Operational research on tuberculosis control in Malawi

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1. INTRODUCTION

1.1.1. Extent of the TB/HIV problem

A third of the world population has been estimated to be infected with *Mycobacterium tuberculosis* (*M. tuberculosis*). There were an estimated eight million new tuberculosis (TB) cases with 8% of the new cases co-infected with human immunodeficiency virus (HIV) and 1.87 million TB deaths in 1997 [1]. Of the global total of 42 million people estimated to be living with HIV/AIDS (PLWH) at the end of 2002, 29.4 million (70%) are in sub-Saharan Africa [2]. In eight countries, all in Southern Africa, the adult HIV seroprevalence rate is above 15% [3]. Of the 36.1 million PLWH worldwide at the end of 2000 about a third were co-infected with *M. tuberculosis* with 68% of those co-infected living in sub-Saharan Africa. Escalating tuberculosis case rates over the past decade in many countries in sub-Saharan Africa are largely attributable to the HIV epidemic [4-14]. Since the mid-1980s, in many African countries, including those with well-organised programmes [15,16], annual tuberculosis case notification rates have risen up to fourfold, reaching peaks of more than 400 cases/100,000 population [17]. More than 70% of patients with sputum smear-positive pulmonary tuberculosis are HIV-positive in some countries in sub-Saharan Africa [8-10,12,16,18-21].

1.1.2. TB control

Tuberculosis is caused by *M. tuberculosis* and is mainly spread through droplet infection. Disease may present as i) smear-positive pulmonary TB (PTB) whereby bacilli are visible on direct microscopy of sputum, as ii) smear-negative PTB whereby no bacilli are detected under sputum microscopy and as iii) Extra Pulmonary TB. Smear-positive patients are the most infectious and can infect 10 - 14 other persons in a year [22-24]. TB control programmes therefore emphasize the detection and cure of smear-positive cases. The overall objectives of TB control are 1) to reduce mortality, morbidity and transmission of TB and 2) to prevent the development of drug resistance.

Case-finding and treatment to ensure cure are the core tuberculosis control activities. The currently recommended approach to case-finding involves detecting cases among people presenting with symptoms (most importantly chronic cough) to general health services [25]. It has been shown that from a TB control point of view poor treatment is worse than no treatment, resulting in more transmission and an increased risk of developing drug resistance [26]. Hence, achieving a high cure rate
is of vital importance. To ensure relapse-free cure while preventing the emergence of drug resistance the strategy is to provide short course chemotherapy under direct supervision at least during the initial phase of treatment to at least all identified smear-positive TB cases. As *M. tuberculosis* is a slow growing aerobic organism which can remain dormant for a prolonged period, prolonged treatment with multiple drugs is required [27-34]. As rifampicin is the major sterilizing drug and the basis for modern short course chemotherapy [35-39], directly observed therapy (DOT) was introduced to prevent the emergence of resistance to rifampicin [37,40]. Intermittent regimens have been shown to be as highly efficacious as daily regimens [41-50] and greatly facilitate direct observation of drug-intake [33] and ambulatory treatment. Ambulatory treatment has been shown to be highly effective without increasing the risk of infection for close family contacts as multiplication of susceptible organisms stops during the first days of effective treatment [35,42,43,51-56].

For the control of TB the World Health Organization (WHO) formulated a policy package called the DOTS (directly observed therapy, short course chemotherapy) strategy based on previous experience in TB control [57,58], and comprising five elements:

1. political commitment to TB control at all levels
2. case detection through case-finding by sputum smear microscopy examination of TB suspects in general health services
3. standardised short-course chemotherapy to at least all smear-positive TB cases under proper case management conditions, i.e. DOT when rifampicin is used [25,59]
4. regular, uninterrupted supply of all essential anti-TB drugs and diagnostic materials
5. a standardised monitoring system for programme supervision and evaluation using treatment outcomes such as cure, death, smear positivity at 5 months indicating the efficacy of the regimen used, default reflecting the organization of services, and transfer outs

The targets set are:

- to detect 70% of estimated new sputum smear-positive TB cases [60]
- to cure 85% of the detected new cases of sputum smear-positive TB resulting in immediate decrease in TB prevalence and rate of transmission, gradual decrease in TB incidence and reduction in acquired resistance [25,61,62]
The DOTS strategy has led to improved TB control in a number of countries [15,44, 48,60,62-75] and has shown to be cost-effective [60,63-89]. Coverage globally was still only 32% in 2001 [90]. To achieve worldwide coverage accelerated expansion is needed and will need to be based on a multi-sectoral approach building on national and global partnerships to maintain commitment and resources [56].

