in a cohort of 286 patients (Agutu 1997). On the other hand, in Liberia a cure rate of 50–60% forced MSF to stop its involvement in the National TB Programme in 1994 (Zachariah 1994).

For initiating TB control programmes in complex emergencies, most agencies follow the international

guidelines for TB control in refugee situations (MSF, unpublished observations; WHO & UNHCR 1997). These guidelines suggest that TB programmes should focus on sputum positive pulmonary tuberculosis (PTB (+)) patients and aim to achieve 85% cure rate with directly observed treatment (DOT) for 6 months. In this paper, a programme fulfilling these conditions of cure rate and a 6-month treatment follow-up is defined as 'optimal'. A 'sub-optimal' programme describes any situation that does not achieve a 85% cure rate and a follow-up of 6 months.

Since such a long treatment duration and high level of cure rate may not be achievable in many complex emergency situations, TB programmes are often postponed until preconditions, such as stability and security, are fulfilled to guarantee an optimal programme. However, clinicians face ethical dilemmas when not offering treatment for tuberculosis cases. Programme managers, on the other hand, are concerned with the instability that characterises complex emergencies, which will increase the risk of the development of drug resistance, resulting from a sub-optimal TB programme. The main barriers encountered and reinforced by the prevailing insecurity are: (i) the absence of a good supervised programme, allowing for possible bad management (Zachariah 1994); (ii) frequent expatriate staff evacuations (Van Ham, 1998; Van Herp, 1998); (iii) sudden closures of programmes, disruption of supply lines or displacement of people. Outbursts of violence constitute a serious threat for the continuity of TB programmes.

Nevertheless, successful programmes have been able to overcome security and continuity constraints through imaginative contingencies, such as placing a limited number of patients on treatment (Van Herp, 1998), run-away packs with fixed-dose combination drugs, and treatment cards to help patients get further treatment at a new centre (Van Ham, 1998). However, in other complex emergencies like Afghanistan, Angola, Sierra Leone and Burundi, TB programmes were never started or were postponed for several years (MSF, personal communications), although the local security situation had become quiet. In complex emergencies, many areas remain indeed stable for longer periods of time. These situations could allow small-scale treatment opportunities. Meanwhile, private practitioners, such as drug sellers, medical practitioners and traditional healers compete with humanitarian agencies in health care provision. They are likely to offer inadequate TB treatment under much less supervised circumstances, with little or no consideration of combined drug therapy and continuity of treatment and follow up (MSF, personal communications).

This paper provides information that continues to explore the case of TB control in complex emergencies. To assist agencies in running TB programmes in such settings, it investigates the public health risks and benefits of sub-optimal TB programmes, i.e. programmes with less than 85% cure rate and where patients follow less than 6 months of treatment. It then considers whether, in a complex emergency situation, a sub-optimal TB programme would be preferable to no TB programme at all.

Methods

Two different perspectives are used to assess the public health risks and benefits of sub-optimal TB programmes, as compared to no treatment programme at all. First, a simplified mathematical model is constructed to calculate the health consequences of poor treatment compliance, and secondly, findings are discussed further in an economic analysis which looks at the trade-offs between the extra costs of treating relapses and failures and the savings in future treatment costs.

Risk and benefit indicators

The model was created using information from: (i) the work of Murray *et al.* (1993) on TB transmission; (ii) from the same authors (1990) and from WHO (1997) regarding drug resistance; and (iii) from the work of Vynnycky and Fine (1998) on TB modelling. The health risks and benefits of a sub-optimal TB programme for one transmission cycle were defined by the following outcome indicators: (i) number of patients cured (confirmed by sputum examination, not suffering relapse); (ii) number of deaths averted; (iii) number of new PTB cases averted as a result of ending TB transmission; (iv) number of cases in which (single and multiple) drug resistance developed (isolates from cases of treatment failure or relapse that became resistant to anti-TB drugs); and (v) number of chronic TB excreters created (patients who after treatment remain infectious). To keep the model simple, all treatment failures and relapses were considered as chronic excreters.

