Measurement and determinants of tuberculosis outcome in Karonga District, Malawi

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Evaluation of disease outcome is central to the assessment of tuberculosis (TB) control programmes. In the study reported in this article we examined the factors influencing the measurement of outcome, survival rates during and after treatment, smear conversion rates, and relapse rates for patients diagnosed with TB in a rural area of Malawi between 1986 and mid-1994.

Patients with less certain diagnoses of TB were more likely to die than those with confirmed TB, both among those who were seropositive and those who were seronegative to human immunodeficiency virus (HIV). The mortality rate among smear-positive patients with a separate culture-positive specimen was half that of patients with no such diagnostic confirmation. Patients not registered by the Ministry of Health had much higher mortality and default rates than did registered patients. Among smear-positive patients, HIV serostatus was the most important influence on mortality both during and after treatment (crude hazard ratios (95% confidence intervals) = 5.6 (3.0–10) and 7.7 (3.4–17), resp.), but HIV serostatus did not influence smear conversion rates. The initial degree of smear positivity influenced smear conversion rates, but not mortality rates. No significant predictors of relapse were identified.

Unless considerable care is taken to include all TB patients, and to exclude nontuberculous patients, recorded TB outcome statistics are difficult to interpret and may be misleading. In populations with high rates of HIV infection, TB target cure rates of 85% are unrealistic. When new interventions are assessed it cannot be assumed that factors which influence the smear conversion rate will also influence the mortality rate.

Introduction

Mycobacterium tuberculosis causes around 3 million deaths a year worldwide, more deaths than are caused by any other single pathogen. Tuberculosis (TB) control policies emphasize the importance of case finding and treatment, particularly of smear-positive cases, aiming for a "cure" rate of 85% (*1*). A high cure rate is seen as the key priority. Incomplete treatments add to the pool of infectious cases and increase drug-resistant TB, and it is argued that good quality treatment services will attract new patients and lead to increased case detection.

Measurement of outcome is thus central to TB control, and outcomes are often reported (*2*, *3*). Cure rates are usually calculated using a cohort approach based on registered patients (*4*, *5*). If some patients are not registered, for example, because they die before or shortly after hospital admission, the results obtained will be misleading. Outcomes recorded may also depend on the diagnostic criteria used; mortality may be higher among patients misdiagnosed as having TB than among those correctly diagnosed and treated. The impact of these factors on recorded outcomes is largely unknown, and the data required to define it are not routinely available. None the less, knowledge of these factors is essential for assessing TB programme performance, since the failure to register all diagnosed patients is likely to lead to over-optimistic reporting of treatment outcomes, and diagnostic failures leading to the treatment of patients with other diseases as TB patients have costs to both patients and the health service, and could worsen measured outcomes.

Interpretation of outcome data depends on knowledge of the characteristics of the patients included. Even in the best-run programmes, TB cure rates of 85% may no longer be possible because of the high mortality rates experienced by patients co-infected with human immunodeficiency virus

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(HIV). We present a detailed analysis of factors influencing outcome among smear-positive TB patients in a rural area of northern Malawi, considering survival during treatment and subsequent survival among those successfully treated, smear conversion rates, and relapse rates.

Methods

Karonga District is the site of the Lepra Evaluation Project/Karonga Prevention Study (KPS), a large epidemiological study of leprosy and TB (*6*, *7*). During the 1980s, the KPS carried out two total population surveys in this area, whose current population is approximately 180000. The second survey formed the recruitment phase for a vaccine trial of repeat BCG vaccination and BCG combined with killed *Mycobacterium leprae* (*7*). In the surveys, the population was screened for leprosy by physical examination and for TB by enquiring about any coughs that had lasted at least one month and by examination for cervical lymphadenopathy. From 1990 case finding has included "enhanced passive ascertainment": all individuals who attended health centres for whatever reason and had not been for the previous 12 months were screened for leprosy and TB as in the surveys. Patients could also self-report with cough or other symptoms of TB at any time, and the majority of TB patients were ascertained in this way. Further suspects were identified among patients already admitted for other reasons.

TB suspects were asked to produce three sputum specimens, and those with positive microscopy or culture results were referred to hospital for initial intensive phase treatment. All TB patients treated in the hospital were registered by the Ministry of Health as part of the national TB programme. Irrespective of how they were initially identified, all patients were seen on the ward by KPS staff to establish contact and identify place of residence because the KPS was responsible for outpatient care of all TB cases in the district. Since 1988 all adult patients who gave their consent have been tested serologically for infection with HIV using a four-test protocol, as previously described (*8*). Sputum specimens were taken for diagnosis, and for sputum smear-positive patients after 2 months, 5 months, and at the end of therapy.

Since 1986 all sputum specimens have been examined by microscopy and cultured at KPS headquarters in Chilumba, Malawi. Cultures suggestive of TB were sent to the PHLS Mycobacterium Reference Laboratory, in Cardiff, Wales, for species identification and drug sensitivity testing (*9*).

Treatment followed Malawi Government guidelines and was free (*10*). The current regimens were started in the district in 1986. Smear-positive patients received a regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide for 2 months in hospital followed by 6 months of isoniazid and thiacetazone as outpatients. If the sputum smear was still positive after 2 months, the initial phase was prolonged, and if follow-up specimens were smear-positive the patient was readmitted. Smear-negative patients received the standard regimen of streptomycin, isoniazid, and thiacetazone for 1 month in hospital, followed by isoniazid and thiacetazone for 11 months as outpatients. Smear-positive patients who failed or relapsed received a regimen including ethambutol. A few patients with extrapulmonary TB diagnosed by KPS were treated as outpatients before the new regimens were well established.

