Epidemiology and control of tuberculosis and sexually transmitted infections in Thyolo District, Malawi
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CHAPTER 11

GENERAL DISCUSSION
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The studies presented in this thesis, focus on cotrimoxazole prophylaxis in TB patients, early TB mortality, sexually transmitted infection among specific population groups and voluntary counseling and HIV testing.

In each of these areas, I discuss some of the principal findings, possible limitations, and their influence on policy and practice. Where relevant, I suggest areas requiring further research.

The study on voluntary counseling, HIV testing and adjunctive cotrimoxazole (Chapter 2) showed a very high overall acceptance rate of both interventions among TB patients registered under routine programme conditions. Approximately 90% of all TB patients underwent voluntary counseling and HIV testing and 93% of all those who were HIV positive actually took cotrimoxazole.

A recent study which compared the impact of offering a package of voluntary counseling and HIV testing and cotrimoxazole in Thyolo district with a neighboring district (Mulange) that did not offer such a package showed that there was a significant improvement in TB treatment outcomes in Thyolo. This finding is encouraging in that it further supports offering such a package to TB patients in Malawi.

One of the main encouraging findings was the high acceptability of voluntary counseling and HIV testing among TB patients and this trend has continued after the completion of the operational research study\(^2\). This is important for a number of reasons. First, TB is an early opportunistic infection which often brings the HIV positive individual to medical attention. There is thus an opportunity for introducing a wide range of prevention and care related interventions. Second, the prevalence of HIV in TB patients in our setting is high like the case in many other sub-Saharan African countries. Targeting this group of individuals for voluntary counseling and HIV testing is worthwhile as a large proportion of the group might benefit from available interventions\(^3,4\). Third, according to recent World Health Organization guidelines on scaling up highly active antiretroviral treatment in developing countries, HIV positive TB patients are classified in WHO stage III (active pulmonary TB) or stage IV (extrapulmonary TB) and would be eligible for antiretroviral treatment on purely clinical grounds\(^5\). Offering voluntary counseling and HIV testing to this group could thus provide a potential entry-door to highly active antiretroviral treatment\(^6\).

Encouraging findings with respect to the uptake of voluntary counseling and HIV testing have also been reported from Abidjan, Cote d'Ivoire\(^7\) and public health experts have argued that voluntary counseling and HIV testing should be introduced routinely in out-patient TB centers\(^8\).

The most encouraging finding was the reduction in mortality of 22 % in the cohort of TB patients who were offered the package of voluntary counseling, HIV testing and cotrimoxazole when compared with a historical control cohort that was not offered these interventions.

Given the ethical impossibility of a placebo-controlled study, Malawi decided to use a historical cohort for comparison. The primary outcome, death while on TB treatment is clear-cut and shows significant improvement in the recent cohort compared to the historical one.
Unlike the Cote d’Ivoire study\textsuperscript{10}, The Malawi study however failed to demonstrate a mortality benefit among smear positive TB patients and the possible reasons for this difference have been addressed in Chapter 2. The main reason for this difference might however be the smaller proportion of smear positive TB patients in Thyolo who were HIV positive and received cotrimoxazole. This is likely to have reduced the cohort benefit of the drug in these patients when compared to other types of TB.

Although the results of the Thyolo study add to the existing evidence for advocating cotrimoxazole prophylaxis for HIV positive TB patients in sub-Saharan Africa\textsuperscript{11}, the overall evidence base upon which WHO/UNAIDS\textsuperscript{12} released their blanket recommendation on cotrimoxazole remains limited. Both Malawi and Senegal which at the time, were running similar UNAIDS randomized placebo controlled trails as that of Cote d’Ivoire, had to prematurely terminate their studies as UNAIDS felt that the evidence from Cote d’Ivoire study\textsuperscript{1} rendered further cotrimoxazole-placebo controlled trials unethical.

The results of the study from Senegal\textsuperscript{12} did not demonstrate any effect on morbidity, but inadequate power due to early termination of the study might explain this difference. The study from Malawi faced a similar problem. Zambia which, at the time was running a randomized controlled cotrimoxazole trial decided to continue their study. They justified their position by saying that it would be unsafe to generalize the results from Cote d’Ivoire to Zambia as cotrimoxazole resistance among common pathogens were relatively higher in their setting\textsuperscript{14}. The results of this trail are yet to be published.

