Control of chronic infectious diseases in low resource settings
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Background

Over the last decades, a considerable amount of evidence has been generated on how certain health interventions can lead to dramatic reductions in mortality and disability, often at modest cost. Yet analyses and debates on prioritization of health interventions often do not take into account the specific contexts of individual countries. In this thesis I will explore some of the interventions related to the control of three communicable diseases: tuberculosis, visceral leishmaniasis and human African trypanosomiasis (HAT), in three specific settings: Uzbekistan, India and the Democratic Republic of the Congo (DRC). The aim of the research presented is to identify ways to increase the effectiveness of these interventions. The terms communicable and infectious are used interchangeably in this text; communicable disease being defined as: ‘a disease caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi; the disease can be spread, directly or indirectly, from one person to another’. Apart from being communicable, all three are also chronic diseases, defined by the World Health Organization (WHO) as diseases of long duration and generally slow progression. Moreover they mainly affect low income countries. For the purpose of this thesis I will define control of communicable diseases as: ‘measures to prevent transmission of disease from person to person or from animal to man, as well as measures to prevent unnecessary suffering from disease once infected.’

Whereas tuberculosis is found all over the world, visceral leishmaniasis and HAT have a more focal distribution. Visceral leishmaniasis occurs mostly on the Indian Subcontinent, in East Africa, in Southern Europe and in Latin America; HAT is found exclusively in sub Saharan Africa (figure 1-3). Tuberculosis is transmitted from man to man, transmission of visceral leishmaniasis and HAT involves an arthropod vector. Though tuberculosis can also infect a number of animal species, humans are considered to be the main reservoir. The same applies to visceral leishmaniasis in East Africa and on the Indian subcontinent, where *Leishmania donovani* is the causative organism. HAT occurs in two different clinical forms, caused by two different parasites. Over 90% of HAT cases are caused by *Trypanosoma brucei gambiense*, and are also referred to as West African sleeping sickness; the remainder are caused by *Trypanosoma brucei rhodesiense* and are also referred to as East African sleeping sickness. West African sleeping sickness is an anthroponosis; humans are assumed to be the only reservoir. Currently over 60% of all cases of West African sleeping sickness reported are from the Democratic Republic of the Congo (DRC).
Chapter 1. General Introduction

Figure 1: Estimated annual tuberculosis incidence (all forms) in 2008 (Source: WHO Global Tuberculosis Control, A short update to the 2009 report)

Figure 2: Number of West African HAT cases reported per year by country (Source: Fevre et al. The Burden of Human African Trypanosomiasis, 2008)

Figure 3: Countries affected by visceral leishmaniasis (Source: Chappuis et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control, 2007)

Control of chronic infectious diseases requires not just treatment of individuals but also eradication of the disease reservoir. If the reservoir of the causative organism is mainly or exclusively human, as in the case of tuberculosis, visceral leishmaniasis caused by *Leishmania donovani* and West African HAT, treatment of patients and
eradication of the disease reservoir go hand in hand. A well functioning health system will then be of key importance in controlling the disease. It is not enough for patients just to be diagnosed and treated; preferably they should be diagnosed and treated at an early stage, before they have been able to transmit the disease to others. Thus health care services that are accessible, affordable and permanently available are a prerequisite. If transmission of the disease involves a vector, vector control may further reinforce disease control measures.

In this thesis I will focus on the different aspects of control of the three diseases: prevention, case detection and treatment, and surveillance. This requires consideration not only of the epidemiology and clinical presentation of disease but also of the social and health care system contexts. For West African HAT the focus will be on the DRC, the most endemic country; for visceral leishmaniasis the focus will be on Bihar, India, the state from which the bulk of visceral leishmaniasis cases caused by *Leishmania donovani* originate. For tuberculosis the focus will be on Uzbekistan, a low income former Soviet country with a moderately high incidence of tuberculosis. For each of the three diseases the main research focus is on improving disease control taking into account the existing health care system and limited resources available. We studied healthcare seeking behavior and the way the health systems manage suspect cases and patients; for visceral leishmaniasis we also studied risk factors as a way to identify potential preventive measures or target control measures.