Patients were included in the present analysis if they were diagnosed after 1 January 1986 and were not known to have had previous TB. This date coincided with the establishment of routine culture and the start of the new treatment regimens. Patients diagnosed after 30 June 1994 have been excluded to ensure that outcome data were complete on all patients. Diagnosis was based on clinical symptoms and signs, chest X-ray, sputum smear and culture, histology of suspect TB skin lesions or lymph nodes, and, in some children, on tuberculin results. For pulmonary TB, "certain" cases were culture positive on at least one sputum specimen and had at least one other specimen positive on culture or microscopy; "probable" cases were all other patients with positive sputum microscopy or culture results, except those with only a single microscopy-positive sputum with fewer than 10 bacilli per 100 fields; and "possible" cases were those diagnosed by X-ray and those with a single positive microscopy result with fewer than 10 bacilli per 100 fields.

Extrapulmonary cases were "certain" if the biopsy was classified as confirming TB, or if culture or microscopy of aspirated fluid (pleural, ascites, or cerebrospinal fluid) was positive. Clinically diagnosed cases of tuberculous lymphadenitis and other extrapulmonary TB cases for whom the biopsy was suggestive of TB were classified as "probable". All other cases registered by the Ministry of Health or diagnosed only by KPS staff were classified as "possible". A smear-positive patient was any patient with a positive smear within 2 months of diagnosis (excluding those for whom the relevant culture showed only atypical mycobacteria). The same criteria were used to classify relapses.

Outpatient follow-up was carried out by KPS staff, who saw the patients monthly. Patients were visited at agreed meeting places or in their own homes; tablets were counted to check compliance, the patient was asked about any drug reactions, and

was given the next month's supply of drugs. Follow-up sputum specimens were taken if appropriate.

Patients with certain or probable TB registered since January 1988, who were resident in the district and had been discharged at the end of treatment, were followed up at yearly intervals. If found, they were asked about any coughs, and sputum was collected if appropriate. If they were not found, information was sought from other household members or neighbours as to whether they were known to have died or to have left the district. Patients who relapsed were identified by the continued monitoring at health centres and the hospital.

Analyses of the determinants of outcome used survival analysis and Cox's proportional hazards models. For analyses of outcome of the disease episode, subjects were "censored" when they were discharged or lost to follow-up. For longer-term outcomes subjects were censored when they left the district or were lost to follow-up. The proportional hazards assumption was checked by inspection of the plots and by tests for interaction with time. If nonproportional hazards were found, stratified models were used and the effect of the variable was assessed for different time periods, defined using the median time to the outcome of interest (the median event time). These analyses were restricted to "certain" or "probable" smear-positive cases who received the correct short-course therapy.

The risk factors considered are shown in Table 4. The degree of smear positivity was taken as the maximum observed within the first 2 months, recorded in four categories, ranging from 1–9 acid-fast bacilli (afb) per 100 fields to 10–99 afb per field. Drug resistance was recorded if results were available on a specimen taken within 1 month of the start of treatment. BCG status was assessed on the basis of scars (*11*) and vaccination records from the 1980s repeat BCG trial or childhood vaccinations. Since the characteristics of patients who were not in the trial may differ from those who were included (e.g. recent immigrants to the district were not part of the trial population), patients who neither took part nor refused to take part in the trial were also considered separately in the analyses of the effect of BCG on outcome.

The rate of sputum smear conversion was also studied. The date of conversion was taken as the midpoint of the interval between the last positive and the first subsequent negative microscopy result. This should be a reasonable approximation if the interval is short, but is likely to be inaccurate for patients who fail to have specimens taken between diagnosis and the end of therapy. The analysis was therefore re-run, excluding patients for whom the interval was >3 months. If there was no negative specimen after one or more positive specimens, the record was censored at the time of the last positive specimen.

For estimating the effect of diagnostic certainty on outcome, the crude figures are potentially misleading since patients who survive longer have more chance of having their TB confirmed. Therefore, for these analyses the certainty groups were based only on data available within the first 2 months, and the outcome beyond 2 months was analysed.

Results

Information was available on 1655 certain, probable or possible TB patients who were either registered by the Ministry of Health as TB cases (1524), or diagnosed only by KPS staff (131 (8%)). Patients failed to be registered because they were treated as outpatients (10 patients), died (82), defaulted (38), or for unknown reasons (1). Overall, 22.5% of the patients died before the end of treatment, 57.9% reached the end of treatment and were discharged, 4.3% were transferred out of the district, and the remaining 15.3% defaulted and were lost to follow-up. Of the deaths, 23% occurred among the 8% of patients who were not registered by the Ministry of Health. Excluding individuals who were not registered, the case fatality rate (defined as death before the completion of treatment) was 19.0%, 62.4% were discharged, 4.7% were transferred, and 14.0% were lost to follow-up.

Overall case fatality

Case fatality rates were similar in those classified as pulmonary and extrapulmonary, but were lower among those with confirmed TB. The trend in mortality rates with diagnostic certainty was evident among those surviving beyond 2 months (χ^2 test for trend = 22; $P < 0.001$) (Table 1) and persisted after stratifying for HIV (Table 2). Since type of disease and treatment both influence outcome, further analysis of the effect of certainty of diagnosis on mortality beyond 2 months was restricted to smear-positive patients who received short-course therapy (Fig. 1). Compared to certain cases, probable and possible cases had higher mortality rates: hazard ratios of 2.0 (95% confidence interval (CI) = 1.1–3.9) and 4.2 (95% CI = 2.0–8.7), respectively. This effect was unchanged by controlling for possible confounders (age, sex, HIV serostatus, year of diagnosis, degree of smear positivity, and BCG status) in a Cox's regression analysis.

