Treatment outcome of patients with smear-negative and smear-positive pulmonary tuberculosis in the National Tuberculosis Control Programme, Malawi

National Tuberculosis Control Programme, Community Health Science Unit, Lilongwe, Malawi; Department of Medicine, College of Medicine, Private Bag 360, Chichiri, Blantyre, Malawi

Abstract
National tuberculosis control programmes (NTCPs) in sub-Saharan Africa do not routinely record or report treatment outcome data on smear-negative pulmonary tuberculosis (PTB) patients. Twelve-month treatment outcome on patients with smear-negative PTB registered in all district and mission hospitals in Malawi during the year 1995 was collected, and was compared with 8-month treatment outcome in smear-positive PTB patients registered during the same period. Of 4240 patients with smear-negative PTB, 35% completed treatment, 25% died, 9% defaulted and 7% were transferred to another district with no treatment outcome results available. In 24% of patients treatment cards were lost and treatment outcome was unknown. These results were significantly inferior to those obtained in 4003 patients with smear-positive PTB in whom 72% completed treatment, 20% died, 4% defaulted, 2% were transferred and 1% had positive smears at the end of treatment. These differences between patients with smear-negative and smear-positive PTB were similar when analysed by sex and by most age-groups. Higher mortality rates in patients with smear-negative PTB are probably attributable to advanced HIV-related immunosuppression, and higher default and treatment unknown rates probably reflect the lack of attention paid by TB programme staff to this group of patients. As a result of this country-wide study the Malawi NTCP has started to record routinely the treatment outcomes of smear-negative TB patients and has set treatment completion targets of 50% or higher for this group of patients.

Keywords: tuberculosis, chemotherapy, treatment outcome, smear-positivity, smear-negative pulmonary tuberculosis, Malawi

Introduction
In many countries in sub-Saharan Africa smear-negative pulmonary tuberculosis (PTB) has become an increasing problem with rising case numbers, difficulties in establishing an accurate diagnosis and inadequate information about the outcome of treatment. Lack of information about treatment outcome is a result of the low priority given to patients with smear-negative PTB in the pre-HIV era when case numbers were low, infectivity was considered minimal (Grzybowski et al., 1975) and treatment outcome was good even with standard chemotherapy using drugs such as streptomycin, isoniazid and thiacetazone (Briggs et al., 1968; East African and British Medical Research Council, 1973). Efficient national TB control programmes (NTCPs), following guidelines from the International Union against Tuberculosis and Lung Disease (Snarson et al., 1996) and the World Health Organization (WHO, 1997), have traditionally recorded and reported on treatment outcome of smear-positive PTB cases, but not of patients with smear-negative PTB. A study carried out in Zomba central hospital, Malawi, found that the treatment outcome of patients with smear-negative PTB was considerably inferior compared with smear-positive PTB patients (Harrries et al., 1998). Smear-negative PTB patients had a treatment completion rate of 37% and a case-fatality rate of 46%, these findings being largely attributable to concurrent HIV infection. As a result of this study it was suggested that NTCPs record and report on treatment outcome of smear-negative PTB patients. We have collected treatment outcome data on smear-negative PTB patients registered in all district and mission hospitals in Malawi during the year 1995, and have compared the results with those obtained in smear-positive PTB patients registered during the same period.

Methods
Diagnosis, registration, treatment and treatment outcomes
In 1995, patients with smear-negative PTB and smear-positive PTB were diagnosed and registered in 41 treatment centres (3 central hospitals, 21 district hospitals and 17 mission hospitals) throughout Malawi. Methods of diagnosis and registration have been previously described (Harrries et al., 1998). Diagnosis of PTB is based on passive case-finding. Adult patients who have been coughing for 3 weeks or more, particularly if there is associated weight loss, are regarded as PTB suspects. All such patients first submit 3 sputum specimens for smear microscopy for acid-fast bacilli (AFB). Patients who are sputum-smear positive for AFB are classified as smear-positive PTB and usually undergo no further investigations. In patients who are sputum-smear negative, routine chest radiography is performed and a diagnosis of smear-negative PTB is made on patients showing radiographic abnormalities consistent with TB (i.e., cavities, fibrosis, hilar and/or para-tracheal lymphadenopathy, and infiltrations) in whom there has been no response following a course of antibiotics. At all district and mission hospitals, new patients with smear-negative PTB were treated with 12 months' standard treatment comprising 1 month of daily treatment in hospital with streptomycin, isoniazid and thiacetazone, followed by 11 months of continuation treatment at home with isoniazid and thiacetazone. The central hospitals had adopted a different 8-month treatment regimen from 1991 because of the problems of congestion on TB wards. New patients with smear-positive PTB in all hospitals were treated with 8 months of short-course chemotherapy comprising 2 months of initial treatment in hospital with daily streptomycin, isoniazid, rifampicin and pyrazinamide, followed by 6 months of continuation treatment at home with isoniazid and thiacetazone. In all patients, if they agreed to HIV testing and were found to be HIV- seropositive, ethambutol was substituted for thiacetazone. Treatment outcome of smear-negative PTB patients at 12 months and smear-positive PTB patients at 8 months was recorded according to standardized definitions as previously described and as shown in Table 1.