**Tuberculosis in Uzbekistan**

Tuberculosis is caused by infection with mycobacteria belonging to the *Mycobacterium tuberculosis* complex, which includes the pathogenic species *M. tuberculosis*, *M. bovis* and *M. africanum*. The species most commonly affecting humans, and of which humans are also the main reservoir, is *M. tuberculosis*. Transmission of *M. tuberculosis* is directly from man to man through inhalation of infectious droplets. The main sources of infection are tuberculosis patients with concentrations of bacilli in their sputum high enough to be detected by direct smear microscopy. These patients, known as sputum smear-positive tuberculosis patients, disseminate infectious droplets when coughing. Of all those infected with *M. tuberculosis*, only an estimated 10% go on to develop clinical disease; about 50% of those tuberculosis patients will be sputum smear-positive cases. WHO estimates that during 2008 worldwide 9.4 million new cases of tuberculosis disease occurred and 1.8 million died from the disease. A vaccine for tuberculosis, Bacille de Calmette Guérin (BCG), has been available since 1921. However BCG does not prevent infection and is not very effective at preventing the infectious forms of the disease.

Until anti-tuberculosis drugs became available, the only effective tuberculosis public health measure was to isolate infectious tuberculosis patients in sanatoria. They were to remain on admission until they were cured spontaneously or until they died. With the advent in the 1950s of effective anti-tuberculosis drugs, early case finding and treatment have become the mainstay of tuberculosis control. Approaches to ensure early case detection have changed over the years. Whereas in the 1960s mass population screening by X-ray was widely practiced, this practice was abandoned in most countries in the 1970s in response to the results from studies in
Czechoslovakia, Canada and the Netherlands which showed that the yield of active case finding was very low. Most patients presented themselves to the health services at their own initiative because of symptoms arising in between two screening rounds.\textsuperscript{13,14,15,16} In the countries of the Soviet Union the practice of active case finding by mass X-ray screening was continued.

The first anti-tuberculosis drugs became available in the mid 1940s and early 1950s. Tuberculosis patients were still admitted to sanatoria but now for the first time they could effectively be treated.\textsuperscript{11} Soon it became apparent that when patients are treated with a single anti-tuberculosis drug, resistance to this drug develops. Preliminary results of a trial published in 1949 showed that development of resistance could be prevented by using combinations of two or more drugs.\textsuperscript{17} Resistance to anti-tuberculosis drugs was shown to be the result of selection of resistant mutants; this can be prevented by combining drugs since the probability of a tubercle bacillus being resistant to several drugs at the same time is very small. Combined treatment regimens thus became one of the axioms of tuberculosis treatment. A course of anti-tuberculosis treatment in those days took 18-24 months. With the advent of rifampicin as an anti-tuberculosis drug in the mid 1960s and the rediscovery of pyrazinamide, shorter regimens could be devised. In the meantime a study from Madras in India had shown that even under very poor socio economic conditions; results of home based treatment were not inferior to results of hospital based treatment.\textsuperscript{18} There was also no increase in the proportion of close contacts being infected when a patient was treated at home; those household contacts infected were apparently already infected by the time the index case was diagnosed. In most countries this led to the adoption of ambulatory treatment for tuberculosis and the closure of sanatoria; in the Soviet Union however in-patient treatment remained the standard.

Control of tuberculosis became very much standardized worldwide when the World Health Organization launched the DOTS strategy in 1995.\textsuperscript{19} The strategy encompasses 5 key components:

1. Sustained political commitment
2. Access to quality-assured sputum microscopy
3. Standardized short-course chemotherapy for all cases of tuberculosis under proper case management conditions, including direct observation of treatment
4. Uninterrupted supply of quality-assured drugs
5. Recording and reporting system enabling outcome assessment of all patients and assessment of overall program performance.

Under the DOTS strategy, case finding, diagnosis and treatment of tuberculosis are integrated into general health care services. Key elements are the focus on smear microscopy for diagnosis and the standardization of treatment regimens. Case finding is based on screening by sputum smear microscopy of suspect cases presenting themselves to the health services at their own initiative. Treatment regimens are not only standardized but are also provided preferably on an ambulatory basis. To prevent irregular treatment and thus protect the key drug, rifampicin, treatment is provided under direct supervision of a health worker. Treatment outcomes are closely monitored using a standardized recording and reporting system. Though the DOTS strategy was successfully implemented in many countries, it met with a lot of skepticism and reluctance in most countries of the former Soviet Union.\textsuperscript{20}
Chapter 1. General Introduction