Overall, 35% of HIV-positive patients died before the end of treatment, compared with 11% of

Table 1: **Outcome among TB patients who survived the first 2 months, by type of disease and certainty of diagnosis, Karonga District, Malawi, 1986–94**

	Pulmonary TB			Extrapulmonary TB			Unknown
	Certain[a]	Probable[a]	Possible[a]	Certain[a]	Probable[a]	Possible[a]	Possible[a]
No. discharged	268 (78.4)[b]	228 (72.8)	229 (66.0)	34 (77.3)	16 (59.3)	139 (69.2)	44 (67.7)
No. transferred	14 (4.1)	13 (4.2)	14 (4.0)	1 (2.3)	0 (0.0)	6 (3.0)	0 (0.0)
No. lost	33 (9.7)	24 (7.7)	32 (9.2)	4 (9.1)	8 (29.6)	23 (11.4)	8 (12.3)
No. died	27 (7.9)	48 (15.3)	72 (20.7)	5 (11.4)	3 (11.1)	33 (16.4)	13 (20.0)
Total	342	313	347	44	27	201	65

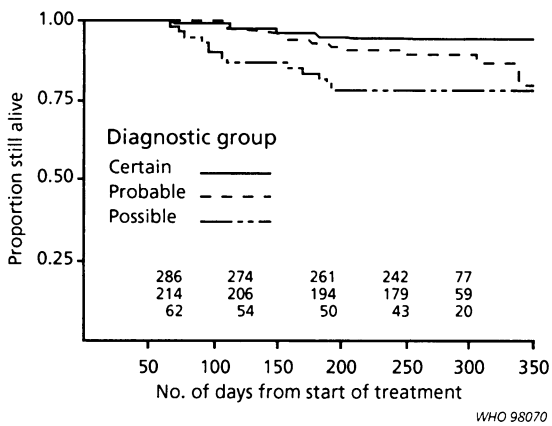
[a] Diagnostic groups were defined on the basis of data available within the first 2 months.
[b] Figures in parentheses are percentages.

Table 2: **Outcome, by human immodeficiency virus (HIV) serostatus and certainty of diagnosis, among TB patients who survived the first 2 months, Karonga District, Malawi, 1986–94**

	HIV positive:			HIV negative:			Unknown HIV status:		
	Certain[a]	Probable[a]	Possible[a]	Certain[a]	Probable[a]	Possible[a]	Certain[a]	Probable[a]	Possible[a]
No. discharged	61 (57.0)[b]	46 (51.7)	69 (49.9)	183 (88.4)	119 (85.0)	134 (74.0)	58 (80.6)	79 (71.2)	209 (71.6)
No. transferred	8 (7.5)	5 (5.6)	6 (4.3)	5 (2.4)	2 (1.4)	5 (2.8)	2 (2.8)	6 (5.4)	9 (3.1)
No. lost	17 (15.9)	9 (10.1)	14 (10.0)	13 (6.3)	12 (8.6)	18 (9.9)	7 (9.7)	11 (9.9)	31 (10.6)
No. died	21 (19.6)	29 (32.5)	51 (36.4)	6 (2.9)	7 (5.0)	24 (13.3)	5 (6.9)	15 (13.5)	43 (14.7)
Total	107	89	140	207	140	181	72	111	292

[a] Defined on the basis of data available within the first 2 months.
[b] Figures in parentheses are percentages.

Fig. 1. **Kaplan–Meier plot of the influence of diagnostic certainty group on mortality of smear-positive TB patients who received short-course therapy and survived at least 2 months. The diagnostic groups were based on data available within the first 2 months.** Shown also is the number of people still being followed up in each category.



HIV-negative patients and 25% of those whose HIV serostatus was unknown. Among those with unknown HIV serostatus, 235 were aged > 14 years and were diagnosed after 1988 and so should have been tested if their consent had been given. The reason for the lack of testing was not recorded, but 111 of such patients died, transferred, or were lost to follow-up within the first 3 months.

Smear-positive patients

The main analysis of risk factors for outcome was restricted to smear-positive patients. In total, 682 patients were smear positive, of whom 642 were registered. Of the registered patients, 591 received the correct short-course therapy, 20 the standard regimen, and two the retreatment regimen. All but one of the unregistered patients received no treatment. The treatment received by the other patients is not known. The outcomes for smear-positive patients are shown in Table 3. Overall, 16.0% died before the end of treatment, 13.1% of those registered by the Ministry of Health, and 62.5% of those not regis-

tered. A total of 64.2% completed treatment, of whom 91% were cured as indicated by two negative smears including one at the end of treatment. However, five of the patients classified as cured on the basis of smears, and one classified as "putative cure" (Table 3) had positive cultures at the end of treatment.

Mortality among certain and probable smear-positive patients receiving short course therapy

Of the certain or probable smear-positive patients, 527 received short-course therapy and were included in the survival analyses (Table 4). In the crude analysis, mortality rates were higher among HIV positives (Fig. 2), among those without evidence of BCG vaccination, among older patients, and in more recent years. The mortality rate for HIV-positive patients was 42 per 100 person-years at risk (pyar) (95% CI = 29–59), and for HIV-negative patients 7.6/100 pyar (95% CI = 4.6–12.6).