Following the encouraging findings from Thyolo, and similar encouraging results from another district in Malawi (Karonga)\textsuperscript{15} that was implementing a similar package of interventions, the Malawi Ministry of Health decided to go ahead with a phased implementation of voluntary counseling, HIV testing and cotrimoxazole prophylaxis to the 25 districts in the country. By July 2003, phased implementation of voluntary counseling, HIV testing and cotrimoxazole prophylaxis to registered TB patients covered 15 of 43 hospitals in Malawi. 16 more hospitals are scheduled to start offering the package by the end of 2004. This phased implementation process is eventually meant to cover all hospitals country-wide.

This decision to scale up voluntary counseling, HIV testing and cotrimoxazole was justified on the basis of the following: First, Malawi had deferred implementing cotrimoxazole prophylaxis for HIV positive TB patients pending the results of its own operational research. The data from Thyolo and Karonga both showed that offering voluntary counseling, HIV testing and cotrimoxazole is feasible, safe and effective in reducing deaths rates in TB patients.

In public health terms, implementing this package on a country-wide level for the 25,000 or so registered TB cases in Malawi (and assuming similar uptakes as in Thyolo) would translate into approximately 2000 prevented deaths during anti-TB treatment per year. The Ministry of Health thus considered this intervention worthwhile. Second, the evidence from Cote d’Ivoire and the additional operational evidence from Malawi inclined policy makers to think that denying HIV positive TB patients such an intervention (in the absence of other evidence that shows ineffectiveness or harm) would be unjustified.
Third, it was felt that cotrimoxazole was a well known drug in the community and HIV positive individuals were already procuring the drug in a rather anarchic manner from private pharmacies, and vendors. Resistance development is likely to be more a result of such practice than its correct and controlled use in the public service.

It was finally felt that the prophylaxis of opportunistic infections and particularly the use of cotrimoxazole would be a logical first step towards implementing highly active antiretroviral treatment. The package of voluntary counseling, HIV testing and cotrimoxazole would serve as a foundation upon which highly active anti-retroviral treatment could be built.

There are still a number of specific unanswered questions. What really caused the reduction in deaths observed in Thyolo? Was it really the cotrimoxazole, was it voluntary counseling and HIV testing and the subsequent knowledge by health care staff, patient and carer alike of the patients HIV status and subsequently better care for those who were HIV positive?

Another issue is the lack of evidence linked to clinical effectiveness of cotrimoxazole among HIV positive children in Africa. The WHO/UNAIDS guidelines includes the recommendation for empiric cotrimoxazole for infants (which by definition includes HIV positive children with TB) which emerged shortly after the publication of the two Abidjan studies. This is remarkable given that neither of the two studies provided any information about the optimal efficacy of cotrimoxazole in children. To date, no randomized trials of cotrimoxazole’s efficacy in children have been conducted.

The study that assessed compliance to cotrimoxazole during anti-TB treatment (Chapter 3) showed a compliance rate of 94%. An additional finding was that compliance with cotrimoxazole as an adjunct to anti-TB treatment could be assessed simply and practically by verbal verification and pill counts. This study also demonstrated that it is important to provide a excess stock of pills as a safety-net for continued prophylaxis. High compliance to cotrimoxazole prophylaxis during anti-TB treatment has previously been reported under research conditions in Abidjan, Cote d’Ivoire.

Since the results of this study became available, subjective verification of compliance pill balance-counting, and a safety stock have been introduced for TB patients receiving cotrimoxazole in Thyolo.

The study that assessed compliance with cotrimoxazole after completing anti-TB treatment (Chapter 4) showed that 93% of individuals were still taking the drug when assessed 3 to 6 months after completing anti-TB treatment. The study also showed that close to 70% of individuals on cotrimoxazole would find it difficult to pay for the drug. In a rural setting where close to 60% of all TB patients earn less than 4 USD per week, this reemphasizes the importance of making sure that the drug is provided free of charge. Since the most common reported reason for stopping the drug was long distances to certain health centers the study raises the importance of ensuring geographical access for long-term prevention.

