Control of chronic infectious diseases in low resource settings
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In this thesis we report on studies on tuberculosis, visceral leishmaniasis and human African trypanosomiasis (HAT) conducted in three different settings, Uzbekistan, India and the Democratic Republic of the Congo (DRC). All three diseases are chronic infectious diseases associated with significant morbidity and mortality that disproportionately affect impoverished segments of the population of low income countries. Because the three diseases each have a mainly or exclusively human reservoir, early case finding and treatment are crucial in their control. Consequently efforts to control these diseases are very much dependent on the health system context.

Tuberculosis is caused by mycobacteria belonging to the *Mycobacterium tuberculosis* complex and occurs all over the world. Visceral leishmaniasis and HAT are caused by parasites and have a more limited geographical distribution. In both diseases there are different clinical presentations that reflect different strains of the causative parasites. The most common parasite strain causing visceral leishmaniasis is *Leishmania donovani*; more than 50% of all cases due to this parasite strain are reported from the Bihar focus in India. Though there are two parasite species that cause HAT, over 90% of cases belong to the West African variety caused by *Trypanosoma brucei gambiense*. The country worst affected by West African HAT is the DRC from which currently over 60% of all cases reported worldwide originate.

We studied tuberculosis control in Uzbekistan, a lower middle income country that used to be part of the Soviet Union and as such has a fairly specific epidemiological and health systems context. We conducted four studies on the management of tuberculosis by the healthcare system. We studied case finding, prescribing policies and adherence to treatment; on the latter we conducted both a quantitative and a qualitative study.

Although Uzbekistan has adopted the Stop TB strategy, elements of the old Soviet system are still in place, such as active case finding based on mass X-ray screening. According to the criteria used, 50% of the population is eligible for screening. Because it is not possible to actually screen that many, quota are assigned to the numbers to be screened within each of the groups targeted. Thus annually about three million people are being actively screened; just over 10% of the population. Reportedly 73% of all pulmonary tuberculosis patients are detected through these active screening campaigns. We conducted a study in two provinces and found that 16% of all pulmonary tuberculosis patients had been diagnosed through some form of active case screening. The yield was much lower than the official figure of 73% and comparable to the yield reported in earlier studies from Canada, Czechoslovakia and the Netherlands. Those earlier studies led these countries to abandon mass radiography as a case finding tool. We also found that the screening efforts in Uzbekistan are poorly targeted, missing out on key risk groups.

Treatment for tuberculosis in Uzbekistan has traditionally been individualized and managed by specialists. The Stop TB strategy advocates standardized regimens, depending primarily on whether or not there is a history of previous treatment. Our study on prescribing practices showed that anti tuberculosis drug regimens prescribed to new tuberculosis patients in Uzbekistan are by and large adequate and meet the standards of the Stop TB strategy. However there was significant over-
prescription of non-tuberculosis drugs, with a median prescription of eight such drugs per patient. This so-called ‘pathogenetic treatment’ is another remnant of the Soviet tradition. We found that the rationale for prescribing these drugs is questionable and that there is no apparent relation to concomitant diseases. Some of the drugs prescribed are potentially dangerous and patients incur substantial costs when purchasing them.

Our studies on adherence to treatment were conducted in Tashkent, the capital of Uzbekistan. The studies revealed various obstacles, most related to the healthcare system, at times in interaction with personal factors. We found that most patients who default do so during or immediately upon completion of the intensive phase of treatment; we also identified a number of personal factors that were associated with default. Pensioners, unemployed, people abusing alcohol and homeless are more at risk than others. Another notable finding was the fact that one third of defaulters did in fact continue treatment but outside the official system.

Lack of information on tuberculosis and its treatment, fear of being stigmatized and the opportunity cost of being hospitalized are important underlying reasons for default. Many patients did not know that tuberculosis is curable and they did not know for how long they were supposed to be treated. Also there were many irrational beliefs about side effects of tuberculosis treatment. Communication between patients and doctors is poorly developed; moreover there are conflicting guidelines because of elements of the old Soviet system still being in place. Fear of being stigmatized is further enhanced by the conditions under which treatment is provided, i.e. being admitted in special tuberculosis hospitals and receiving ambulatory treatment from specifically designated ‘DOTS’ rooms. Mandatory hospitalization during the intensive phase of treatment is a problem because of poor hygienic and general conditions in tuberculosis hospitals and because of the related opportunity costs. Pensioners and unemployed need to engage in informal daily labor to make ends meet and therefore cannot afford to be hospitalized. Being on admission in a tuberculosis hospital also has substantial direct costs because of patients having to buy additional non-tuberculosis medicines.

Our studies on visceral leishmaniasis were conducted in a highly endemic district of Bihar State, India. In a neighborhood, age and sex matched case control study investigating whether keeping domestic animals inside the house is a risk factor for visceral leishmaniasis, we found no evidence to support this hypothesis. We did find evidence for an association between housing conditions and visceral leishmaniasis; the association remained statistically significant after controlling for potential confounding by socio-economic status.