1.2.1. Difficulties in TB control

Case detection

Early case detection is important in order to reduce the transmission of TB. However, early diagnosis is often difficult to achieve due to several months of patient and health services delay. Patients are usually diagnosed as a consequence of the interaction between their active efforts in seeking health and the passive case-finding activities of health care workers in health centres. Several factors cause the delays. First, since people live in a pluralistic medical society they make their own choices on where to seek treatment (traditional versus allopathic), depending in part on their cultural beliefs regarding disease and of being at risk for disease [92]. Some may not be worried about a persisting cough until haemoptysis appears [93-97]. Others may reject treatment based on allopathic medicine completely [98]. Second, as TB is a contagious disease, it is a stigmatising condition that may elicit fear and avoidance rather than sympathy. This results in patient isolation during treatment by the community and sometimes the family in view of the risk of infection [95, 97,99-103] or may lead to self-stigmatisation and self-ostracism by the patient for fear of being blamed for spreading the disease [104]. As a consequence it will prevent them from seeking health care and social services [94,96,97,104-106]. Third, time constraints due to a heavy workload (often higher for women) may delay health seeking till the illness becomes more serious [95,107-110]. Fourth, factors affecting accessibility to public health services may include limited accessibility geographically [111] (and therefore incomplete coverage by the services), inconvenient clinic times and fixed clinic days [112,113]. Access to services may be more difficult for women [114-117]. Fifth, the perception of quality of services provided is important as well. Lack of drugs and diagnostic supplies, poorly trained staff resulting in diagnostic delays [113,118, 119], and frequent referrals to other facilities reduce its credibility [95-97]. Lack of attention and poor communication by staff to the patient [112], whether due to socio-economic, educational, cultural or linguistic differences [120,121], also affects the perceived quality. Sixth, services provided by the private sector are often perceived to be of better quality as patients often have little faith in the drugs provided by the public health services. The private sector is however also often
poorly trained to diagnose and treat TB [95, 104, 112, 122-126] and when the informal unqualified private sector is initially approached, this often causes additional delays [127]. Finally, economic costs involved in seeking health care, whether direct or indirect costs (i.e. transport, lost wages), will play a role in when and where to seek services [128].

Case holding

Prematurely interrupting or stopping treatment is the most serious impediment to the control of TB. Among patients with active disease who do not adhere to treatment sputum conversion to smear-negative will be delayed, relapse rates will be higher and drug resistance may develop [129-133]. Other consequences of non-adherence include the need for additional treatment leading to additional expense and possibly death [134, 135].

Patients have their own ideas about taking medications and evaluate the doctor's recommendations with what they themselves know about disease and medication. As they need to manage their daily existence of which medical regimens are only a part [136] they weigh up the costs, like the stigma of having to take drugs or attending the clinic, and the benefits of taking particular medications, like improvement in symptoms or the promise of relief in the longer term, as they perceive them within the contexts and constraints of their everyday lives and needs [137]. Drugs are taken on trial and patients adhere with medical advice when it makes sense to them and their own lay beliefs [138]. Often a pragmatic decision is taken [139, 140].

