

# Smear-negative pulmonary tuberculosis: defining better approaches to case finding and care in Malawi

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## Abstract

This is a report of a meeting that took place on 6th December 2000, arranged by the National Tuberculosis Control Programme (NTP) in Lilongwe to i) review research carried out in Malawi during the last few years on smear-negative pulmonary tuberculosis (PTB) and ii) to define better approaches to case finding and care of patients with smear-negative PTB. The meeting was attended by participants from the NTP, College of Medicine, Medecins sans Frontieres-Luxembourg, local health staff and the private sector. The following report is a summary of the presentations, discussions and resulting recommendations.

## 1. CASE FINDING AND DIAGNOSIS

The following persons made formal presentations based on operational research carried out in Malawi: Dr FML Salaniponi; Mr JH Kwanjana; Mr RG Madiwati; Dr NJ Hargreaves; Professor AD Harries; Mr HT Banda; Mr GS Kachisi and Dr JR Kemp. The main points arising from the presentations will be summarised here.

### 1.1 Rising smear-negative case-load and link with HIV infection

The number of patients registered nationally with smear-negative PTB has risen in the last 10 years, and in 1999 there were 10,013 registered cases. In various studies, between 80 - 90% of patients registered with smear-negative PTB are HIV-seropositive.

### 1.2 Current diagnostic guidelines

The NTP currently recommends that the diagnosis of smear-negative PTB should be based on 4 criteria of (i) cough for more than 3 weeks, (ii) 3 sputum smears negative for acid-fast bacilli (AFB), (iii) no response to an antibiotic, and (iv) a chest x-ray compatible with PTB.

### 1.3 Some patients with smear-negative PTB do not get diagnosed in time to start anti-TB treatment

Qualitative research in Ntcheu and Lilongwe suggests that significant numbers of PTB suspects on receiving negative sputum smear results are told "there is nothing wrong" and further investigations such as chest radiography are not carried out. Some respondents also report having repeated sputum examinations, without being referred for other investigations. In suspects submitting sputum at health centres in Zomba, only 11% underwent a chest x-ray. Whether more patients were referred but did not have a chest x-ray because of difficulties travelling to the hospital or because of x-ray machine malfunction is not known. These findings suggest that there may be a large number of smear-negative PTB patients in the community who are never given the opportunity to access full

investigation and treatment, and research is required to investigate the reasons for this.

### 1.4 Adherence to recommended diagnostic guidelines

For patients who are eventually registered for smear-negative PTB, over 90% are given a diagnosis based on one or more of the recommended criteria, but in only 60% of cases is the diagnosis based on all 4 criteria. Health care staff are not rigorously adhering to guidelines, especially regarding the required x-ray criteria. Operational research suggests that in-service clinical training must be carried out to improve diagnostic practices. However better clinical performance will not provide all the answers because TB control in Malawi also relies on the district health system to provide functioning x-ray services and essential drugs such as antibiotics. Of patients who submit sputum specimens, many are registered within 3 weeks of submitting sputum, but there are some delays with 15% being registered after a 3-week interval and 6% after a 6-week interval. Such delays may contribute to the poor outcome in smear-negative PTB patients as described below. The reasons for delay are not yet known, but the number of times a patient is required to visit a health facility during the investigation of smear-negative PTB may be a contributing factor. Wherever possible health care staff should seek to minimise the demands placed on patients during the diagnostic process, such as ensuring that sputum results are available in timely fashion, and that chest x-rays can be interpreted on the same day that they are taken.

### 1.5 How many smear-negative PTB patients really have TB?

In Malawi the diagnosis of smear-negative PTB is not usually confirmed microbiologically, and therefore there is concern that many patients being treated for smear-negative PTB may not have TB at all. A detailed bronchoscopy study in Lilongwe of patients with smear-negative PTB who were about to be registered for TB treatment found that 40% had microbiologically confirmed TB, about 20% had another diagnosis such as *Pneumocystis carinii* pneumonia (PCP, confirmed in 5% of the total study cohort, but 9% of those patients being investigated by bronchoscopy) or pulmonary Kaposi's sarcoma. In the remainder no aetiological agent could be found. There was considerable overlap in clinical features between the different groups making it difficult to confidently diagnose conditions such as TB and PCP in routine clinical practice. This overlap may be partly explained by concurrent HIV infection which can mask some of the classical features of PTB. For example, although a history of exertional dyspnoea was invariable in PCP patients it was also very common (74%) in patients with confirmed TB, so that the predictive value of this symptom was reduced, and not of practical use. Participants agreed that there is an urgent need for new, cheap diagnostic agents with a good sensitivity and specificity for HIV-associated PTB. Ideally such tests should be simple enough to be performed in peripheral health centres and remove the requirement for patients to have a chest x-ray.