For different treatment durations, risks of treatment failure (failure to convert to sputum Acid-Fast-Bacilli (AFB)-negative at the time of discontinuing treatment), risks of relapse (sputum becoming AFB-positive after discontinuing treatment within 60 months post-treatment) and of drug resistance development were estimated or derived from a variety of studies (East African/BMRC study 1981; Singapore TB Service/BMRC 1981, 1986, 1988; Hong Kong Chest service/BMRC 1982, 1987; TB Research Centre of Madras 1983; Baba *et al.* 1984; Hong Kong Chest service/TB Research Centre, Madras/BMRC 1984, 1989; TB Research Centre of Madras and National TB Institute of Bangalore 1986, 1990; Dutt *et al.* 1989) (Table 1). The construction of the model indicators can be found in Table 2.

Table 1 Maximal treatment failures (TF), Relapse (Rel) and new single and multi-drug resistance rates obtained from previous studies

	Drug sensitive population				Drug resistant population (i)			
			New single drug resistance on (i)				New MDR on (ii)	
Treatment duration (M)	TF (%)	Rel (%)	TF (%)	Rel (%)	TF (%)	Rel (%)	TF (%)	Rel (%)
<2	N.A.	N.A.	0.0	0.0*	N.A.	N.A.	2.2	2.2¶
2	15	32†	0.0	0.0	15.0‡	38.0†	2.2	2.2¶
3	4	20	0.0	0.4	6.1	23.3	2.2	0.0
4	1	16	0.0	1.0	5.0‡‡	20.0‡‡	0.0	1.0§
5	1#	8.5	0.0	0.0	4.0‡‡	10.0‡‡	1.0	0.0
6	1	3.4	0.0	0.0	3.0‡‡	5.5	0.7	0.0

M: months; N.A.: not available; (i) resistant to 1 or 2 drugs; (ii) percentages on acquired MDR have been calculated by pooling data from several studies with similar treatment duration; † based on relapses of smear negative cases; ‡ estimates from drug sensitive population; ‡‡ estimated from outcomes of 3 months treatment; * based on reference of 2 months treatment; ¶ based on reference of 3 months treatment; § based on PTB (−), culture (+); # based on reference of 4 months treatment.

Table 2 Mathematical model indicator constructions

Total cured = Total number starting treatment (*N*) – (treatment failures + relapses + deaths while on treatment)
New PTB averted = (total cured – chronic excreters) × number of new infections, created by a TB patient in one year†† × the probability of developing clinical TB × probability of new infection leading to new PTB
Deaths averted = Total cured × probability of dying within 5 years without TB treatment†
Single drug resistant PTB = (Total number starting treatment × probability of single drug resistance on treatment failures and relapses) × number of new infections, created by a TB patient in one year†† × the probability of developing clinical TB × probability of new infection leading to new PTB
Multi-drug resistance PTB = (Total number starting treatment × probability of MDR on treatment failures and relapses) × number of new infections, created by a TB patient in one year†† × the probability of developing clinical TB × probability of new infection leading to new PTB
Chronic excreter = All patients failing treatment and all patients relapsing within the first 60 months after ending treatment

† The majority of these (80%) dying within the first 2 years; †† only one transmission cycle studied.

Model construction

When constructing the model, the following assumptions were made from a variety of papers, which investigate and discuss the TB transmission and control. Each is referenced after the assumption created: (i) without TB treatment, 50% of PTB (+) patients will die within 5 years, 25% will be cured spontaneously and 25% will continue to remain infectious (Grzybowski & Enarson 1978; Murray *et al.* 1993; WHO & UNHCR 1997); (ii) there is a 8% risk of dying while on TB treatment (Murray *et al.* 1993; Enarson & Rouillon 1994); (iii) each smear positive TB patient will infect 12 patients of which 8% will develop clinical TB (85% of these will be PTB equally distributed between smear positive and negative cases (Murray *et al.* 1993; Dejonghe *et al.* 1994)); and (iv) patients defaulting less than 2 months after the onset of treatment are considered as 100% treatment failures.