Data collection and treatment outcomes
During 1998, the 38 district and mission hospitals in the country were visited with the objective of collecting data on new patients with smear-negative and smear-positive PTB who were registered for treatment between 1 January and 31 December 1995. The central hospitals were excluded from this study because of their different treatment regimens. In 3 district/mission hospitals no
data could be collected: in 1 district hospital the treatment cards for 1995 had been collected from health centres but were destroyed in the room in which they were kept during a flood; in 1 mission hospital the TB register for 1995 had been lost, and in another mission hospital all the treatment cards for 1995 were lost. Data were collected from 35 hospitals (20 district and 15 mission hospitals), and included age, sex, TB registration number and treatment outcome. For patients with smear-negative PTB, treatment outcome data were obtained either from the TB register (if indicated) or from treatment cards which were collected from the TB office or from health centres for the purpose of this study. For patients with smear-positive PTB, treatment outcome was collected from the TB register.

Analysis

Data were entered into an EpiInfo software package (EpiInfo, version 6.0). Treatment outcomes between smear-negative and smear-positive PTB patients and in relation to age and gender were compared using \( \chi^2 \) test, with differences at the 5% level being regarded as significant. Relative risks (RR), their 95% confidence intervals (CI) and \( P \) values were also calculated where appropriate.

Results

There were 4240 patients with smear-negative PTB (2203 males and 2037 females, mean age 30 years) and 4003 patients with smear-positive PTB (2159 males and 1844 females, mean age 35 years) who were registered for treatment during 1995. Treatment outcome for all patients is shown in Table 1. Significantly fewer patients with smear-negative PTB completed treatment and significantly more patients with smear-positive PTB died, defaulted or transferred to another district compared with smear-positive PTB patients. In patients with smear-negative PTB, treatment outcome was unknown in 24% of cases because treatment cards could not be found and no information had been entered into the TB register. Of 3217 patients with smear-negative PTB for whom data on treatment outcome were available, 47% completed treatment and 38% died.

There were similar differences in treatment outcome between smear-negative and smear-positive PTB patients with respect to gender. In patients with smear-negative PTB, treatment outcome was no different between men and women. Where data on treatment outcome were available, 34% of 1676 male patients and 32% of 1541 female patients died before the end of treatment.

Treatment outcome in relation to age is shown in Table 2. The outcome of very young children with smear-negative PTB aged from birth to 4 years was poor, and was difficult to compare with smear-positive cases because of small numbers. Significant differences in all treatment outcomes (completed, died, defaulted and transferred) were found between smear-negative and smear-positive PTB patients in the age-ranges 15–44 years. In the younger (5–14 years) and the older (>45 years) age-groups, there were no significant differences in mortality between smear-negative and smear-positive patients. In patients with smear-negative and smear-positive PTB there was a significantly lower mortality in the age-range 5–14 years compared with all older age-groups (\( P < 0.05 \)), and of smear-negative PTB patients those aged 15–24 years also had a significantly lower mortality compared with older age-groups (\( P < 0.05 \)).

Discussion

The results of this country-wide survey of district and mission hospitals in Malawi show that smear-negative PTB patients in 1995 had in every respect an inferior treatment outcome to smear-positive PTB patients. The loss of nearly one-quarter of the treatment cards and the high rates of default indicate the general lack of attention paid by NTP staff to treatment outcome in this group of patients.

Case-fatality rates in smear-negative PTB patients were higher than those seen in smear-positive PTB patients. In this regard our survey may have been biased towards a poorer treatment outcome in smear-negative PTB patients because their outcome status was determined at 12 months rather than 8 months. However, previous work from Zomba Central Hospital, using survival analysis techniques and Cox regression models, still showed very significant differences between smear-negative and smear-positive PTB patients (HARRIES et al., 1998).