### 1.6 Problems interpreting the chest x-rays of smear-negative PTB suspects

About 25% of patients in Malawi with typical clinical features of PTB and negative sputum smears will have a normal chest x-ray, and about 20% of these patients are culture positive for *M.tuberculosis*. This is a consequence of weak immune responses to TB infection in advanced HIV disease.

In routine circumstances, these *M.TB* culture-positive patients with a normal chest x-ray are denied anti-TB treatment as mycobacterial cultures are not part of the diagnostic work-up. Identifying these patients as having TB is difficult. If they are followed up for up to 3 months, less than 5% develop positive sputum smears and less than 50% develop an abnormal chest x-ray; i.e. many patients remain smear-negative and continue to have a normal chest x-ray. Almost all these patients are HIV-seropositive. They may forever be denied anti-TB treatment, or TB treatment may be delayed resulting in a poor treatment outcome.

### **1.7 Recommendations for improving case-finding and diagnosis**

The NTP recommends that the 4 criteria should continue to form the basis of the diagnosis of smear-negative PTB, and that all health facilities in Malawi should be regularly audited to determine whether these guidelines are adhered to. However some modifications to the guidelines were suggested, as listed below.

#### **1. Need for clear messages to be given to smear-negative PTB suspects**

Clinicians should be clear in the messages that they give to patients when explaining the results of negative sputum examinations, in particular the message "there is nothing wrong" should be avoided. This is likely to lead to delays, confusion and loss of patient confidence in the clinician. It may also cause symptomatic patients to begin the diagnostic process all over again with other health care providers, including traditional healers.

#### **2. Recommendations regarding recurrent cough after antibiotics**

Some patients with PTB may also have a secondary bacterial infection and their symptoms may therefore initially improve after treatment with standard antibiotics (40% of patients in the Lilongwe study). This may confuse both the patient and clinician, but if TB is present the cough usually returns within a short time of completing the antibiotics. Patients should be advised to return if their cough recurs, as they may have PTB and must be investigated further. Consistent use of the new Malawi 'Health Passport' for recording each clinical interaction would help identify patients with presenting with recurrent cough that require further investigation.

#### **3. Recommendations for smear-negative PTB suspects with normal chest x-rays**

The participants at the meeting discussed possible recommendations about the management of smear-negative PTB suspects with normal chest x-rays, in view of the concern that a considerable number of true smear-negative PTB cases might never receive TB treatment using the current guidelines. However, the NTP advised that current guidelines should not be changed without further research as this may lead to many patients with chronic cough not caused by TB being incorrectly commenced on TB treatment. This contentious issue requires further operational research.

## **2. TREATMENT OUTCOME**

The following persons made formal presentations based on operational research carried out in Malawi: Professor AD Harries, Mr. C Kang'ombe, Mr HT Banda, Dr NJ Hargreaves,

Mrs O Kadzakumanja, Mr. F Gausi, and Dr. R Zachariah. The main points arising from the presentations were as follows:-

### **2.1 Smear-negative PTB outcomes and high mortality rates**

Before the HIV epidemic the majority of smear-negative PTB patients had a good outcome, and one third would even recover without TB treatment. In the past the NTP did not even monitor smear-negative outcomes as they were not thought to be important. Recent country-wide operational research in Malawi has shown that patients with smear-negative PTB now have worse end of treatment outcomes compared with smear-positive PTB patients. Reported case fatality in smear-negative PTB patients nationally is about 25%, which is the same as for smear-positive PTB patients. However, the treatment outcome is unknown in about 20 - 30% of smear-negative PTB patients (i.e. treatment cards are lost and there is no information in the TB register) and this may mask a large number of excess deaths. This research has led the NTP to now routinely follow up and report on treatment outcome in smear-negative PTB patients.