The outcome indicators depend on the baseline level of drug resistance, the type of treatment and the compliance or treatment duration. Thus, if the baseline single-drug resistance is kept constant at 25% and if all patients are offered 6 months chemotherapy consisting of 2SHRZ/4HR (2 months of treatment with streptomycin (S), isoniazid (H), rifampicin (R) and pyrazinamide (Z); followed by 4 months of treatment with isoniazid and rifampicin), then the above mentioned indicators can be expressed as a function of the level of compliance, i.e. the actual duration of drug intake.

Eight different programme scenarios have been constructed, representing each of the 100 patients under treatment. Each scenario presents varying proportions of patients adhering to TB treatment for specific durations. These scenarios are designed to show a decreasing adherence to treatment and can be considered therefore as 'increasingly sub-optimal'. Each outcome indicator was estimated for each scenario in the following model: $Y1 = \sum x_a y_a + x_b y_b + \ldots + x_{nyn}$; where $Y1$ = probability of outcome y in scenario 1, x_a to x_n are the proportions of patients complying with treatment for a specific duration and y_a to y_n are the probability of outcome y per treatment duration.

Economic analysis

A simple economic analysis has been used in this paper, using a public sector perspective, which excludes costs incurred by the private sector and by private consumers and collates only those costs incurred by the public sector in implementing tuberculosis control.

As patients who require re-treatment after failing the first treatment or after relapse need a more expensive and longer drug regimen, we compared these expected extra costs per scenario to the savings implied by the number of new PTB cases averted as a result of ending TB transmission in the same scenario. The economic implications of sub-optimal TB programmes were thus looked into through incremental cost analysis, i.e. the extra cost or gain per sub-optimal TB programme scenario of 100 treatments, including programme management, laboratory, drugs, hospitalisation and outpatient care costs, but assuming that the organisational infrastructure already exists. This incremental cost analysis based itself on a range of average marginal costs of TB programmes from three African countries calculated by Dejonghe *et al.* (1994).

Results

Health benefits and risks

Table 3 and Figure 1 show the risks and benefit indicators of sub-optimal TB treatment programmes per 100 or 1000 treatments, as predicted by the mathematical model. Scenario 0 (the baseline case scenario to which all other scenarios should be compared) represents 100 PTB (+) patients, left untreated in a 5-year period, while scenario 1 represents an optimal situation with 100% adherence of all patients to 6-month treatment. All other scenarios, from 2 to 8, represent 'increasingly sub-optimal treatment' scenarios. In scenario 8, e.g. all patients default within 3 months. The percentages refer to the number of people complying with the treatment for a certain period.

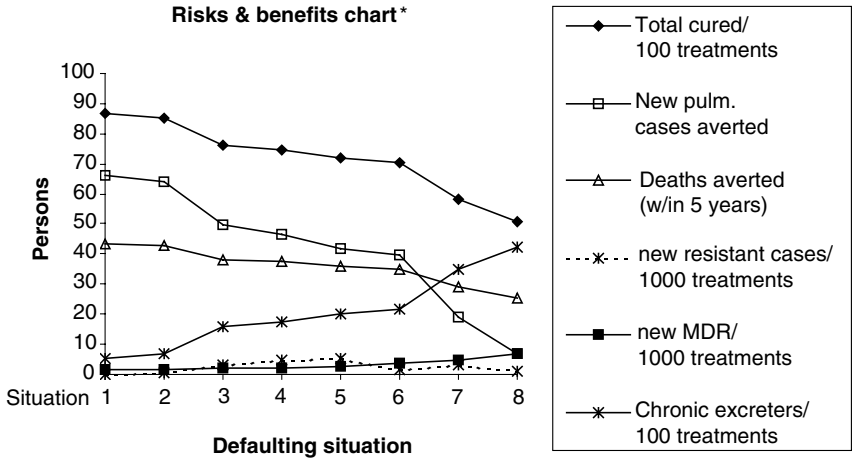
The benefits of sub-optimal programmes are inversely related to the level of defaulting. Compared to a scenario without treatment, even scenario 6, with a high level of defaulter rate (60% taking treatment for ≤ 4 months), induces interesting benefits: 70 out of 100 TB patients would be cured and 40 new pulmonary cases and 35 deaths would be averted. Benefits decrease considerably when the defaulter rate increases beyond this level, as in scenarios 7 and 8.