Reasons for dropping out are several. First, reasons at a personal level are feeling symptom free (usually after one or two months of effective chemotherapy [141]), loss of faith in the therapy and the unwillingness to accept the unpleasantness of the therapy [142]. Second, there are social reasons such as the stigma attached to being a TB patient or lack of social support [93, 100]. Third, factors relating to public health services as mentioned above remain valid for case holding [142]. Fourth, economic reasons, either due to direct cost of treatment or the indirect costs of transport and lost wages, whether in the public or private sector, force patients to interrupt treatment [85, 93, 97, 100, 104, 112, 142]. And fifth, there are no defaulter retrieval systems in place in the private sector [143, 144].
Directly observed treatment

Of the 5 elements of the DOTS strategy directly observed treatment (DOT) is the controversial one. On the one hand, in western countries such as The Netherlands where, with the exception of high risk groups, self administered treatment (SAT) is applied, treatment success rates are reportedly high and drug-resistant levels low. It is argued that DOT may have benefits but that it may not be needed universally [145-147] and that DOT should be accompanied with other inputs such as incentives and enablers [90,134,148-156]. On the other hand, identification of likely defaulters is difficult as other studies have shown that age, gender, ethnicity, racial origin, occupation, socio-economic status, educational level, marital status, cultural background and religious beliefs are not helpful in identifying who will or will not be compliant with treatment [90,156-159]. DOT has therefore been advocated as a fundamental part of the DOTS strategy, in particular to prevent multi-drug resistance [61,160]. This can be provided by a health worker in hospital or at a clinic [161,162], but has posed problems of coverage in developing countries. There has been a shift to involve trained lay people such as household members, community health workers, community health volunteers [153,163], community leaders, storekeepers [59,164], religious leaders, peer groups [143,165] and others [99,166]. Lay workers have shown to be at least as effective in observing treatment resulting in high treatment success rates among patients [99,164,167-179].

Randomly controlled trials looking at DOT have shown mixed results. While some did not show additional benefit to DOT [180-184] another study did [171].

1.2.2. Difficulties in TB control in high risk populations

In settings where people at higher risk for TB and HIV are concentrated, intensified case-finding will lead to detecting more cases with on average a shortened duration of infectivity. High risk populations for tuberculosis include the homeless, migrants, those living in refugee camps [185,186] and captive populations such as in prisons, police stations, remand centres, penal colonies, prisoner of war camps, detention centres for asylum seekers and secure hospitals.

Prisoners often belong to disadvantaged groups in which TB and HIV incidence is higher than in the average population [187]. Though few prisons systematically report tuberculosis case-finding and treatment outcomes [188], TB incidence in prisons can be as high as 7000 per 100,000 population [189-195]. Increased transmission of TB in prisons can be attributed to [196-199]:

Introduction
late case-finding through delays in diagnosis due to failure of medical services in remand custody or holding centres to refer tuberculosis suspects for diagnosis or to initiate treatment and provision of sub-standard treatment resulting in failure to cure patients and prolonged infectiousness

- transfer of prisoners with infectious tuberculosis between and inside prisons and failure to separate the infectious cases from other prisoners
- overcrowding (limited cell space per person and prolonged confinement inside cells), poor ventilation, poor nutrition and poor hygiene

Sex between men and use of drugs by injection are common and may promote the transmission of HIV infection. Prison conditions therefore promote tuberculosis transmission within the prison directly and indirectly through facilitating HIV transmission and to the community at large as the prison population is a fluid one [200].

Intensified case-finding for TB may involve screening all for a chronic cough of more than three weeks or less [201] and examining their sputum [202] or include CXR screening in some settings and has proven to be valuable in prisons [203].

1.2.3. Difficulties due to the HIV epidemic

HIV infection results in the decrease of CD4 cells with a progressive loss of immune function and appearance of opportunistic infections [204,205]. HIV promotes progression to active tuberculosis in people with recently acquired *M. tuberculosis* infections [206] and is the most powerful known risk factor for reactivation of latent tuberculosis infection to active disease [10,207]. The annual risk of developing tuberculosis in a PLWH who is co-infected with *M. tuberculosis* ranges from 5-15% [10].

Since the mean CD4 cell count is around 300/mm$^3$ in HIV-infected tuberculosis patients [208], tuberculosis often occurs after PLWH have already suffered from several different illnesses [209]. Also, increasing tuberculosis cases in PLWH pose an increased risk of tuberculosis transmission to the general community, whether or not HIV-infected [6,210]. TB however also alters the course of HIV infection as it induces cell mediated immunity and therefore more HIV viral replication and more rapid progression to AIDS [211-214]. TB/HIV co-infection has caused the following problems in relation to TB control:
1. **Increase in cases**: Since the mid-1980s, in many African countries, annual tuberculosis case notification rates have risen up to fourfold [7-9,11-17].