Although the two studies on cotrimoxazole compliance (Chapter 3 and 4) address the question of compliance in the course of anti-TB treatment and three to six months after, the findings might not necessarily reflect compliance in the longer term. After completing anti-TB treatment, there was a 7% drop out rate to prophylaxis within a three to six months period. Although we can not assume that this would continue to be the trend over time, if indeed such a trend continues, our studies would over-estimate long term compliance. In any case it would
be worthwhile to assess longer term compliance (say after a period of 5 years of starting prophylaxis) with cotrimoxazole.

The study (Chapter 5) which assessed changes in Escherichia coli resistance to cotrimoxazole showed that among TB patients, baseline resistance to cotrimoxazole was high (60%) and this increased with time. The increase in resistance (89%) was found to be very significant among HIV-positive TB patients who were taking cotrimoxazole prophylaxis for a period of 6-8 months (89%).

Non-typhoid Salmonella bacteremia particularly with Salmonella Typhimurium and S. enteritidis is known to be among the leading causes of morbidity and mortality in HIV infected patients in Africa. A finding of high resistance to E. coli such as in our setting heralds rapid plasmid-mediated transfer of resistance to other Enterobacteriaceae including the Salmonella species. It is thus likely that resistance in the latter is also high in Thyolo.

A study from Blantyre, a neighboring district to Thyolo reported the predominance of non-typhi salmonellae among adult patients with bacteraemia. Mortality in those that had non-typhoid salmonella bacteremia (n-100) was extremely high (47%) and so was the rate of recrudescence (43%). In that particular study, resistance levels of Non-typhoid salmonella to cotrimoxazole was 73% among adults and 72% among children. In Cote d’Ivoire, susceptibility of non-typhoid Salmonella to cotrimoxazole was high (91%) and protection from non-typhoid Salmonella bacteremia and enteritis accounted for much of the beneficial effect of cotrimoxazole seen in that setting. The results of the Thyolo study (and those from Blantyre) suggests that baseline resistance of non-typhoid Salmonella to cotrimoxazole is rather high and the protective effect of the drug wanes with time. This would herald limitations to the short and long terms benefits to be expected from the use of cotrimoxazole prophylaxis in preventing non-typhoid Salmonella related morbidity and mortality in Malawi.

There are several questions and concerns related to the development of cotrimoxazole resistance associated with wide-spread implementation of prophylaxis in high HIV prevalence settings such as Malawi.

The list of pathogens (other than E. coli) whose epidemiology could be altered by cotrimoxazole exposure includes Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, and Neisseria species. We do not know the baseline cotrimoxazole susceptibility levels among these organisms nor do we know the eventual impact wide-spread cotrimoxazole prophylaxis would have on its development.

Cotrimoxazole is still first-line therapy for a variety of childhood infections under the World Health Organization integrated management of Childhood Infections (IMCI) guidelines. Malawi currently follows these guidelines and resistance development could impair the effectiveness of the IMCI program and thus merits surveillance.

Widespread use of cotrimoxazole is also likely to foster the growing or already high sulfadoxine-pyrimethamine (Fansidar) resistance in Plasmodium falciparum, an organism which globally kills approximately one million children each year – the most attributable to any single childhood pathogen. Cotrimoxazole and sulfadoxine-pyrimethamine are close pharmacologically, and share extensive in-vitro cross-resistance. Malawi currently uses sulfadoxine-pyrimethamine as first line therapy for malaria and wide-spread use of cotrimoxazole prophylaxis is likely to reduce the useful life of sulfadoxine-pyrimethamine as an effective first line treatment for Malaria. Contrary to expectations, sulfadoxine-pyrimethamine has retained good efficacy (80%) after 10 years as the first line antimalarial.
drug in Malawi. Resistance to this drug is however growing or already high in most African countries and it has been suggested that malaria treatment needs to change to artemisinin-class combination therapies. There is also the concern on whether cotrimoxazole prophylaxis could impede the acquisition of natural malaria immunity by infants. Because of maternal antibodies, infants in areas of high malaria incidence are often born with immunity to malaria. As this passive immunity wanes, natural immunity emerges after exposure to infectious mosquitoes. Cotrimoxazole reduces both clinical malaria and asymptomatic parasitemia and, in so doing, could hypothetically attenuate the normal acquisition of immunity. This creates an ethical dilemma since HIV-exposed infants discontinuing prophylaxis, after a negative HIV test at one year of age, might be more vulnerable to severe malaria than if they had never received prophylaxis.