Concerning the risk of creating single-drug resistance, no scenario compares favourably with scenario 1, where the risk of creating single-drug resistance is zero. In sub-optimal settings, there is an increased risk of creating single-drug resistance, with a predicted average of three

Table 3 Risks and benefits of sub-optimal TB programmes per 100 or 1000 treatments, as predicted by the mathematical model

Benefits and risks indicators	S0	S1		S2		S3		S4		S5		S6		S7		S8	
	No treatment given	TD (M)	%	TD (M)	%	TD (M)	%	TD (M)	%	TD (M)	%	TD (M)	%	TD (M)	%	TD (M)	%
		6	100	6	85	6	20					6	20	4	20	3	50
				5	10	5	20	5	20			5	20	3	20	2	40
				4	5	4	45	4	80	4	80	4	20	2	20	<2	10
						3	15			3	20	3	20	<2	10		
												2	20				
Total cured/100	25	87		87		76		75		72		70		59		51	
New PTB averted/100 (i)	−82 to > −100 (ii)	66		64		50		47		42		40		19		7	
Deaths averted/100 (i)	> −50 (iii)	43		43		38		37		36		35		29		25	
New resistant PTB/1000	None	None		0.3		3.1		4.9		5.4		1.7		3.2		1.2	
New MDR PTB/1000	None	1.4		1.5		2.3		2.1		2.5		3.8		4.9		6.7	
Chronic excreters/100	25	5		7		16		17		20		22		35		42	

TD: Treatment duration; M: months; (i): a negative number represents the creation of new cases; (ii): depends on the net reproductive rate of TB in the region; (iii): mortality rate in 5 years time.



* Note the 10-fold difference in scale between the various benefits & the proportion of chronic excreters and the creation of resistant cases & MDR

Figure 1 Risks and benefits of sub-optimal TB treatment programmes.

Table 4 Cost analysis per scenario for one transmission cycle

Scenario	Cases needing re-treatment/100 treatments	Cost for re-treatments (US$) (i)	New PTB(+) averted/100 treatments (ii)	Gain in costs of averted cases (US$) (iii)	Net gain: = (iii – i) (US$)
1	5	880	33	3531	2651
2	7	1232	32	3424	2192
3	16	2816	25	2675	141
4	17	2992	23	2461	−531
5	20	3520	21	2247	−1273
6	22	3872	20	2140	−1732
7	35	6160	9	963	−5197
8	42	7392	3	321	−7071

(i): One re-treatment costs US$176; (ii): each new pulmonary case has a 50% chance to be PTB+. It is assumed that in the first years post-conflict, only PTB(+) cases will be treated; (iii): one treatment costs US$107.

cases per 1000 treatments. The risk of acquired MDR is increasing constantly per treatment scenario and in scenario 5, the MDR risk is nearly the double of the best scenario (2.5‰ *vs.* 1.4‰) while in scenario 7 the model predicts a nearly 3-fold increase compared to scenario 1.