There are a number of possible reasons for the higher overall mortality rates seen in smear-negative PTB patients. In Malawi, a higher proportion of smear-negative PTB patients are HIV-seropositive compared with smear-positive PTB patients (HARRIES et al., 1998). In this regard, data from Queen Elizabeth Central Hospital between 1986 and 1995 showed that HIV-seroprevalence rates were lower in children aged 5–14 years compared with younger children and compared with

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Table 1. Treatment outcome of smear-negative and smear-positive tuberculosis patients registered in 1995 in Malawi

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Smear -ve</th>
<th>Smear +ve</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed treatment</td>
<td>1499 (35%)</td>
<td>2889 (72%)</td>
<td>0.48 [0.46–0.50]</td>
</tr>
<tr>
<td>Died</td>
<td>1054 (25%)</td>
<td>799 (20%)</td>
<td>1.14 [1.09–1.20]</td>
</tr>
<tr>
<td>Defaulted</td>
<td>373 (9%)</td>
<td>175 (4%)</td>
<td>1.35 [1.27–1.44]</td>
</tr>
<tr>
<td>Transferred</td>
<td>285 (7%)</td>
<td>95 (2%)</td>
<td>1.49 [1.40–1.59]</td>
</tr>
<tr>
<td>Failed</td>
<td>6</td>
<td>45 (1%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1023 (24%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>4240</td>
<td>4003</td>
<td></td>
</tr>
</tbody>
</table>

*Definitions: Completed treatment = completed either 12 months of treatment for smear-negative patients or 8 months of treatment for smear-positive patients (for smear-positive patients this includes 2712 patients who completed treatment with negative sputum smears and 17 patients who completed treatment with no sputum smears submitted).

Died = all deaths during treatment, irrespective of cause.

Defaulted = patients who did not collect drugs for 2 or more consecutive months.

Transferred = transferred to another district and whose treatment outcome was unknown.

Failure = patients who were smear-positive at 5 months or more of treatment.

Outcome unknown = no information on treatment outcome.

\( P < 0.05 \) for relative risk between patients with smear-negative pulmonary tuberculosis and smear-positive pulmonary tuberculosis.
adults aged 15–44 years (HARRIES et al., 1997), and this probably explains in part the lower case-fatality rates seen in this group of patients in the study.

In PTB patients who are HIV-seropositive, those with smear-negative PTB are likely to have more advanced immunosuppression compared with patients who have smear-positive disease (DE COCK et al., 1992). More profound clinical immunosuppression (NUNN et al., 1992) and low CD4 lymphocyte counts at the time of diagnosis (ACKAH et al., 1995; PERRIENS et al., 1995) are associated with higher mortality rates during treatment. "Standard treatment" is associated with an inferior outcome compared with short-course chemotherapy. In Uganda (OKWERA et al., 1994), a study examining 1-year survival rates found that the risk of death for "standard treatment" (streptomycin, isoniazid and thiacetzone) was 60% higher than with treatment with rifampicin, isoniazid and pyrazinamide in HIV-positive smear-positive PTB patients. The improved survival in patients receiving short-course regimens may be due to the broad-spectrum antibacterial activity of rifampicin preventing bacterial infections which are responsible for much morbidity and mortality in HIV-positive patients (GILKS et al., 1990).

In HIV-seropositive patients, thiacetzone is associated with a high frequency of cutaneous drug reactions, some of which can be fatal (NUNN et al., 1991). Although TB patients registered in 1995 could receive ethambutol instead of thiacetzone if found to be HIV-seropositive, very little routine counselling and HIV testing of TB patients were carried out in district hospitals at this time. The large majority of patients received thiacetzone, which for smear-negative PTB patients would have been throughout treatment and for smear-positive PTB patients would have been in the continuation phase only. Although we have no supporting data, this difference may also have been a factor in higher mortality rates in smear-negative patients, especially as drug reactions are more common with advancing immunosuppression (NUNN et al., 1993). All anti-tuberculosis drugs are free in Malawi, and there is also a good drug supply and drug distribution system, making it unlikely that different drug availability between smear-positive and smear-negative patients was a factor that could explain the different mortality rates.

