Antituberculosis drug resistance in Karonga District: pattern and trend, 1986-2001

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ABSTRACT

Multi-drug resistant tuberculosis (MDR-TB) is difficult to cure, treatment is expensive and will put further strain on already overburdened TB control programmes. We have studied patterns and trends of drug resistance in Karonga District from 1986-2001. Initial drug sensitivity results were available on isolates from 1610 culture-positive patients. Initial resistance to at least one drug was found in 139 cases (8.6%): 67 were resistant to isoniazid alone and 9 cases (0.6%) were resistant to at least isoniazid and rifampicin (i.e. MDR-TB). There was no association between initial resistance and age or sex, nor was there association between drug resistance and HIV status. There was no evidence of an increase in initial drug resistance over the study period. Among those with drug resistance, cure rate was low (38.9%), and death rate (25.5%) and failure rate (11%) high compared with those with fully sensitive strains. The proportion of acquired resistance was low. There are grounds for optimism that in Karonga District, initial drug resistance is not increasing and the proportion of both acquired resistance and MDR-TB has remained very low.

Introduction

Resistance of *Mycobacterium tuberculosis* has been encountered against all antituberculosis drugs. It usually arises from selection of naturally occurring mutant strains in situations in which there are inadequate concentrations of drugs at the site of action. This may be due to inappropriate prescriptions, drug shortage, poor compliance, substandard drug quality e.g. due to use of expired drugs, inadequate TB programme support and supervision, or malabsorption. Drug resistant tuberculosis poses a serious challenge to TB control programmes and is a global problem.[9] Information of susceptibility patterns of *M. tuberculosis* isolates against antituberculosis drugs is an important aspect of tuberculosis control and surveillance. Analysis of rates of resistance is helpful in the detection of MDR strains and provides an indicator of the quality of TB control in the country. In the early 1990s the WHO, jointly with the International Union Against Tuberculosis and Lung Disease (IUATLD) launched a global project on antituberculosis drug resistance surveillance to know the extent and severity of the problem in a standardised manner at country level world wide.[3] However, most TB control programmes in sub-Saharan Africa including Malawi, where the highest TB rates are, lack resources to carry out routine culture and sensitivity on sputa.

Information about drug resistance in Malawi itself is limited. Recent data from WHO indicated that MDR-TB is lowest in sub-Saharan Africa and very high in India and South-East Asia.[3] Some studies have shown an association between MDR-TB and HIV10,11 while others have not.[1,2] However, despite lack of this association, HIV may fuel the spread of resistant TB by increasing susceptibility to infection and accelerating the progression from infection to disease.[8] Therefore in sub-Saharan Africa which is already burdened by increasing rates of HIV associated TB[12] and limited access to second line drugs against TB, the emergence of MDR-TB will further threaten efforts at TB control.

As part of the epidemiological study of mycobacteria and HIV in Karonga, we have been collecting data on drug resistance since 1986. Presented here is the overall trend of resistance from 1986 to 2001, focusing on recent data from 1997 to 2001.

Methods

The Karonga Prevention Study developed from the Lepra Evaluation Project and the Karonga Prevention Trial. It was set up in Karonga District, Malawi in 1978 as a large epidemiological study of leprosy. Two total population surveys were carried out in 1980-1984 and 1986-1989. The current population is about 200,000 and a third total population survey is currently underway. During the second survey, the population was screened for leprosy by physical examination and for TB by asking for a history of chronic cough and examining for cervical lymphadenopathy. Since 1989, the project has placed paramedical staff at peripheral clinics and at the hospital to screen patients with chronic cough , and patients may self report at these clinics at anytime.

Treatment

Patients diagnosed with tuberculosis start treatment in hospital following Malawi National TB Programme guidelines. From 1986 to 2000, smear positive patients received the daily short course regimen consisting of streptomycin, isoniazid, rifampicin, and pyrazinamide. At two months they were changed to isoniazid and ethambutol (fatol). Patients with smear negative and extra pulmonary TB received the daily standard regimen consisting of one month of treatment in hospital with streptomycin and fatol and were then discharged to continuation phase on fatol for eleven months. From 2001, all patients have been receiving the 'decentralised' regimen without streptomycin. In this regimen, the smear positives receive daily isoniazid, rifampicin, ethambutol and pyrazinamide for two weeks while in hospital, followed by intermittent supply (three times a week) of the same drugs while at home for six weeks and then discharged to continuation phase on fatol for six months. The smear negatives and extra-pulmonary TB cases receive daily isoniazid, rifampicin and pyrazinamide for two weeks while in hospital, followed by intermittent supply of the same drugs for six weeks while at home and then discharged to continuation phase on fatol for six months.