Economic consequences

Average marginal costs analysis of TB programmes shows that treatment for Category I patients (new PTB + never treated before) costs on average US$107, while for Category II patients (PTB + relapses and treatment failures), the cost is on average US$176 or 64% more expensive (Dejonghe *et al.* 1994). This is important, as the chronic excreters created in a sub-optimal programme will need a Category II re-treatment, while the gain in future costs, because of the averted new PTB(+) cases, will be calculated on a Category I treatment. Table 4 shows this trade-off per defaulting scenario. The trade-off is calculated 1 year after the outcome of each scenario. Initial treatment costs of the 100 patients of each scenario are taken out for simplification, as in scenario 0 most of the initial 100 untreated people also would still need treatment after that. Discounting costs and savings for the future did not show major changes.

Discussion

This paper suggests that when evaluating sub-optimal TB programmes it is important to consider not only the public health risks of the programme but also its benefits. Currently, few articles have stressed the importance of this issue (Borgdorff *et al.* 2002).

If the health risks and benefits of sub-optimal programmes are studied, it may be found that a threshold

scenario is produced after which benefits drop steeply. In this model, this event occurs around scenario 6 (60% follow at least 4-month treatment). If defaulting becomes worse, the risks increase more significantly and gradually outweigh the benefits. Such sub-optimal programmes would lead to more adverse public health situations as compared to offering no TB treatment programme at all. We can therefore safely argue that a sub-optimal scenario (between scenarios 5 and 6) in which 75% of the TB patients receive at least 4 months of treatment is preferable to a situation without a TB programme at all.

Of course the validity of the model and its assumptions can be criticised. Changing certain assumptions and parameter values certainly modifies the benefits and risks predicted by the model. Increasing risks for MDR creation, treatment failures and relapses weaken our assertion, while lower risks confirm it. As we have used the highest risk per parameter found in the various sources and realistic estimates for these scenarios, the model predictions of risks and benefits are unlikely to be overestimated. Moreover, the probability of increased transmission of TB associated with war situations was not taken into account, and the number of new infections created by a TB patient was calculated for one year of survival only, while the majority of patients survive an average of 2 years. The number of new cases and deaths averted thus tend to be underestimated. The studies from which the model parameters were obtained are clinical trial settings, where the situation is obviously very different from field conditions. However, the lack of data under field conditions makes them the only source of information available for this study. The data are considered appropriate for the following reasons: (i) estimates of parameters are consistent between 13 studies; (ii) parameters were defined according to the internationally accepted criteria; (iii) the results of these studies have been used previously to define TB treatment guidelines; (iv) some studies had a long follow-up period ranging from 19 to 60 months; and (v) where no data exist, realistic estimates were proposed.

There are also other and longer treatment regimens (e.g. 2EHRZ/6EH) that might be considered. They would create less MDR-TB and need less supervision. These regimens have not been studied in this model because, in chronic emergencies settings, most humanitarian agencies prefer to adhere to the standard WHO regimen and complete treatment as quickly as possible.

One important remark should be made on the effect of HIV on the prevalence and cure rates of TB. The present HIV epidemic dramatically increases TB incidence (e.g. Schulzer 1992). Mortality rates in HIV (+) patients are reported to increase significantly: 21% *vs.* 6% in sero-negative (HIV (−)) patients in Nairobi (DeCock 1994). The response of HIV (+) TB patients on a 6-month short course chemotherapy regimen (SCC) is usually satisfactory and comparable to HIV (−) patients (e.g. Perriens *et al.* 1995). It is also similar to the assumptions used in the model. However, relapse rates can differ between HIV (+) and HIV (−) patients, as shown in one study in Zaire (from 9 to 5.3%, respectively) (Perriens *et al.* 1995). Other studies have not shown different relapse rates, probably owing to the increased mortality of HIV (+) patients (DeCock 1994; Sonnenberg 2001). Acquired single-drug resistance among relapses seems frequent in some studies (March *et al.* 1997; Centers for Disease Control and Prevention 2002), while no difference is seen in others (Perriens *et al.* 1995). Although the creation of resistance depends mainly on the number of anti-TB drugs used (Murray *et al.* 1990; WHO 1997), selective malabsorption may be at the origin of this higher acquired drug resistance (Lutfey *et al.* 1996; Perlman *et al.* 1996).