After controlling for age, the effect of HIV serostatus on mortality was increased, and that of BCG vaccination status was decreased (Table 5). After controlling for HIV serostatus, the effect of age became significant (Table 5) and that of year of diagnosis was lost (hazard ratio = 1.0; 95% CI = 0.9–1.2). There was no other confounding and no statistically significant interactions between the risk factors examined. However, the apparent reduction in mortality associated with BCG was seen primarily among HIV-positive patients. After controlling for age, comparison of those who had not been BCG vaccinated to those who had, the hazard ratio of dying was 3.4 (95% CI = 1.5–7.8) among HIV positives, and 1.5 (95% CI = 0.5–4.5) among HIV negatives.

A total of 208 patients were not included in the 1980s repeat BCG vaccine trial. Among these patients, 2/53 of those with BCG scars and 20/86 of those without such scars died (hazard ratio = 6.5; 95% CI = 1.5–27.6). After controlling for age and HIV serostatus, those without BCG scars still

Fig. 2. **Kaplan–Meier plot of influence of HIV serostatus on death during treatment for "certain" and "probable" smear-positive TB patients who received short-course therapy, Karonga District, Malawi 1986–94**. Shown also are the number of people still being followed up in each category.

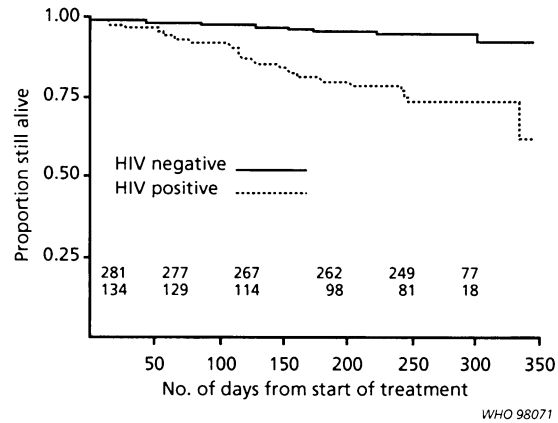


Table 3: **Distribution of outcomes among smear-positive TB patients, Karonga District, Malawi, 1986–94**

Outcome[a]	Ministry of Health registered	Not Ministry of Health registered	Total
Cure	397 (61.8)[b]	0	397 (58.2)
Putative cure	34 (5.3)	0	34 (5.0)
Treatment completed	7 (1.1)	0	7 (1.0)
Failure	23 (3.6)	0	23 (3.1)
Transferred	38 (5.9)	0	38 (5.6)
Lost	59 (9.2)	15 (37.5)	74 (10.9)
Died	84 (13.1)	25 (62.5)	109 (16.0)
Total	642	40	682

[a] Cure implies negative smears on at least two occasions, including one at the end of treatment. Putative cure implies one negative smear at the end of treatment or at least two negative smears after the last positive smear, but none at the end of treatment. Treatment completed implies discharged from treatment apparently cured but not fulfilling the other criteria. Failure implies the patient became smear positive again at least 5 months after starting treatment (two of these patients subsequently died and three were lost to follow-up).
[b] Figures in parentheses are percentages.

Table 4: **Associations between various risk factors and outcome of smear-positive TB among "certain" and "probable" TB patients who received short-course therapy, Karonga District, Malawi, 1986–94**

Risk factor	No. of patients	Death during treatment: Hazard ratio[a]	Death during treatment: *P*-value[b]	Sputum smear conversion: Hazard ratio[a]	Sputum smear conversion: *P*-value[b]
Age (years)					
≤ 30	181 (13)[c]	1		1	
31–45	171 (22)	1.82; *0.93–3.57*[d]	0.08	0.87; *0.70–1.07*	0.2
>45	175 (17)	1.24; *0.61–2.51*	0.6	0.69; *0.56–0.85*	0.001
Sex					
Female	238 (21)	1		1	
Male	289 (32)	1.30; *0.75–2.26*	0.3	0.85; *0.71–1.02*	0.08
HIV serostatus					
Negative	281 (15)	1		1	
Positive	134 (32)	5.59; *3.02–10.4*	<0.001	1.23; *0.99–1.52*	0.07
Degree of smear positivity:					
1–9 afb/100 fields	50 (4)	1		1	
1–9 afb/100 fields	209 (23)	1.48; *0.51–4.28*		0.99; *0.72–1.35*[e]	
1–9 afb/field	149 (17)	1.43; *0.48–4.28*		0.72; *0.52–0.99*[e]	
≥10 afb/field	109 (9)	0.97; *0.30–3.14*	0.6	0.63; *0.45–0.88*[e]	<0.001
Drug resistance:					
None	342 (27)	1		1	
1 drug	29 (3)	1.30; *0.40–4.30*		1.10; *0.74–1.62*	
≥2 drugs	12 (2)	2.18; *0.52–9.17*	0.3	0.79; *0.42–1.48*	0.7
Year of diagnosis	527 (53)	1.22; *1.08–1.39*	0.001	0.99; *0.96–1.03*	0.7
BCG status					
Positive	306 (22)	1		1	
Doubtful	20 (2)	1.52; *0.36–6.47*	0.6	0.93; *0.59–1.48*	0.8
Negative	139 (21)	2.26; *1.24–4.11*	0.008	1.01; *0.82–1.24*	1.0

[a] Results are not adjusted for any confounders.
[b] Except for BCG status and age, *P*-values quoted are for linear trend across the groups.
[c] Figures in parentheses are number of deaths.
[d] Figures in italics are the 95% confidence intervals.
[e] Nonproportional hazards, see text for details.