The project Medical Officer(s) and paramedical staff contribute to inpatient care. Since 1988 patients have been counselled for HIV testing and tested if consent is given. For the period of this study, project staff were also responsible for outpatient care. Patients were followed up monthly, either at agreed meeting places or in patients' homes. Tablets were counted to check for compliance and patients were asked about any drug reactions, and then they were given the next month's supply of drugs. Follow-up sputum specimens were collected if appropriate. In cases where patients were identified with drug resistant tuberculosis, they were usually put on re-treatment schedule consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. Second line drugs were not routinely available.

Specimens

All suspect and five or eight month sputum specimens were examined in the project's laboratory by microscopy *and* culture. Cultures were set up on acidified Lowenstein - Jensen media with pyruvate (and until November 1996 in duplicate with glycerol). Cultures resembling *Mycobacterium tuberculosis* were sent to the Public Health Laboratory Service Mycobacterium Reference Laboratories in the United Kingdom (Cardiff until 1996, Dulwich from 1996 to date) for species identification and drug sensitivity testing. Specimens were initially tested for resistance to streptomycin, isoniazid, rifampicin, and ethambutol, and since 1999 to isoniazid and rifampicin only. Tests for other first line, and second line drugs were only done if any resistance was found. Thus since 1999, monoresistance to ethambutol or streptomycin will not have been identified.

Definitions

The following standard definitions were used[13,17]

i. Initial resistance - drug resistant isolates from patients with no previous history of TB treatment.

ii. Acquired resistance - drug resistant isolates in a patient with previous antituberculosis treatment, (or previous fully sensitive strains but developing resistance in the course of the illness).

iii. Any resistance - resistance to any of the primary TB drugs

iv. Multi Drug resistance (MDR-TB) - isolates resistant to at least isoniazid and rifampicin.

v. Cured - negative smears or cultures at completion of treatment or negative smears or cultures at or after two months with completion of treatment.

vi. Died - death occurring at any time during the course of treatment.

vii. Failure - Smear and/or culture positive at five months or at end of treatment

viii. Transferred out - transferred out to another centre outside Karonga.

ix. Defaulter - unknown outcome but lost before end of treatment

Results

Overall (1986-2001)

From the 15 years of follow-up (1986-2001), initial drug sensitivity results were available on 1610 patients (Table 1). Total patient numbers have fluctuated over the period and data is only available for the first half of 2001. Initial resistance to at least one of the major drugs tested was found in 139/1610 cases (8.6%) with 67/1610 (4.2%) having resistance to isoniazid alone. Initial resistance to at least isoniazid and rifampicin (MDR) was seen in 9 patients (0.6%) (Figure and Table 1). No initial resistance to ethambutol was found. The overall proportion of resistant strains showed no consistent trends over time and the proportion of MDR has remained below 2%.

Figure: Resistance patterns to antibiotics among 139 patients with initial drug resistance in Karonga District, 1986-2001

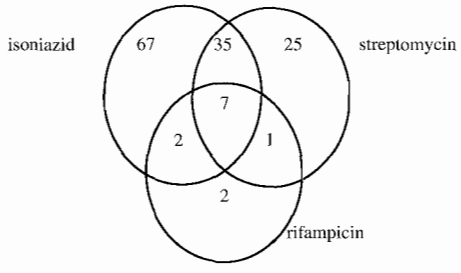

Table 1: Initial drug sensitivity patterns in Karonga District, Malawi, 1986 - 2001

Year	Total (n)	Any resistance (%)	INH resistance((%)	INH + RMP resistance((%)
(%)				
1986	28	(7.1)	(7.0)	(0.0)
1987	33	(12.1)	(12.1)	(3.0)
1988	54	(16.7)	(11.1)	(0.0)
1989	72	(16.7)	(11.1)	(0.0)
1990	126	(11.9)	(7.1)	(0.0)
1991	100	(9.0)	(4.0)	(0.0)
1992	103	(6.8)	(6.8)	(0.0)
1993	77	(10.4)	(6.5)	(1.3)
1994	95	(8.4)	(6.3)	(1.1)
1995	91	(8.8)	(7.7)	(0.0)
1996	75	(2.7)	(1.3)	(0.0)
1997	185	(9.7)	(9.2)	(1.6)
1998	177	(7.3)	(6.2)	(1.1)
1999	149	(4.0)	(4.7)	(0.0)
2000	156	(6.4)	(6.4)	(0.0)
2001	89	(7.9)	(7.9)	(1.1)
Total	**1610**	**(8.6)**	**(6.9)**	**(0.6)**

INH = Isoniazid, RMP = Rifampicin; (assuming those with missing results were fully sensitive

1997-2001

Between 1997 and 2001, initial drug sensitivity results were available on 54 patients (Table 1). Of these 29 (53.7%) were females and 25 (46.3%) were males. The age distribution of those with initial drug resistance was similar to those with fully sensitive isolates. There were few cases among children with culture results available: the youngest patient with drug resistance was aged 7 months and had TB adenitis. HIV results were available on 36/54 (67%) people with initial drug resistance. Of these 23/36 (64%) were HIV positive, a similar proportion to that for TB patients overall (69%). Of 4 people with MDR-TB who had HIV results available, only one was HIV positive.