This study with large numbers of patients has important implications for the Malawi NTP. First, we feel it is unacceptable to ignore the treatment outcome of smear-negative PTB patients, nor for that matter patients with extra-pulmonary TB (EPTB), who together constitute about 60% of the country’s TB burden. All NTP staff at district, mission and central hospitals have now been requested to obtain treatment cards routinely and to record the 12-month treatment outcome of these patients 15 months after they have been registered for treatment. The data will be collected on a quarterly basis by regional TB officers, and results assessed for the 3 regions in Malawi and for the whole country. This exercise will be closely monitored during the next 12 months as we are aware that it increases the work burden on district and regional NTP staff, which may be to the detriment of treatment outcome in smear-positive PTB patients. Second, there is evidence from studies performed in HIV-positive smear-positive PTB patients in sub-Saharan Africa that short-course chemotherapy with rifampicin is associated with a survival advantage compared with 12-months' "standard treatment" (OKWERA et al., 1994; ELLIOTT et al., 1995). In 1996, the use of short-course chemotherapy using 2 months of rifampicin, isoniazid and pyrazinamide followed by 6 months of isoniazid and ethambutol was piloted for all patients with smear-negative PTB and EPTB in 1 district of Malawi. Promising results have led to this regimen being used in another 4 districts, and it is hoped that this will be a country-wide regimen in the next 1–2 years.

As part of Malawi’s 5-year TB development plan, one

| Table 2: Treatment outcome of smear-negative and smear-positive tuberculosis patients in relation to age |
|---|---|
| Age (years) | Completed treatment (%) | Died (%) | Other (%) | Unknown (%) |
| 0-4 | 51/12 | 30 | 25 | 11 | 11 |
| 5-9 | 23/23 | 50 | 22 | 22 | 11 |
| 10-14 | 35/35 | 22 | 36 | 27 | 26 |
| 15-19 | 45/45 | 35 | 36 | 27 | 28 |
| 20-24 | 45/45 | 30 | 30 | 28 | 29 |
| 25-29 | 45/45 | 45 | 35 | 30 | 31 |
| 30-34 | 45/45 | 40 | 29 | 32 | 30 |
| 35-39 | 45/45 | 40 | 29 | 32 | 30 |
| 40-44 | 45/45 | 35 | 36 | 34 | 35 |
| 45-49 | 45/45 | 29 | 29 | 29 | 30 |

Note: For smear-positive PTB patients there is no treatment-unknown category.
of the targets to be reached is that treatment outcome of smear-negative and EPTB patients will be recorded on a routine basis and treatment completion rates will reach 50% or more. Completion rate target may be adjusted as the NTP gets better information with fewer treatment cards being lost at the end of treatment.

Acknowledgements
We thank all TB officers in district and mission hospitals who assisted in the gathering of data for this study. We thank the Department for International Development, UK, for financial assistance as part of its support for the Malawi NTP. The study received support from the TB Programme Steering Group and ethical approval from the Malawi Health Science Research Committee.

References


Received 16 November 1998; revised 23 February 1999; accepted for publication 2 March 1999.

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Book Review


The publication of the second edition of this deceptively small paperback, written by 3 very experienced tuberculous physicians, is timely. Tuberculosis is now responsible for over 3 million deaths annually, which occur mostly in developing countries. It is thus opportune that the latest developments in the management of tuberculosis are being made available through this book to health workers in developing countries.

The book consists of 222 pages divided into 6 chapters and 6 appendices condensed into a format that can be fitted into the side pocket of the health worker’s coat. The rapid increase of human immunodeficiency virus (HIV) infection in many developing countries has caused problems with diagnosis and treatment of tuberculosis in HIV/tuberculosis co-infected individuals. Accordingly, the chapter on tuberculosis/HIV/AIDS has been completely re-written and enlarged. Similarly, the sections on treatment of tuberculosis in adults and children have been completely re-written, citing the latest recommendations from the World Health Organization and the International Union Against Tuberculosis and Lung Disease (IUA/TLD). Written in simple and easy-to-read English, this book is extensively illustrated with numerous line-diagrams and tables. Non-specialist doctors and health workers will find the glossary of medical terms used in the textbook immensely helpful.

In partnership with the IUA/TLD, Teaching Aids at Low Cost (TALC) and some other generous donors, the cost of the book has been kept at a minimal affordable price of £3.50 and is an essential clinical text on tuberculosis for all health workers in developing countries. The first edition was translated into 16 different languages and 75,000 copies were distributed in 125 countries. This updated volume will no doubt have a similar success.

A. Zumla

University College London Centre for Infectious Diseases

Geneva Street Campus

Windsor Institute of Medical Sciences, Room G41

46 Cleveland Street

London WIP 6DB, UK