In our second study on visceral leishmaniasis we explored health care seeking behavior and case management in the government primary healthcare system. We enrolled a random sample of 150 patients, registered for treatment at government PHC facilities during 2008. We observed delays of one to two months before patients presented to the appropriate level of the primary healthcare system. Most patients first presented to unqualified local practitioners. Delay was not much shorter for those who first presented to the outreach workers of the primary healthcare system, the auxiliary nurses/midwives (ANM) and accredited social health activists (ASHA). We found that patients interviewed had incurred substantial direct costs related to their
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disease episode; the median expenditure being equivalent to nearly 2 months of household income. We assessed treatment outcomes and observed differences between the official reports and the outcomes documented at the community health centers. Such differences were even more pronounced when comparing data from patient interviews to the official reports. Of all patients assessed, 48% were still treated with antimonials despite the official guideline that all patients should be treated with miltefosine. Altogether 27.5% of patients assessed had required a second treatment course, for those treated with antimonials this was the case for 40%. These problems were not picked up by the recording and reporting system in use.

Our two studies on HAT were conducted in the DRC and were both related to screening tests. We evaluated a new format of the CATT-test, the CATT-D10, designed to be thermo-stable. The CATT-D10 performed equally well as the classical format and there was no significant loss in reactivity even after exposure to high or alternating temperatures over an 18-months period. The new format is therefore highly suited for use in peripheral health facilities in the DRC which generally do not have functional cold chains. The CATT-D10 is packaged in 10-dose vials, rather than the 50-dose vials in which the classical CATT is packaged; this is another major advantage when used at the level of peripheral health centers since utilization rates of such facilities in the DRC are generally low.

In our second study on HAT we investigated the theoretical feasibility of a surveillance system using samples collected on filter paper. The current approach for HAT surveillance is based on mobile teams going from village to village and screening the entire populations. If samples can be collected on filter paper, this could be done by a resident health worker and over a longer time period. In our study the samples were collected and stored under routine field conditions and processed in research laboratories in Kinshasa and Antwerp. We validated two test formats, MicroCATT and ELISA/T.b.gambiense; both tests were found to have acceptable sensitivity (92.7% and 82.8% respectively) and very high specificity (99.4% and 99.8% respectively), which makes them suitable for use in an early warning system in low prevalence areas. We simulated their use in a lot quality assurance sampling (LQAS) approach and found that theoretically a filter paper based system using MicroCATT or ELISA/T.b.gambiense can reliably distinguish a 2% prevalence from a zero prevalence at village level. However this requires a high sampling proportion; on a village population of 1000, at least 600 would need to be enrolled. Alternatively, test results can be used to identify individual HAT suspects.

An important advantage of this type of surveillance system would be the fact that it can be implemented through the general healthcare system. Further investigations are needed to see whether such a system can eventually replace the current strategy using mobile teams and whether it should be based on LQAS or on an individual approach. A key aspect will be the cost effectiveness of a filter paper based system when compared to the current approach.

For all three diseases in all three settings we found some common ground and scope for cross-fertilisation with regard to organisation of disease control measures. Though the reasons are different for the three diseases and in the three settings, in all our studies we found a need for more involvement of first line health services in disease
control activities. In Uzbekistan, being a former Soviet country, service delivery for tuberculosis control is only very partially integrated into general healthcare. Further progress towards greater integration is hampered by the existence of a dual governance structure made up of the national research institute of phthisiatry and pulmonology (NRIPP) which adheres to the Soviet tradition and the national tuberculosis control program ($DOTS$ Center) which embraces the Stop TB strategy. Based on our findings we recommend reinforcing $DOTS$ Center in its role as national tuberculosis control program and restricting the role of NRIPP to that of a research institute.

Integration of service delivery for visceral leishmaniasis control in India has progressed far but further gains could be made by making better use of the available networks of village health workers. We recommend greater involvement of ANMs and ASHAs in case finding and monitoring of treatment. Since a dipstick test is available that is inexpensive, easy to use and does not require a cold chain, diagnosis of uncomplicated cases could be decentralized to the level of ANMs. The treatment regimen currently recommended is a fully oral regimen; therefore for uncomplicated cases even diagnosis and initiation of treatment could be decentralized to ANM level. ASHAs could be involved in identifying suspect cases, monitoring treatment intake and reporting on treatment outcomes. We also recommend changing the recording and reporting system to a system based on that used in tuberculosis control. A key element in this system is the systematic monitoring of treatment outcomes.

Control of HAT in the DRC is still very much a vertical program and is fully donor dependent. With the decreasing incidence observed, there is also a diminishing efficiency of blanket population screening. There is therefore an urgent need to explore alternative strategies for HAT surveillance and control. The alternative approach needs to be more cost effective and should be appropriate for implementation by regular health services. The CATT-D10 can be used to identify HAT suspects even in peripheral general health facilities. The options for a surveillance system using samples collected on filter paper need to be further explored.