Table 5: **Hazard ratios for death during treatment among "certain" and "probable" smear-positive TB patients who received short-course therapy, Karonga District, Malawi, 1986–94**

Risk factor	*n*	Hazard ratio: Crude	Controlled for age	Crude, but limited to 377 patients with data for all three risk factors	Controlled for each other
HIV serostatus					
Negative	281	1	1	1	1
Positive	134	5.59; *3.02–10.4*[a]	6.65; *3.48–12.7*	5.30; *2.75–10.2*	6.30; *3.18–12.5*
Age (years)					
≤30	181	1		1	1
31–45	171	1.82; *0.93–3.57*		2.27; *0.99–5.23*	2.64; *1.12–6.23*
>45	175	1.24; *0.61–2.51*		1.48; *0.62–3.52*	2.49; *0.99–6.27*
BCG status					
Positive	306	1	1	1	1
Doubtful	20	1.52; *0.36–6.47*	1.33; *0.31–5.72*	1.97; *0.46–8.49*	1.95; *0.44–8.56*
Negative	139	2.26; *1.24–4.11*	1.98; *1.08–3.65*	2.90; *1.53–5.48*	2.53; *1.34–4.80*

[a] Figures in italics are the 95% confidence intervals.

had higher mortality rates (hazard ratio = 8.6; 95% CI = 1.8–40.9).

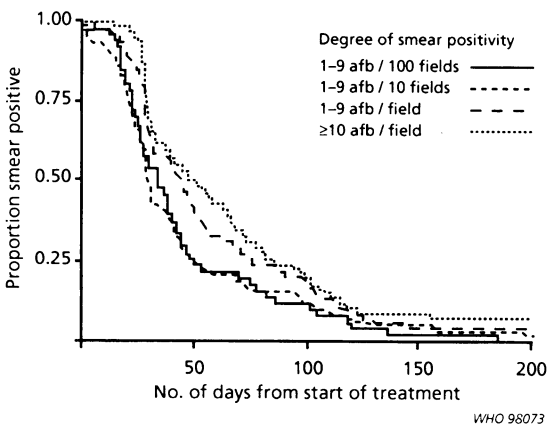
Smear conversion among patients receiving short-course therapy

The rate of sputum smear conversion depended on the initial degree of smear positivity, being slower among individuals with large loads of bacilli (Fig. 3). It was also slower in older patients and was weakly associated with sex and HIV status (Table 4). The results were similar after excluding the 86 patients who had an interval of >3 months between the last positive and first negative specimen.

Since the hazard functions for the effect of degree of smear positivity on smear conversion were not proportional the multivariate analysis was stratified for smear positivity. The effects of sex and HIV serostatus were lost after controlling for age and smear positivity. The effect of age was not altered by stratifying for smear positivity, and there was no other confounding.

To assess the effect of degree of smear positivity without violating the proportional hazards assumption of Cox's survival analysis, we used different time periods. Half the smear conversions occurred within the first 35 days, but within this period the hazards for the effect of degree of smear positivity were still nonproportional. The period was therefore divided again using the median event time. Within the first 25 days the hazards were proportional and the degree of smear positivity was very strongly (negatively) associated with smear conversion (hazard ratio = 0.6; 95% CI = 0.4–0.7) for each 10-fold increase in smear positivity). Beyond 25 days the hazards were again proportional and the degree of smear positivity had only a slight effect: hazard ratio = 0.9 (95% CI = 0.8–1.0). These estimates were little altered by controlling for possible confounders.

Fig. 3. **Kaplan–Meier plot of sputum smear conversion, by degree of smear positivity, among "certain" and "probable" smear-positive TB patients who received short-course therapy, Karonga District, Malawi 1986–94** (afb = acid-fast bacilli).



Outcome beyond the end of treatment

A total of 431 patients with certain or probable TB who were discharged at the end of therapy were actively sought in the follow-up. Further information was available on 322 (75%) patients — 78% of those who were HIV seronegative and 64% of those who were HIV seropositive at diagnosis. The median follow-up time was 2.3 years (10th centile: 9 months; 90th centile: 4.4 years). Follow-up was similar for males and females and in different age groups. The major influence on subsequent mortality was HIV status: 13/207 (6.3%) HIV-negative patients and 20/61 (33%) HIV-positive patients were known to have died within 2 years.

Detailed analysis of outcome beyond the end of treatment was restricted to certain or probable TB patients who had had smear-positive disease treated with short-course therapy and who had been shown to have become smear negative (cure and putative cure in Table 3). Four patients who were culture positive at the end of treatment were also excluded. A total of 291 patients fulfilled these criteria, 204 (70%) of whom had information available from the follow-up period.

The same possible risk factors were considered as for outcome during treatment (Table 4). In the univariate analysis only HIV serostatus and year of diagnosis influenced the mortality rate (Table 6). Mortality rates for HIV-positive patients were 22/100 pyar (95% CI = 13–38) and for HIV-negative patients 2.9/100 pyar (95% CI = 1.6–5.2). After controlling for HIV status an effect of age became apparent. There was no statistically significant interaction between the factors, but the effect of year of diagnosis on the mortality rate only occurred among the HIV-positive patients (Fig. 4, hazard ratio = 1.7; 95% CI = 1.1–2.7) and not among the HIV-negative patients (hazard ratio = 1.2; 95% CI = 0.7–2.0, after controlling for age).