2. **Higher risk of nosocomial transmission**: In high HIV prevalence settings over 50% of admissions may be HIV sero-positive and up to 25% may have TB [215]. Due to the delay in diagnosis of TB in hospital [216], HIV sero-positive patients and staff are at great risk of acquiring new TB infection and subsequent disease [206,217-222].

3. **Difficult diagnosis**: In early HIV infection with mild to moderate immunodeficiency, TB disease resembles that seen in those without HIV infection. However, many programmes have reported an increase in smear-negative TB and EPTB [7,13,223-225]. This is because more advanced immunodeficiency is associated with an increased frequency of pulmonary disease resembling primary pulmonary tuberculosis and of extrapulmonary (including disseminated) disease [48,217,226]. In these patients, the bacillary load in sputum samples may not be representative of the actual number a patients harbours [10]. These smear-negative PTB patients can pose diagnostic problems as chest X-Rays (CXR) become more atypical with declining CD4 cell count. For instance, the CXR may be normal in some patients with disseminated disease. Further, a number of patients will be wrongly diagnosed as TB patients [227,228].

4. **Higher mortality and shorter survival**: Although HIV-infected TB patients respond as well as HIV-negative TB patients to anti-tuberculous chemotherapy [10,217,229,230], at the level of immunodeficiency at which PLWH develop tuberculosis, susceptibility to a range of diseases is associated with high case fatality rates by the end of tuberculosis treatment, typically about 20% for new sputum smear-positive and up to 50% for new sputum smear-negative cases. Many deaths take place early in treatment and 2 year survival is low [10,19-21,208,229-239].

5. **Higher risk of side effects of drugs**: HIV-infected patients are more likely to experience toxic and sometimes fatal side reactions to medications, in particular cutaneous hypersensitivity to thiacetazone [217,223,236,238,240-245]. Thiacetazone has been replaced with ethambutol in most TB programmes for this reason. Ethambutol is well tolerated and has similar efficacy.

6. **Increased risk for recurrence**: Relapse following cessation of chemotherapy due to exogenous re-infection, appears to be more frequent among HIV-infected compared to non-HIV-infected individuals [20,47,209,217,238,246-250].

7. **Community perception that TB is HIV**: In those countries with a high HIV prevalence the community starts perceiving TB and HIV to be the same disease. This might influence treatment seeking behaviour and adherence to treatment and makes DOT even more important in HIV-infected TB patients [67,226].
1.2.4. Interventions to control TB in high HIV prevalence populations

HIV fuels the tuberculosis epidemic. To control TB, firstly expansion of the DOTS strategy is needed as it is thought that the DOTS strategy has reduced the increase in TB cases due to HIV [251]. Second, HIV prevention will have a major impact on TB control. Highly active antiretroviral therapy (HAART) has also shown to prevent or delay the emergence of TB in HIV-infected and thereby transmission of TB [252,253]. Whether funds should be spent on prevention only or on HAART as well in poor resource countries is still a matter of debate [254,255,256]. Third, intensified case finding will be efficient in groups of people with a higher likelihood of having TB or HIV such as people with respiratory symptoms attending general health service providers in the public, private and non-governmental organisation (NGO) sectors (out-patients, in-patients and health care workers [257]), people attending sexually transmitted disease (STD) clinics, centres for voluntary counselling and testing (VCT) for HIV [258] and household contacts of HIV-positive index infectious tuberculosis cases [259]. Whether or not intensified case finding is worth undertaking in these groups depends on factors such as the TB prevalence/incidence, the cost of screening and, the adequacy of passive case finding which may vary from setting to setting. Fourth, in view of the high mortality and low survival of TB patients, even with TB treatment [248], interventions such as isoniazid (INH) prophylaxis, cotrimoxazole prophylaxis and possibly HAART should be included in the package of services to be delivered to TB patients as well [251].

