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Relapse and recurrent tuberculosis in the context of a National Tuberculosis Control Programme

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Abstract

The proportion of patients with recurrent tuberculosis (TB) is reported to be increased in TB patients with human immunodeficiency virus (HIV) infection after they have completed treatment. Despite rising HIV seroprevalence amongst TB patients in Malawi, notifications of patients with relapse smear-positive pulmonary TB (PTB) and recurrent smear-negative TB have remained stable during the past 12 years. We suspected that patients with recurrent or relapse TB were being missed under routine programme conditions. Forty-three hospitals in Malawi were visited in 1999, and TB inpatients who had been registered as 'new' cases in the TB register and treatment card were interviewed about previous episodes of TB. A previous history of TB was elicited in 94 (7·5%) of 1254 patients who were being treated as new cases. Compared with patients with smear-positive PTB, a previous episode of TB was significantly more common in patients with smear-negative PTB (OR 3·5, [95% CI 2·1–5·7], $P < 0·001$) and patients with extrapulmonary TB (OR 2·0, [95% CI 1·1–3·7], $P < 0·05$). Of 94 patients with a previous episode of TB, 76 had completed treatment and 18 had defaulted from treatment during this episode. Patients with recurrent or relapse TB are being incorrectly registered within the Malawi TB Control Programme, and in the case of smear-positive PTB patients this is associated with administration of incorrect treatment. Measures have been put in place to rectify the situation, and further operational research is planned to monitor treatment outcomes of patients with recurrent smear-negative TB.

Keywords: tuberculosis, *Mycobacterium tuberculosis*, recurrence, relapse, disease control, Malawi

Introduction

There have been several clinical studies conducted in sub-Saharan Africa which have focused on recurrence rates of tuberculosis (TB) after treatment has been completed. Most studies have found that recurrence is increased in patients who were infected with the human immunodeficiency virus (HIV) at the start of treatment (PERRIENS *et al.*, 1991; HAWKEN *et al.*, 1993; ELLIOTT *et al.*, 1995; KELLY *et al.*, 1999), although this is not a universal finding (KASSIM *et al.*, 1995; VAN DEN BROEK *et al.*, 1998). Where the prevalence of recurrence is higher, it may be due to reactivation of disease or acquisition of another infection (GODFREY-FAUSSETT *et al.*, 1994), although the relative importance of each of these reasons for recurrence in sub-Saharan Africa is unknown.

In the past 10–15 years, Malawi, as with other countries in the region, has experienced a dramatic increase in HIV infections in the general population. The strong association that has developed between HIV and TB has resulted in a large upsurge in notified TB cases during this time period. HIV-seroprevalence studies conducted in different sites in the country among TB patients have shown a rising prevalence of HIV infection from 26% in 1986 (KOOL *et al.*, 1990), to 52% in 1988 (KELLY *et al.*, 1990), to 67% in 1991 (KELLY *et al.*, 1999) and 75% in 1993 (HARRIES *et al.*, 1995). With rising HIV seroprevalence in TB patients, it might be expected that the number of patients with recurrent TB should increase.

Patients with recurrent smear-positive pulmonary TB (PTB) are classified as relapse cases provided they took a full course of treatment and were declared cured. Patients with recurrent smear-negative TB [PTB and extrapulmonary TB (EPTB)] are classified as 'other' cases in the TB registers. Since 1984, Malawi has collected good data on national TB notifications which include annual reports of the number of patients with new smear-positive PTB, relapse smear-positive PTB, new smear-negative PTB and new EPTB. According to these annual reports (Malawi National TB Control Programme) the number of patients with relapse TB has remained fairly constant between 1985 and 1997, and the proportion of patients with relapse TB has in fact declined (Table 1). Patients classified as 'other' do not appear in these reports, but the number appearing in TB registers is always very minimal (personal observations).

This mismatch between what we expect from knowledge of the HIV seroprevalence in TB patients and what we observe in national TB notifications and TB registers made us suspect that patients with relapse PTB and recurrent TB were being missed under routine programme conditions. We decided to carry out an operational study to investigate this hypothesis further.

Methods

Data collection

There are 43 hospitals in Malawi (3 central, 22 district and 18 mission) that are involved in the registration and treatment of TB patients. All these hospitals were visited as part of a country-wide operational research study. In each hospital, the general wards and TB wards were visited, and all TB patients who were currently receiving the initial phase of treatment in hospital with either short-course chemotherapy or 'standard treatment' were identified. Details of the different types of treatment regimen used in Malawi are given elsewhere (KELLY *et al.*, 1999).