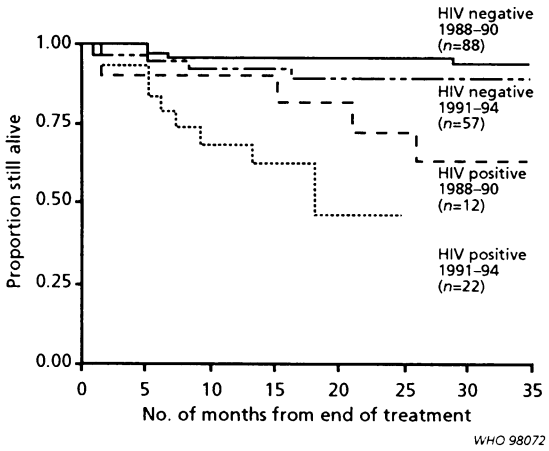
Relapses that were classified as certain or probable occurred for 11 of the 204 previously cured smear-positive patients. Four patients with possible relapses were excluded. None of the potential risk factors was associated significantly with relapse either in the crude analysis or after adjusting for confounders. Relapses occurred in 2/32 (6.3%) HIV-positive patients and 6/144 (4.2%) HIV-negative patients (hazard ratio = 2.62; 95% CI = 0.52–13.1).

Table 6: **Hazard ratios for death after discharge from treatment among "certain" and "probable" smear-positive TB patients who received short-course therapy and were shown to be smear-negative, Karonga District, Malawi, 1986–94**

Risk factor	*n*	Hazard ratio: Crude	Hazard ratio: Controlled for each other
HIV serostatus			
Negative	145 (11)[a]	1	1
Positive	34 (14)	7.66; *3.44–17.1*[b]	9.38; *3.89–22.6*
Age (years)			
≤30	69 (10)	1	1
31–45	60 (5)	0.65; *0.22–1.90*	0.97; *0.31–3.02*
>45	75 (15)	1.68; *0.75–3.77*	2.73; *1.03–7.18*
Year of diagnosis	204 (30)	1.41; *1.09–1.83*	1.55; *1.14–2.11*

[a] Figures in parentheses are the number of deaths.
[b] Figures in italics are the 95% confidence intervals.

Fig. 4. **Kaplan–Meier plot of influence of HIV serostatus and year of diagnosis on survival beyond the end of treatment for "certain" and "probable" smear-positive TB patients who received short-course therapy and for whom smear conversion had been demonstrated, Karonga District, Malawi.** The number of people in each category at the start of follow-up is shown.



Discussion

In judging the success of a TB control programme much emphasis is placed on the outcome among diagnosed cases, particularly the cure rate among smear-positive patients. If patients are not included in the statistics because they die or default early, the results obtained will be over-optimistic. We have been able to quantify this bias in Karonga District. When patients who failed to be registered were included, the main change was in the case fatality rate, the true rate among diagnosed smear-positive patients being 16%, rather than the 13% recorded among registered patients. The proportion of defaulters increased from 9% to 11%, and the proportion discharged at the end of treatment fell from 72% to 68% (Table 3). The proven cure rate was low compared with results from the 1980s in Malawi (*10*), but was consistent with more recent data (*2*).

Another important influence on recorded outcome is the definition used for a TB case. Patients with less definite diagnoses had higher mortality rates (Table 1). The difference between the certain and probable smear-positive patients is particularly striking since both groups would normally be considered to have strong evidence of TB, and this difference did not result from confounding by HIV serostatus or other factors. The higher mortality with less certain diagnoses is presumably due to inclusion of some patients who have severe illnesses other than TB for which they received inappropriate or inadequate treatment. This may be generally true. In two national samples of TB patients in Kenya in the 1960s and 1970s, mortality was lower among individuals with positive cultures than among those with negative cultures or who failed to produce sputum specimens (*12*, *13*).

The major determinant of mortality among TB patients in Karonga District in recent years, both during and after treatment, has been HIV serostatus. The hazard ratio of 6 among smear-positive patients for death during treatment is consistent with results from elsewhere in Africa (*14–17*). It has previously been shown that the mortality rate depends on the severity of the immune deficiency (*17*) and that

many of the excess deaths are not directly attributable to TB (*15*, *16*). We had no information on the cause of death in our study.

The mortality rate increased over the years of this study. After controlling for HIV serostatus, the effect of year of diagnosis on death during treatment disappeared, but the mortality rate after the end of treatment increased 1.4 times each year (Table 6). This effect was seen principally among the HIV-positive patients and is likely to reflect the growing proportion of patients with more advanced HIV disease later in the epidemic.

The association between BCG vaccination and mortality of smear-positive patients was surprising. A study in Kenya found no effect of BCG vaccination on 6-month mortality (*15*). In Karonga District, BCG vaccination does not protect against pulmonary TB (*18*, *19*). In the vaccine trial carried out in this population in the 1980s all participants without BCG scars received BCG vaccine (*7*), so the group of patients without BCG includes a high proportion of recent immigrants to the district who may differ in other ways from the other patients. Excluding trial participants removes this bias, but there may still be many differences between those who had been and those had not been BCG vaccinated. For example, in this population individuals without BCG scars were less likely to have had any schooling (*11*). We had information on schooling and housing conditions in the early 1980s for 57% of the smear-positive patients. Controlling for these factors had no influence on the effect of BCG vaccination (results not shown) but they may not closely reflect current socioeconomic conditions. In the repeat BCG trial, the case fatality rate among previously scar-positive patients was 13/54 (24%) for those who had received a second dose of BCG vaccine and 4/47 (8.5%) among those who received placebo, corresponding to a relative risk of 1.8 (95% CI = 0.7–4.5) after stratifying for HIV status (Karonga Prevention Trial, unpublished results). These results, which go in the opposite direction, make it very unlikely that BCG vaccination has a protective effect.