Research carried out in Lilongwe, Blantyre and Zomba where treatment outcomes were rigorously sought by visiting patients' homes and villages have shown that the true end-of-treatment case fatality rates are between 30 - 45%, confirming the impression that unknown outcomes mask a large number of deaths. These high death rates are strongly linked to HIV-infection, and to markers of AIDS such as oral candida or Kaposi's sarcoma. The Lilongwe study looked at whether the poor outcomes of smear-negative PTB patients are due to the fact that many of them actually have diagnoses other than TB.

This study was able to compare the mortality rate of confirmed smear-negative PTB patients with that of patients who had been incorrectly diagnosed with TB and who had other non-TB diagnoses. These 8-month mortality rates were 31% and 57% respectively (RR 1.90; 95%CI: 1.38-2.62), showing that incorrect diagnosis contributes to the high mortality of smear-negative PTB cohorts, but that mortality is still high in those patients with confirmed TB.

Duration of symptoms for greater than 7 weeks also predicted a poor outcome. In addition it is apparent from these studies and from recent country-wide research that up to 40% of all the deaths in smear-negative PTB occur in the first month of treatment. This could be due to disseminated TB disease, delayed diagnosis, or to the advanced stage of HIV-related immunosuppression in many of these patients.

A different approach may be needed to reduce these early deaths compared with approaches needed to reduce death rates during the whole duration of anti-TB treatment

### **2.2 Could cotrimoxazole preventive therapy help to reduce deaths?**

A placebo-controlled study of the use of cotrimoxazole preventive therapy in HIV-positive smear-positive TB patients in Cote d'Ivoire showed a 40% reduction in mortality in patients treated with cotrimoxazole in addition to TB treatment. Due to the strong link with HIV infection smear-negative PTB patients could also be assumed to benefit from cotrimoxazole. However, the NTP decided that local operational research was required before this intervention is implemented routinely in Malawi, because the spectrum of opportunistic infections may be different from West Africa, and because cotrimoxazole resistance in commonly occurring pathogens is much higher in Malawi compared with Cote d'Ivoire.

Preliminary results of operational research in Thyolo on use of cotrimoxazole to reduce death rates in HIV-positive patients with all types of TB is encouraging, but does not show the dramatic effect seen in Cote d'Ivoire. Compared with historical controls, death rates in the cohorts of Thyolo patients offered cotrimoxazole were less than those not offered cotrimoxazole. The completed results of the study are awaited with interest.

### 2.3 Recommendations

1. Monitor smear-negative PTB outcomes: The NTP must continue to monitor and report on treatment outcomes in those patients with smear-negative PTB. It is important that the NTP reduce the 'unknown' treatment outcomes in these patients in order to obtain regular and accurate information about treatment completion and death. Operational research studies are planned for 2001 to address this issue.

2. Research focused on improving treatment outcomes: Ways of reducing case fatality apply to patients with all types of TB, and should focus on the common underlying problem of HIV infection. Clinical research needs to focus on the adequacy of anti-TB drug absorption, adjunctive treatments with cotrimoxazole, other antibiotics, corticosteroids, and even anti-retroviral drugs. Further research will help to determine further whether diagnostic delays are related to poor outcomes. Interventions to reduce delays in TB suspects' presentation to health facilities (for example due to fear of stigma) and diagnosis are likely to benefit patients. The main causes of death in the first month of treatment need to be elucidated and interventions to reduce these early deaths must be assessed.

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### Conclusion

The meeting was useful in reviewing what is known about smear-negative PTB in Malawi and in trying to reach a consensus about the ways forward. However, many of the problems will still remain and will not be solved until i) better diagnostic tests are found, and ii) effective ways of tackling the ravages of HIV-infection find their way into routine use in resource-poor countries like Malawi. Readers interested in reading more about the research summarised here are welcome to contact NTP staff at the Community Health Science Unit, Lilongwe for more details.

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*The organisers thank all those who attended and actively participated at this meeting, especially those who travelled from outside Lilongwe.*

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