Table 1. National tuberculosis notifications in Malawi, 1985–97

	Number (%)[a] of notified patients	
Year	All types of TB	Relapse smear-positive PTB
1985	5334	469 (8·8%)
1987	7581	497 (6·6%)
1989	9450	373 (3·9%)
1991	14322	594 (4·1%)
1993	17105	534 (3·1%)
1995	19155	551 (2·9%)
1997	20676	507 (2·5%)

[a]% of all types of TB.
TB, tuberculosis; PTB, pulmonary TB.

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TB patients who had been registered as 'new' cases in the TB register and on the treatment card were interviewed by one of us (A.D.H.) at the bedside. The following information was recorded into a structured questionnaire proforma: TB registration number, age, sex, type of TB (smear-positive PTB, smear-negative PTB or EPTB) and previous history of TB. For those who gave a previous history of TB the following details were recorded as a result of the interview with the patient: date and year of previously diagnosed TB, type of previous TB, whether treatment had been completed, whether the patient had defaulted from treatment and wherever possible the reasons for default from treatment. Whenever possible the response by the patient was verified from the patient's old out-patient identity card: however, these cards were available for only a few patients, and most of the information provided by the patient could not be checked.

Management of patients with recurrent TB who had been incorrectly registered as new TB

For all patients with smear-positive PTB, the treatment regimen was changed from short-course chemotherapy to a re-treatment regimen (ENARSON *et al.*, 1996; WHO, 1997). All other patients with smear-negative PTB and EPTB remained on the treatment regimen that they were currently taking.

Analysis

Data were entered using EpiInfo 6.01 software (Centers for Disease Control, Atlanta, GA, USA). χ^2 test was used to assess differences in proportions between groups, with differences at the 5% level being regarded as significant. Odds ratios (OR), their 95% confidence intervals (95% CI) and P values were calculated as appropriate.

Results

There were 1254 patients registered with new TB. There were 575 men and 679 women, whose mean age (SD) was 35 (12) years. Upon re-interview, altogether 94 (7·5%) patients gave a previous history of TB: 48 men (8·3%) and 46 women (6·8%), the difference not being significant. For all patients, the previous episode of TB was a median of 4 years before the current episode (range 1–49 years), and for each type of TB the length of time between episodes was: smear-positive PTB, median 5 years (range 1–49); smear-negative PTB, median 4 years (range 1–15 years); EPTB, median 2 years (range 1–10 years). The frequency of the previous episode of TB together with the type of TB and the treatment outcome of the previous episode for patients with all types of TB, smear-positive PTB, smear-negative PTB and EPTB are shown in Table 2. Compared to patients with smear-positive PTB, a previous episode of TB was significantly more common in patients with smear-negative PTB (OR 3·5, [95% CI 2·1–5·7], $P < 0.001$) and patients with EPTB (OR 2·0, [95% CI 1·1–3·7], $P < 0.05$). Of 94 patients who had a previous episode of TB, 76 completed treatment and 18 defaulted from treatment; according to the patients none had failed treatment while taking the previous regimen. Of 18 patients who defaulted from treatment, 17 gave the length of time of the previous treatment which ranged from 1 to 7 months (median 3 months). No patient was able to explain why he/she had defaulted from treatment.

Discussion

This study confirms our hypothesis that in the setting of a TB control programme patients with a previous episode of TB were not being identified and were not being properly registered as either 'relapse PTB' or 'recurrent TB'. Incorrect registration was more common amongst patients currently being treated for smear-negative PTB and EPTB compared with patients with smear-positive PTB.

We think that the results of this study are representative for the country as a whole. All government and mission hospitals that register and treat TB patients in the country were visited, a large number of patients were interviewed and the same method of selecting patients for interview was used in each site. However, there are some limitations. First, the episode of previous TB was based in most cases upon the patient's history, and only in a few cases was there any documented proof from old TB out-patient identity cards. However, there seems no reason why patients should give the interviewer incorrect information. Second, this was an operational study and we have no information about how many patients who were treated for smear-negative PTB or EPTB (in the previous or current episode) actually had TB. HIV-positive patients are at increased risk of developing other HIV-related respiratory diseases which are difficult to diagnose in this setting (HARRIES *et al.*, 1998). Third, we do not know whether these recurrent episodes of TB were due to reactivation of disease or due to re-infection. Sophisticated molecular epidemiology studies are required to answer these questions. Finally, we did not carry out a systematic enquiry of the reasons why TB programme staff failed to register correctly the previously treated patients.