Although HIV serostatus and BCG status were both associated with mortality among smear-positive patients, they had no effect on the rate of smear conversion. An influence of HIV on early mortality but not smear conversion rates has also been reported in Zaire (*20*). Conversely, the initial degree of smear positivity strongly influenced smear conversion rates but had no effect on mortality. Smear conversion rates are used as early indicators of TB programme performance and as outcome indicators in treatment trials. Although successful smear conversion is encouraging, our results suggest that caution is needed in using smear conversion rates as a proxy for longer-term successful treatment results. The faster rate of smear conversion among those with fewer bacilli makes biogical sense and has been shown before (*21*), but this may in part reflect the greater sampling variability and difficulty in detecting bacilli when they are present in small numbers, so that repeat specimens may be reported as negative. In so far as degree of smear positivity is a correlate of severity of disease, it is surprising that it appeared to have no influence on mortality.

Compared with older patients younger patients had faster smear conversion and lower mortality rates both during treatment and in the subsequent follow-up. This is consistent with previously published findings (*15*, *16*). The lack of a statistically significant effect of initial drug resistance on either the smear conversion rate or the mortality rate is probably due to the small numbers of patients with multiple drug resistance in this series.

Other studies have found higher rates of relapse among HIV-positive patients than we have reported here (*22*, *23*), but our sample size was small (only 23 HIV-positive patients still being followed up 1 year after discharge) and the confidence intervals are correspondingly wide. In Karonga the relapse rate for HIV-positive patients was 3.6/100 pyar (95% CI = 0.9–15) and for HIV-negative patients 1.6/100 pyar (95% CI = 0.7–3.5). In Nairobi equivalent rates for relapses were 16.7/100 pyar (estimated 95% CI = 8.0–31) and 0.5/100 pyar (estimated 95% CI = 0.01–2.8) (*22*); in Lusaka 22/100 pyar (95% CI = 13–36) and 6/100 pyar (95% CI = 1–17) (*23*); and in Kinshasa 23/100 pyar (95% CI = 9.4–48) and 4.4/100 pyar (95% CI = 1.9–8.8). In Nairobi recurrence was confirmed by two positive cultures; in Lusaka, bacteriologically or histologically in 11/16 HIV-positive cases and 2/3 HIV-negative cases; and in Kinshasa all relapses were smear positive. In Kinshasa, as in Karonga, relapses were only counted for patients who had had previous negative sputum smears and culture. These differences may have arisen because some recurrences are due to new infections, and the chance of these occurring is likely to be greater in large cities than in Karonga, which is a rural district.

Our study has shown that some patients, particularly those with worse outcomes, are missed by the usual processes of registration. To some extent this is inevitable and the magnitude of this bias is likely to vary from place to place and over time. The 8% of patients missed in Karonga District had a small effect on the overall results, but random checks in urban areas of Malawi have found that 10–25% of patients recorded as smear positive in the laboratory register were not entered in the Ministry of Health register (A. Harries, personal communication, 1996) (*24*). It is important that TB control officers appreci-

ate the need to evaluate outcome on all TB patients, and that the incentives to provide "good" outcome statistics do not override the need for accuracy. Methods should be found to collate diagnostic "cough" or laboratory registers with treatment registers in order to identify missing patients. Diagnosed, rather than treated, patients should be the denominator for official statistics. The striking influence of diagnostic certainty group on outcome also makes it difficult to compare results in different places and at different times unless rigorous criteria are used.

In Karonga District, 23% of HIV-positive certain and probable smear-positive patients who received short-course therapy died during treatment. Similarly high risks have been found elsewhere (*14–16*). With case fatality rates of this magnitude and increasing proportions of HIV-positive subjects among TB patients (currently >50% in Karonga District) it will be impossible for control programmes to achieve cure rates of 85%. The increased post-treatment mortality of HIV-infected patients in more recent years demonstrates the changing epidemiology of HIV as the epidemic unfolds and the need for continued monitoring of its effects.

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Résumé

Mesure et déterminants de l'issue de la tuberculose dans le district de Karonga, Malawi

L'évaluation de l'issue des infections tuberculeuses est la pierre angulaire de toute évaluation des programmes de lutte contre la tuberculose, car les résultats peuvent en être faussés si des malades dont la tuberculose n'est pas avérée sont inclus dans les statistiques officielles ou si ceux qui décèdent ou qui sont rapidement perdus de vue sont exclus. Le présent article examine, dans une région rurale du nord du Malawi, les facteurs qui influencent la mesure de l'issue, les taux de survie pendant et après le traitement, les taux de négativation des frottis et les taux de rechute.

Les données concernant 1655 malades chez qui la tuberculose a été diagnostiquée dans le district de Karonga, Malawi, entre 1986 et mi-1994, y compris 682 cas à frottis positif, ont pu être analysées. Un sous-groupe de patients a été activement suivi après la fin du traitement. Une analyse des courbes de survie a été faite pour étudier les facteurs qui influencent les diverses issues de la maladie.