Whatever might be the eventual answers to these questions and concerns, a number of issues are clear. First, the protective effect of cotrimoxazole prophylaxis with respect to bacterial pathogens (and other pathogens) is likely to be time-bound. Currently, there are no alternative choices to cotrimoxazole that have the advantages of providing protection against a range of opportunistic pathogens; being cheap; easy to administer, and relatively safe in terms of incidence of side-effects. There is thus a need to seek for alternative therapies for prophylaxis of opportunistic infections as cotrimoxazole becomes progressively obsolete for this purpose. Second, resistance of *P. falciparum* to sulphadoxine-pyrimethamine is already high or rapidly rising in many African countries and it is high-time to move on to the artemisinin-class combination therapy. The World Health Organization has formulated policy that elevates such therapy as the policy standard for all malaria infections in areas where *P. falciparum* is the predominant infecting species of malaria. Although the high current cost of artemesinin compounds is still a limitation, this barrier must be tackled through advocacy for price reductions combined with access to international funds through the Global Fund to fight TB, AIDS and Malaria.

The best long-term solution for the prevention of HIV related opportunistic infection would be to improve the immune status of individuals and reduce susceptibility to opportunistic infections through the administration of highly active antiretroviral treatment. Countries in sub-Saharan Africa who currently face the challenge of a high HIV prevalence as well as high HIV-related morbidity and mortality need to drive forward in this direction.

The study that tried to test the hypothesis of an association between malnutrition in TB patients and early TB deaths (Chapter 6) showed that more than half (57%) of all TB patients were malnourished and over one third (37%) had moderate to severe malnutrition. TB patients who were malnourished and had a body mass index of less than 17.0 kg/m² had an increased risk of dying in the first month following registration than those who had a higher body mass index.

Despite the fact that nutritional status was assessed in a very large number of TB patients (1181), one of the main limitations of the study is that close to 30% of all early deaths recorded in the study occurred before height and weight measurements could be done. Since these individuals were thus excluded from the analysis, we are unable to ascertain how the nutritional status of these particular individuals might have influenced the association between early mortality and malnutrition.

In the Thyolo study, HIV positive TB patients had a significantly higher risk of dying in the first month and a larger proportion of HIV positive TB patients had moderate to severe
malnutrition than HIV-negative patients. Similar findings have been described in Burundi. Early mortality and its association with low body weight has also been described in South Africa. Another study conducted among hospital inpatients in Bujumbura, Burundi, showed that in patient malnutrition was associated with TB and HIV independently and these variables were in turn associated with higher in-patient mortality rates. Although we have demonstrated that a body mass index of less than 17.0 kg/m\(^2\) is associated with early deaths, we do not know if in our setting, it is the nutritional impairment in its own right that predisposes to early death or whether malnutrition is a simple marker of extensive TB, severe HIV related complications, undiagnosed opportunistic infections, or other adverse factors. These questions remain largely unanswered and merit further study.

Whatever the eventual answers to these questions might be, the body mass index is a simple measurement that can be performed in hospitals managing TB patients and those with a body mass index of 17kg/M\(^2\) or less should be considered a priority for targeting care related interventions. The results of this study have helped alert the Ministry of health and partners in Malawi on the need for considering nutritional supplementation for TB patients as an important aspect of implementing joint HIV-TB activities in Malawi. Continued funding for providing nutritional rehabilitation for TB patients in Thyolo has been made available since the results of this study were published.

The study (Chapter 8) that looked at urethral discharge in men presenting to the district hospital sexually transmitted infection clinic showed; that the majority (61%) of men first seek care at an alternative source, the great majority of individuals with symptoms continue to have sex without using condoms and that the susceptibility of Neisseria gonorrhoeae to gentamicin was below the 95% mark recommended by the World Health Organization for the syndromic management of sexually transmitted infections. The most important alternative source of care was the traditional healer. The mean period with symptoms before presenting at the sexually transmitted infection clinic was relatively long (estimated at about 4 weeks) and the majority of these men (84%) continued to have unprotected sex while symptomatic. These findings are particularly worrying in a setting where the prevalence of HIV among sexually transmitted infection clients range from 53 to 83% with a high subsequent risk of sexually transmitted infection and HIV transmission to sexual partners.