Table 2 shows outcomes of the 54 patients with initial drug resistance. Only 21 (38.9%) patients achieved cure, 14 (25.9%) died and 6 (11.1%) were treatment failures. This compares to

Table 2: Outcome ofpatients with initial & acquired drug resistances, Karonga District, 1997-2001

Outcome	Initial resistance (%)	Acquired resistance(%)
Cure	21 (38.9)	2 (28.6)
Died	14.(25.9)	2 (28.6)
Failure	6 (11.1)	-
Defaulter	1 (1.9)	2.(28.6)
Transfer out	7 (13)	-
Still on treatment	5 (9.3)	1 9(14.2)
TOTAL	54 (100)	7 (100)

data from 1999-2000 when cure rate in all smear positive TB patients in Karonga District (including those with fully sensitive isolates) was 70% and death rate 21%. Six of the 7 transferred out were Tanzanians who had travelled to Karonga for diagnosis and inpatient care. During this study period, there were 7 cases with acquired drug resistance. Six had acquired drug resistance to isoniazid and two had acquired resistance to streptomycin. There was no acquired rifampicin monoresistance. Of the 4 with HIV results available, only 1 was HIV positive. The outcomes are in table 2.

Table 3 shows the pattern of resistance of those who started with initial resistance and subsequently relapsed or failed treatment, and their outcome at the end of re-treatment phase. From 1997-2001, there were 5 people that relapsed, 4 of whom relapsed with same resistance pattern. Four out of five (80%) achieved cure during re-treatment and only one died. All five cases were females. In addition, there were 6 cases of treatment failure among patients with initial drug resistance. Four of them failed with the same drug resistance pattern. In one patient, the strain converted from isoniazid resistance alone to MDR-TB.

Table 3: Initial and subsequent drug resistance patterns in Karonga District, 1997-2001

Initial pattern	Outcome 1 Sex	Subsequent pattern HIV status	OutcomE 2	Age		
RRR	Failurexz	RRR	49	M	N	Died
RRR	Failure	RRR	55	M	N	Died
RRS*	Relapse	?RS**	24	F	P	Cure
RRS	Relapse	RRS	43	F	N	Cure
RSS	Relapse	RSS	36	F	N	Cure
SRS	Relapse	SRS	65	F	N	Cure
SRS	Relapse	SRS	41	F	N	Died
SRS	Failure	SRS	24	F	P	Died
SRS	Failure	SRR	22	F	U	Died
SRS	Failure	SRS	23	F	P	Died
SRS	Failure	RRS	35	M	U	Died

*Note: all specimens were sputum smear positive except those marked * & ***
Outcome 1 = outcome after treating the first episode
Outcome 2 = outcome after re-treatment
F=female, M=male, P=positive, N=negative, U=Unknown.
* = First episode was culture positive on sputa
** = Second episode was culture positive on pleural effusion

Table 4: Pattern and outcome of patients with initial MDR-TB, 1997-2001

Year	Smear/Culture	Pattern	Age	Sex	HIV	Outcome
1997	Smear(-)/Culture (+)	RRR	40	F	N	Cure
1997	Smear(-)/Culture (+)	RRR	20	F	P	Died
1997	Smear (+)/Culture (+)	RRR	55	M	N	Failure
1998	Smear (+)/Culture (+)	RRR	49	M	N	Failure
1998	Smear (+)/Culture (+)	SRR	29	M	U	Transfer out
2001	Smear (+)/Culture (+)	RRR	36	M	U	Still on treatment

Pattern (in order streptomycin, isoniazid, rifampicin)
F=female, M=male, N=negative, P=positive, U=unknown

Amongst the patients with initial drug resistance, there were 6 people that had MDR strains of tuberculosis. Four were sputum smear positive and two sputum smear negative/culture positive. Only one achieved cure, two failed treatment, one died, one was transferred out and one is still on treatment (Table 4). Both cases of failures died later in 1999 and 2000 respectively. One died while on re-treatment phase and the other died while on daily isoniazid and ethambutol for life. HIV results were known on four and of these only one was HIV positive. Five of the 6 cases occurred during 1997/98.