Les malades dont le diagnostic de tuberculose était douteux avaient une plus forte probabilité de décéder que ceux dont la tuberculose était confirmée, et cet effet était observé aussi bien chez les patients positifs pour le virus de l'immunodéficience humaine (VIH) que chez les patients VIH-négatifs. Parmi les malades à frottis positif, ceux qui avaient en outre un prélèvement positif après culture avaient une mortalité moitié moindre que les autres. Chez les malades non enregistrés par le Ministère de la Santé (8% du total) les taux de mortalité et d'abandon étaient beaucoup plus élevés que chez les malades enregistrés: parmi les malades à frottis positif, 23% des décès sont survenus chez ceux qui n'étaient pas enregistrés. Chez les malades à frottis positifs dont le diagnostic était "certain" ou "probable" et qui ont commencé un traitement de courte durée, le facteur ayant le plus d'influence sur la mortalité pendant et après le traitement était le statut sérologique vis-à-vis du VIH (rapports de risque bruts et intervalles de confiance à 95%: 5,6 (3,0–10) et 7,7 (3,4–17) respectivement), mais ce facteur n'avait pas d'influence sur les taux de négativation des frottis. Pour ces derniers, le facteur principal était le degré de positivité des frottis au moment du diagnostic, mais ce facteur était sans influence sur la mortalité. Aucun facteur prédictif significatif n'a été trouvé pour les taux de rechute.

Si l'on ne veille pas de façon très attentive au recensement de tous les malades atteints de tuberculose et à l'exclusion des malades non tuberculeux, les statistiques sur l'issue de la tuberculose sont difficiles à interpréter et peuvent induire en erreur. Dans les populations où le taux d'infection par le VIH est élevé, des taux de guérison cibles de 85% sont irréalistes. Lors de l'évaluation de nouvelles interventions il n'est pas possible de supposer que les facteurs qui

influencent les taux de négativation des frottis influenceront également les taux de mortalité.

References

1. **Kochi A.** The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle*, 1991, **72**: 1–6.
2. **Harries AD et al.** Tuberculosis programme changes and treatment outcomes in patients with smear-positive pulmonary tuberculosis in Blantyre, Malawi. *Lancet*, 1996, **347**: 807–809.
3. **China Tuberculosis Control Collaboration.** Results of directly observed short-course chemotherapy in 112842 Chinese patients with smear-positive tuberculosis. *Lancet*, 1996, **347**: 358–362.
4. **Enarson DA et al.** *Tuberculosis guide for low income countries*, 3rd edit. Paris, International Union against Tuberculosis and Lung Disease, 1994.
5. **Murray CJL et al.** Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet*, 1991, **338**: 1305–1308.
6. **Pönnighaus JM et al.** The Lepra Evaluation Project (LEP) an epidemiological study of leprosy in northern Malawi. I: methods. *Leprosy review*, 1987, **58**: 359–375.
7. **Pönnighaus JM et al.** The Karonga Prevention Trial: a leprosy and tuberculosis vaccine trial in northern Malawi — I: methods of the vaccination phase. *Leprosy review*, 1993, **64**: 338–356.
8. **Sterne JAC et al.** Testing for antibody to human immunodeficiency virus type 1 in a population in which mycobacterial diseases are endemic. *Journal of infectious diseases*, 1995, **172**: 543–546.
9. **Glynn JR et al.** Patterns of initial and acquired antituberculosis drug resistance in Karonga District, Malawi. *Lancet*, 1995, **345**: 907–910.
10. **Nyangulu DS.** The point of view of a high prevalence country: Malawi. *Bulletin of the International Union against Tuberculosis and Lung Disease,* 1991, **66**: 173–174.
11. **Fine PEM et al.** The distribution and implications of BCG scars in northern Malawi. *Bulletin of the World Health Organization*, 1989, **67**: 35–42.
12. **East African/British Medical Research Council.** Tuberculosis in Kenya: follow-up of the second (1974) national sampling survey and a comparison with the follow-up data from the first (1964) national sampling survey. *Tubercle*, 1979, **60**: 125–149.
13. **East African/British Medical Research Council.** Tuberculosis in Kenya: a follow-up of a national sampling survey of drug resistance and other factors. *Tubercle*, 1970, **51**: 1–23.
14. **Perriens JH et al.** Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with "standard" chemotherapy in Kinshasa, Zaire. *American review of respiratory disease*, 1991, **144**: 750–755.
15. **Nunn P et al.** Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya: analysis of early (6-month) mortality. *American review of respiratory disease*, 1992, **146**: 849–854.
16. **Elliott AM et al.** The impact of human immunodeficiency virus on mortality of patients treated for tuberculosis in a cohort study in Zambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1995, **89**: 78–92.
17. **Ackah AN et al.** Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Côte d'Ivoire. *Lancet*, 1995, **345**: 607–609.
18. **Pönnighaus JM et al.** Efficacy of BCG vaccine against leprosy and tuberculosis in northern Malawi. *Lancet*, 1992, **339**: 636–639.
19. **Karonga Prevention Trial Group.** Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet*, 1996, **348**: 17–24.
20. **Colebunders RL et al.** HIV infection in patients with tuberculosis in Kinshasa, Zaire. *American review of respiratory disease*, 1989, **139**: 1082–1085.
21. **Rieder HL.** Sputum smear conversion during directly observed treatment for tuberculosis. *Tubercle and lung disease*, 1996, **77**: 124–129.
22. **Hawken M et al.** Increased recurrence of tuberculosis in HIV-1 infected patients in Kenya. *Lancet*, 1993, **342**: 332–337.
23. **Elliott AM et al.** The impact of human immunodeficiency virus on response to treatment and recurrence rate in patients treated for tuberculosis: two-year follow-up of a cohort in Lusaka, Zambia. *Journal of tropical medicine and hygiene*, 1995, **98**: 9–21.
24. **Ringdal T, Veen J.** *Report on a visit to Malawi. Progress Report No. 23.* Paris International Union against Tuberculosis and Lung Disease, 1995 (unpublished document).