Incorrect registration of previous TB was less frequent in patients with smear-positive PTB compared with patients whose smears were negative. This may reflect the fact that patients with smear-positive PTB are accorded highest priority in the Malawi TB Programme, as in other directly observed therapy, short course (DOTS)–TB programmes. The training given to TB officers emphasizes the importance of asking all smear-positive TB patients whether they have ever had previous TB because this information determines the type of treatment the patient will receive: short-course chemo-

Table 2. Previous episodes of the disease for patients registered in Malawi as having 'new' tuberculosis

	Number (%) of patients			
	Smear-positive TB	Smear-negative TB	Extrapulmonary TB	All types TB
Registered as 'new'	746	282	226	1254
Previous TB	34 (4·6%)	40 (14·2%)	20 (8·8%)	94 (7·5%)
Type of previous TB				
Smear-positive PTB	12 (35%)	20 (50%)	7 (35%)	39 (41%)
Smear-negative PTB	17 (50%)	17 (42%)	5 (25%)	39 (41%)
Extrapulmonary TB	5 (15%)	3 (8%)	8 (40%)	16 (17%)
Outcome of previous TB				
Treatment completed	29 (85%)	28 (70%)	19 (95%)	76 (81%)
Defaulted from treatment	5 (15%)	12 (30%)	1 (5%)	18 (19%)

TB, tuberculosis; PTB, pulmonary TB.

therapy for new cases and a re-treatment regimen for relapse cases (ENARSON *et al.*, 1996; WHO, 1997). Relapse TB is defined as 'a patient who has been declared cured of any form of TB in the past by a physician, after 1 full course of chemotherapy, and has become again sputum smear-positive' (WHO, 1997). Cure means completion of treatment with negative sputum smears. Some TB officers felt that a previous episode of smear-negative PTB or EPTB did not constitute grounds for classifying the patient as a relapse case because such patients cannot be declared cured (i.e., their sputum smears are not routinely checked during treatment). We believe that the majority of incorrect registrations amongst smear-positive PTB patients was based on this misunderstanding, while in some patients there had also been a failure to ask the important questions. However, as there was no systematic search conducted into the reasons for not reporting a previous episode of TB, we cannot quantify this aspect of the study.

In the TB registers, there is provision for the proper recording of smear-negative patients with recurrent TB: they are supposed to be entered into the category of TB column 'Other'. However, there has been less need to ask about previous TB in such patients because the treatment regimen according to Malawi TB Control Programme Guidelines (ANONYMOUS, 1999) is the same whether the patient has new TB or recurrent TB. This approach may be wrong. According to studies conducted by the World Health Organization on global drug resistance (PABLOS-MENDEZ *et al.*, 1998), acquired resistance to any drug (i.e., in a patient previously treated) is always several times higher than primary resistance to any drug (i.e., in a patient who has never been previously treated). We would be worried that a history of previous TB is a pointer towards acquired drug resistance, and such resistance may compromise treatment outcomes especially in patients taking 'standard treatment' with just streptomycin, isoniazid and ethambutol. This would be a particular concern in patients who had been smear-positive and who had defaulted from treatment during their previous episode.

This study has implications for the Malawi TB Control Programme. At our last national TB seminar held in June 1999, the question of incorrect TB registration was discussed with all programme staff, and TB officers were instructed about the importance of getting the registration details right. National notifications will now, it is hoped, begin to match the true situation on the ground. Second, all patients with recurrent TB (smear-negative PTB and EPTB) identified in this study who were receiving treatment regimens designed for new patients will have their treatment outcomes monitored, and these will be compared with patients who truly have new TB. If treatment outcomes of patients with recurrent TB are worse than those of new patients, the Malawi TB programme will have to give considerably more thought to the problem and look into factors such as drug resistance, the proportion of patients with true TB and whether the treatment guidelines should be changed. Finally, the TB programme has just set up a system countrywide according to which all patients being started on a re-treatment regimen will have sputum specimens submitted to the mycobacterial reference laboratory in Lilongwe for culture and drug sensitivity testing. This will include all smear-positive TB patients with a previous episode of TB (those who completed treatment, those who failed on treatment and those who defaulted from treatment) and seriously ill smear-negative TB patients with a previous episode of TB. In this way the TB programme should start to get some useful information about drug resistance, and in particular its relationship to treatment failures and defaulters.

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