Since the effect of HIV on TB treatment results is not accounted for in the model, application of these results to populations with a high HIV prevalence may not be appropriate. A higher relapse rate will decrease benefits dramatically. A higher mortality among HIV (+) patients may decrease this impact. Although some data suggest that the creation of drug resistance is increased in full treatment schemes, nothing is known about this in sub-optimal programme settings. Lack of information makes it impossible to take these influences into account in the model. Decreased benefits should also be challenged with increased benefits of a higher number of averted TB patients due to the earlier TB treatment and a decreased chance of re-infection (Sonnenberg 2001).

Looking at the trade-off between the extra costs of treating relapses and failures and the savings in future treatment costs, the short course chemotherapy (SCC) of 2SHRZ/4HR remains the most appropriate with maximal benefits. Scenario 3 remains also beneficial with US$141 gained on future costs, whereas scenarios 5 and 6 cost more (extra average cost of US$1500). If HIV seroprevalence is high, the gains and costs will again depend on the balance between a higher relapse rate, an increased mortality and a higher number of averted cases. Treatment of MDR-TB cases has not been accounted for, as their number is considered as minimal (average of 3‰) and their treatment impossible in these settings.

These findings should not prevent us from considering the above-mentioned sub-optimal scenarios as beneficial where the majority (i.e. 75%) of patients receive at least 4 months of treatment. Costs will indeed increase with the number of relapses and treatment failures. The extra costs of a treatment scenario between scenarios 5 and 6 can still be accepted, when taking into account the social cost of prolonged human suffering, such as premature deaths,

decreased life quality and the creation of new PTB cases in the absence of a treatment programme.

It is important to stress that this is only a partial economic analysis. One can indeed argue that a 25% cure rate will happen without treatment and that this should be taken into account. Others will argue that at least four transmission cycles should be studied in a cost-effectiveness study of tuberculosis (Murray *et al.* 1993; Dejonghe *et al.* 1994). It should be remembered that other cost-effectiveness studies have compared a 6-month SCC to alternative treatment protocols, whereas the originality of this discussion is in its application to extreme circumstances, where sub-optimal programmes are compared to a scenario without treatment. Moreover, cost-effectiveness is rarely an objective for humanitarian agencies in complex emergencies, when human life and survival are at stake. These agencies aim to ease human suffering and do not delay actions simply because they would appear to be cheaper in a more peaceful environment. If agencies do not start TB treatment programmes in some settings, they do so with the prime concern of 'not harming patients'. The model's outcomes should thus reassure these agencies that treatment programmes, where 75% of the patients can follow at least 4 months multi-drug-treatment, could still be considered as more efficacious as compared to the absence of a TB treatment programme. In addition, these programmes do not represent a major public health threat and the costs are not unacceptably high.

In this article, we conclude that programmes should always aim for a 6-month SCC with an 85% cure rate, according to the international guidelines. However, in complex emergencies 4 months of multi-drug-treatment (2SHRZ/2HR) could represent a minimum, which should be reached by the majority (i.e. 75%) of patients. This article shows that the defaulting rate remains an important indicator for the quality of a programme. By looking at the time of defaulting the public health implications of the TB programme can be assessed. The proportion of patients following at least 4 months of treatment can therefore be considered as an important indicator when evaluating the public health harm and benefits of a TB programme. This indicator should be consolidated with the 'early treatment results' (smear conversion by 2–3 months), as recommended by WHO and UNHCR (1997) to confirm the quality of the early response to treatment.

Humanitarian agencies not only need to follow the international guidelines but also balance the risks and benefits of TB programmes in complex emergencies. No programme may mean that patients seek treatment from unqualified practitioners. In contrast, a sub-optimal programme where patients receive correct treatment for at least 4 months may have a much greater and more positive public health impact.

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