Discussion

Drug resistant tuberculosis is a serious threat to tuberculosis control. Poor or sub-optimal tuberculosis control programmes can lead to rapid emergence of drug resistance in both industrialised and developing countries. An increase in drug resistant tuberculosis is of considerable concern, especially in sub-Saharan Africa, because of the difficulties and cost of treating patients with drug resistance and because of the implications of the effectiveness of tuberculosis control programmes

The levels of initial resistance found in this study are similar to those found elsewhere in Africa. A recent drug resistance survey organised by WHO/IUATLD found primary resistance to at least one drug in about 10% of the strains in the 35 countries included (range 2% - 40%). In the African countries included, proportions ranged from 3%-9%.[9] Initial resistance to at least one drug was found in 5% of adults in Cape Town in 1990-91,14 10% of patients in Tanzania in 1978-805 and 9% of patients in Kenya in 1984.[15]

The proportions of patients with drug resistant isolates to at least one drug in Karonga have not increased over the period of this study. Between 1986-1991, initial resistance to at least one drug was seen in 57/413 (13.8%) patients and resistance to isoniazid alone was seen in 33/413 (8%). From 1992-1996, initial resistance to at least one drug was seen in 33/441 (7.5%) and resistance to isoniazid alone was found in 26/441 (5.9%). In 756 patients seen between 1997-2001, initial resistance to at least one drug was 7.1% and to isoniazid alone was 6.7% (Table 1). The trend is not increasing as a proportion, but the absolute numbers of cases of drug resistance are increasing as the numbers of TB patients increase. The proportions resistant to at least isoniazid and rifampicin (MDR) have remained below 1.6% with only 1 year reaching 3% and no increase over time (Table 1). The absence of increase over time and the low levels of initial rifampicin resistance are encouraging results for the TB control programme, particularly in the wake of an increase in numbers of TB patients due to HIV/AIDS epidemic.

There was no association between initial resistance and age or sex. The youngest individual with initial resistance strains was seven months old. Surprisingly, there was no history of TB in either parent or in any other household member. This may represent nosocomial transmission as the child was born in hospital. There were no associations between drug resistance and HIV status. This lack of association is in line with other findings from other African countries[16] but in contrast to some studies in the United States.[11]

As expected, among those with drug resistant strains, the cure rate was low (38.9%) and death rate high (25.5%) compared with those with fully sensitive strains. Of considerable concern were the transferred out, seven in total, six of whom were from neighbouring Tanzania and returned home shortly after completion of intensive phase of chemotherapy before the sensitivity results could be communicated to them.

We further examined patterns of resistance in cases of treatment failure. There were six cases of treatment failure among those with initial drug resistance, and all of them died during re-treatment. Four of those with treatment failure maintained the same drug resistance pattern while one moved from only isoniazid resistance to MDR-TB. There were also five patients who relapsed after successfully achieving cure in their initial episode. Four of them relapsed with exactly the same pattern (on one streptomycin was not tested). It was particularly interesting and very encouraging to see that four out five (80%) of those that relapsed achieved cure again and only one died.

All these patients were treated with the usual re-treatment regimen as per Malawi NTP guidelines. This means that despite the strains being resistant to antituberculosis drugs *in vitro*, there is still a certain concentration of the drugs that is still active. However, there appears to be little hope for the patients with initial drug resistance who fail to achieve cure at 5 months. With limited resources this could be a group selected to benefit from second line drugs.

Further studies underway at KPS involve fingerprinting of TB isolates that will allow tracking of these resistant strains through the community. There are grounds for optimism that in Karonga District, initial drug resistance is not increasing and the proportion of both acquired drug resistance and multi drug resistance has remained very low. It is not clear whether the findings are generalisable to other districts of Malawi, as in Karonga patients undergo closer monitoring both as inpatients and during continuation phase which may improve compliance, and therefore reduce the potential for developing resistance or transmitting resistant strains.

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MEETING ON GENDER AND EQUITY IN HEALTH IN MALAWI

LILONGWE, 7th- 8th FEBRUARY 2002

The TB Equity Project is the Tuberculosis (TB) Equity Study is a collaboration between the National TB Control Programme of Malawi (NTP), the Department of Sociology, University of malawi and the Liverpool School of Tropical Medicine (UK). The aim is to promote equity in the delivery of TB care.

Through multi-disciplinary research over the past two years , TB Equity Study has identified gender and poverty-related barriers to access to TB care. The findings of this study are not only relevant to access to care for TB but also for other health problems. Similarly, researchers, health professionals and policy makers across the health sector in Malawi have also conducted studies on poverty or gender related barriers to access to health care. It is important to share information and experiences so that wider lessons can be learned to promote equity in health.

The National TB Programme, in collaboration with it's partners and the Malawi Health Equity Network propose to hold a meeting on gender and equity in health in Malawi. The aim of the meeting will be to share information on gender and equity across the health sector and draw together lessons for health policy and practice.

Date: Thursday 7th and 8th February, 2002
Venue: Malawi Institute of Management (MIM), Lilongwe
Participants: Policy makers from Ministry of Health and Population and donor organisations; researchers; health professionals and representatives from NGOs and civil society organisations working in health in Malawi.

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