The important role of traditional healers in the care of sexually transmitted infections in Malawi has been demonstrated in other studies study in Thyolo and Lilongwe. The important role of this group of alternative care providers as regards TB treatment has also been demonstrated in Malawi.

Malawi is one of the few countries where traditional healers are licensed and officially recognized within health services. Despite this, the allopathic and traditional systems of care have led parallel paths over the years. This study and other related studies led the MOH in Malawi to try to bridge existing gaps between the two service providers. In Thyolo, the district coordinator for sexually transmitted infection control and the Non Governmental Organization (MSF) now involve traditional healers in planning and activities related to sexually transmitted infection control. Condoms are also made available at the 48 or so traditional healer sites in Thyolo and these are distributed free of charge to clients with sexually transmitted infections. Traditional healers are also encouraged to refer clients with sexually transmitted infections to
the district clinic. These strategies are integrated along with Information, education and communication sessions encouraging wider use within the community at large.

The National TB control program has been conducting yearly training of all traditional healers country-wide in Malawi and encourages early referral of TB suspects. Efforts are being made to link such an existing initiative to trainings on HIV infection and STI control. This might be one way of encouraging early referral of clients with sexually transmitted infections for effective antibiotic treatment.

This study conducted was the first since 1996 and clearly showed that none of the antibiotics recommended for the syndromic management of sexually transmitted infections approached the 95% mark as recommended by the World Health Organisation. The study led to calls for a complete re-evaluation of the existing syndromic management protocol in Malawi. Although this study provided important insight into some existing gaps in the current control strategy for sexually transmitted infections, it is not designed to provide specific recommendations on antibiotic treatment in men with urethral discharge. Since the focus was on men, there are also unanswered questions as regards the prevalence, patterns and particularly the antibiotic susceptibility of sexually transmitted infections in women. Further studies including clinical efficacy studies are thus justified.

The study on sexually transmitted infections and sexual behaviour among female commercial sex workers (Chapter 8) attending a mobile STI clinics in bars and brothels showed that one out of every four commercial sex workers, in the setting had a sexually transmitted infection, and that the great majority of these individuals (87%) continued to have unprotected sex while symptomatic.

Relatively recent data from Accra, Ghana and Cotonou, Benin adds weight to the growing body of evidence demonstrating the importance of core and bridging groups in the HIV epidemic in sub-Saharan Africa. The data from these two studies strongly suggest that transactional sex accounts for the majority of HIV cases among adult men, in settings where overall HIV prevalence in the general population is still under 5% (moderate). Men then act as a bridging population, transmitting HIV from the core group of commercial sex workers to their other non-commercial sexual partners. In situations such as these, where there is a significant difference between HIV prevalence in sex workers, their clients, and the general population, interventions targeted at commercial sex workers and their clients could substantially delay the onset and reduce the magnitude of a widespread epidemic in the general population.

The scenario is likely to be similar even if less marked in Southern African countries (including Malawi) where the HIV epidemic is more explosive and still on the rise. A study carried out among commercial sex workers in KwaZulu-natal, South Africa showed an HIV prevalence of 56% in this population. The difference between this and the HIV prevalence in the general population of this region at the same time of the survey (20-25%) suggest that, even in explosive epidemics, interaction between commercial sex workers and their clients and subsequently between these men and other women who are not commercial sex workers may be of importance in the dynamics of HIV transmission.

The study in Thyolo and studies in West Africa have clearly shown that it is possible to implement successful preventive interventions targeting commercial sex workers. More recently it has also been shown that clients of commercial sex workers are also a reachable population in terms of increasing condom use and decreasing rates of sexually transmitted
infections. An important aspect of this approach is to involve pimps and bar owners in the sexually transmitted infection and HIV control strategy and focus on strong peer education and empowerment.

In Thyolo like in many other settings, the use of condoms by commercial sex workers often depend on client pressure. This situation of limited assertiveness for safe sex is a serious obstacle to preventing these workers (and their clients) from acquiring and transmitting sexually transmitted infections and HIV infections. The introduction of the female condom is likely to facilitate independent and assertive behaviour on safer sex by commercial sex workers and this female devise was found to have a high acceptability in this group. Access to both male and female condoms are now part of the sexually transmitted infection control package offered to sex workers and their clients in Thyolo.