1.3.1. Research questions for TB control in view of the impact of HIV

The dramatic increase in the tuberculosis burden over the past decade, related to the HIV epidemic in many countries in sub-Saharan Africa has greatly increased the pressure on existing government and NGO health services. It has become more difficult for the public sector to provide diagnosis and treatment [210] and there is a need to rethink the role of service delivery for TB [13,251]. Research questions may be formulated, such as:

- Can decentralization of DOT to the community [260] improve treatment outcomes and reduce costs? On the one hand, medical staff at busy clinics, who often are little aware of the social and economic situation of patients, may not be the best persons to encourage patients to complete their treatment. On the other,
community-based volunteers may lack the skills, authority, or financial incentives to ensure treatment completion.

- Can interventions such as HIV testing and subsequent provision of INH prophylaxis [20,209,261-267], cotrimoxazole prophylaxis [20,21,235,264,266,268,269] and antiretroviral treatment [165,252,264,270-272] to HIV-infected, successful under pilot conditions, reduce HIV-associated mortality among TB patients and transmission of TB under programme conditions?

- Can intensified case-finding to diagnose infectious cases in risk groups with high TB/HIV prevalence reduce transmission of TB?

- Can improved collaboration between TB and HIV programmes contribute to decreasing the tuberculosis burden, and, if so, how can this best be organised [57,251,264,273,274]?

- Can collaboration with the private sector (both for profit and non-profit) increase case finding, reduce the delay in diagnosis, and increase cure rates [57,124,275]?

Further, the development of a more effective vaccine for TB [87,276,277] and a vaccine for HIV [277,278], new diagnostic tools [87,277] and drugs and regimens [87,277,279,280] and multi-drug resistance surveillance are needed.

1.3.2. Operational research for TB control in Malawi

Operational research is aimed at developing interventions that result in improved policy making, better design and implementation of health systems, and more efficient methods of service delivery. It offers relevant gains at low cost and in a short time frame by addressing the programme's priorities [281]. The national tuberculosis programme (NTP) of Malawi carried out operational research in order to identify possible solutions to improve TB control and relieve the overburdened health services by looking at ways to increase the efficiency of tuberculosis management through simplification of tuberculosis control and decentralization of services to the community. Results of the research justified the increase in resources for tuberculosis control.

Research questions were formulated looking at the diagnostic pathway to identify reasons for delay in diagnosis [282-286], proper categorization of patients [287] and initiation of treatment [288], at the laboratory services provided [116,283,289-291], accuracy of X-Ray diagnosis [282,292], the identification of initial defaulters and the need for three sputa examinations [293], at diagnostic problems in sputum smear-negative HIV-infected patients [227,228,294,295], at whether staff are following the national guidelines [294,296] and at the possibility to involve traditional healers...
within the programme. Questions were also formulated around outcomes of the programme such as the association between HIV and TB treatment outcomes [12,20,21,231,287,297-300] and decentralization of services in view of the increase in cases. Other topics were the prevalence of TB in hotspots such as prisons [201] and health institutions (nosocomial transmission) [219,291], surveys of HIV infection among TB patients, provision of cotrimoxazole prophylaxis [301] and detailed monitoring of the ongoing programme [302] and the changes implemented based on earlier research [303].

1.3.3. Outlay of this thesis

This thesis describes operational research carried out in Ntcheu district in Malawi with regard to tuberculosis case detection and case holding and its impact on the policy of the Malawi National TB Control Programme. Chapter 2 describes the TB/HIV epidemic in Malawi and the national tuberculosis programme. The following three chapters describe the research done to identify the extent of TB and TB/HIV co-infection in the district. Chapter 3 compares tuberculosis treatment outcomes of HIV-negative and HIV-positive patients. Chapter 4 explores whether tuberculosis is more common among urban than rural populations. Chapter 5 examine the prevalence of tuberculosis as well as HIV and STDs among new prisoners in a district jail in Malawi. Chapter 6 and 7 look at perceptions of tuberculosis patients and involvement of traditional healers in the programme. The next three chapters deal with the decentralization of care to the community and its evaluation. Chapter 8 and 9 present TB treatment outcomes using a simplified regimen and community-based treatment. Chapter 10 examines whether DOT can be carried out by non-health workers. Finally, in chapter 11 the main findings of the studies and their limitations are discussed, and recommendations are made for tuberculosis control and further research.

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26

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28 Introduction


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