Despite the importance of sexually transmitted infections and HIV control interventions among commercial sex workers, sub-Saharan African countries, including Malawi, do not routinely target this group. Existing interventions are often isolated and run by non governmental organizations or research groups. Given the convincing evidence accumulating about the central role of transactional sex in the HIV epidemic, scaling up interventions that target commercial sex workers (both in intensity and geographical coverage) is urgently required. Preventive and curative services for this group of individuals should be organized with the same goal of nation-wide access as for other public health priorities.

The study on sexually transmitted infections among male prison inmates (chapter 9) revealed a sexually transmitted prevalence of 4.2% and an incidence of 12 new cases/1000 inmates/year. Another study conducted in a district setting in Tchouv, Malawi revealed a sexually transmitted infection prevalence rate of 11% among new male prisoners. In the Thyolo study, about one third of all cases of sexually transmitted infections were acquired within prison walls. In a prison which accommodates only male prisoners, this suggest inter-prisoner same-sex sexual activity.

Providing access to condoms within such prisons is however not allowed as it is felt that such an intervention will encourage homosexuality which is illegal and carries a prison sentence in itself of at least 14 years in Malawi. The issue of providing condoms in prisons is thus one that challenges established social norms and existing laws which lie beyond the jurisdiction of prison authorities. In trying to address the issue of condoms in prisons, we avoided recommendations that would directly challenge the existing law but rather tried to find a pragmatic solution that would bridge the discrepancy between the reality of prison life and prison regulations that are dictated by existing laws.

The Dakar conference on HIV/AIDS in African prisons high-lighted an impenetrable and insular nature of African prison environments as well as legal constraints as the principal obstacles to improving health care for prisoners. Our experience shows that through a process of continuing dialogue the prison authorities in Malawi demonstrated collaboration and a real willingness to work with us. Although we were not allowed to openly distribute condoms to male prisoners, prisoners are now allowed access to condoms through the medical staff present on daily basis.

The TB program in Malawi has similarly demonstrated how they have been able to work with prison authorities to improve the diagnosis and treatment of TB in 22 prisons country-wide. The results of this study from Thyolo helped prison authorities to seek additional help in the management of sexually transmitted infections in prisons in Malawi. Another Non
Governmental Organization (Banga La Tscholo) has started a phased approach to introduce STI control services in the 22 prisons country-wide. Discussions are also being held about setting up voluntary counseling, HIV testing and packages of care for those prisoners who are HIV-infected.

The study conducted on blood donors (Chapter 10) showed that HIV prevalence in blood donors was alarmingly high (22%) raising concerns on the potential dangers of HIV transmission through blood transfusions. What was particularly interesting was the very high uptake (90%) of voluntary counseling and HIV testing among blood donors. In a setting where almost one fourth of all donors are HIV positive, offering voluntary counseling and HIV testing would offer an early opportunity for the early diagnosis of HIV infection to individuals that otherwise might not have made contact with the health services. This opportunity can be used as an entry-point into prevention and care programs.

In 2003, a country-wide situation analysis carried out by the Ministry of health revealed that a total of 60561 HIV tests were done on blood for transfusions in Malawi. The HIV prevalence among those tested was 15% and thus a total of over 9000 HIV positive individuals can be identified and provided an early entry point into possible HIV prevention and care activities.

What has not been addressed in this paper is the problem of incident cases and those in the window period of infection. The use of improved questionnaires to assess recent risk behaviour, implementation of the P24 antigen test and change from blood donors who are family members to true voluntary altruistic blood donors have been suggested.

The different research studies presented in this thesis were all conducted in close collaboration with partners from the Ministry of Health and population. This made it easier for the Government to share ownership of the findings. The strategy also made it easier to disseminate the results within and outside Malawi, and to translate the lessons learnt from the research into policy and practice. The Ministry of health in Malawi and particularly the national TB control programme has a culture of performing operational research, and this encourages non governmental organizations and individuals alike to follow an evidence based approach towards improving and even changing existing strategies in health care.