About a decade after the inception of the DOTS strategy major progress in global tuberculosis control had been made. However it also became clear that the DOTS strategy alone was insufficient to achieve the targets set by the World Health Assembly at the start of the new millennium, i.e. a 50% reduction in tuberculosis mortality and prevalence by 2015 as compared to the 1990 levels. The rapid rise in tuberculosis cases as a result of the HIV-epidemic in sub-Saharan Africa and the major increase in incidence and prevalence of multi-drug resistant tuberculosis associated with the socio-economic crisis that followed the dismantling of the Soviet Union in the early 1990s presented new challenges. Moreover the DOTS implementation depended to a large extent on existing public health systems; as it turned out these health services were often very weak and in need of strengthening. In many countries a substantial part of tuberculosis patients were missed by the DOTS strategy because they were diagnosed and treated in the private sector. Though successful, the DOTS strategy has been criticized as rather paternalistic because of the emphasis on supervised treatment. There was an obvious need to better take into account the point of view of patients and communities affected. Finally there was a clear need for more research, in particular related to diagnostic tests and drugs. When programs were confronted with multi-drug resistant tuberculosis and tuberculosis-HIV co-infection, the need for rapid and sensitive diagnostic tests became more prominent; the increase in multi-drug resistant tuberculosis also necessitated development of new drugs. Taking into account all these new challenges, the ‘Stop TB strategy’ was launched in 2006. The six pillars of the strategy are:

1. Pursue high-quality DOTS expansion and enhancement
2. Address tuberculosis/HIV and multi drug resistant tuberculosis and other special challenges
3. Contribute to health system strengthening
4. Engage all care providers
5. Empower people with tuberculosis and communities
6. Enable and promote research

Although globally there is a unified tuberculosis control strategy, the challenges presented vary widely between different settings. Former Soviet countries traditionally have a very different approach, including elements such as active case finding, diagnosis based on radiography and individualized hospital based treatment. These policies are now being revised in most of these countries but efforts to reform the system often meet with considerable resistance.

The general healthcare system which Uzbekistan inherited upon independence in 1991 was the Soviet Semashko model. This system provided all its citizens with free health care at the point of delivery. In rural areas there was a 4-tiered system with feldsher’ midwifery points (Feldshersky Akushersky Punkt [FAP]) as lowest level, the rural physician ambulatory (Selskaya Vrachebnaya Ambulatoriya [SVA]) as next level, followed by the rural hospital, and with the central district hospital at the top of the pyramid. FAPs served populations of 600-3000 and were staffed by paramedical workers, at SVA level there was usually an internal medicine specialist,

\* A midlevel health worker in rural areas of the (former) Soviet Union
a pediatrician, an obstetrician and a dentist. In urban areas first line healthcare was provided by policlinics, staffed by specialists in internal medicine, pediatricians and other specialists. There were different types of policlinics, e.g. for adults, for children, and for women’s health. Those policlinics were equipped with highly specialized diagnostic and treatment facilities. There were also many hospitals and in-patient care was considered superior to outpatient care irrespective of the clinical condition. In 1994, 64% of all physicians in Uzbekistan were working in hospitals. The most striking feature of the whole set-up, in rural as well as urban areas, was the virtual non-existence of general practitioners.

The Uzbek healthcare system is gradually being reformed, starting with pilots in rural districts of three out of 14 provinces in 1998. Two more provinces were included in the reforms in 2002. In these districts a 2-tier system has been introduced consisting of rural physician points (Selsky Vrachebny Punkt [SVP]) and a central district hospital. SVPs are first line facilities, run by general practitioners. FAPs and SVAs have been phased out and replaced by SVPs. More recently the reforms have been extended to urban policlinics which have been transformed into family policlinics, run by general practitioners and providing care for all groups of the population.

The tuberculosis control system of the Soviet Union was a fully vertical system. The whole population was screened by X-ray or fluorography once yearly; those found to be suffering from tuberculosis were treated as in-patients in specialized hospitals and sanatoria. Treatment regimens were individualized. Upon completion of treatment patients were kept under continued observation for at least 3 years or as long as cavities remained visible on X-rays. During this period additional anti-tuberculosis treatment courses were prescribed in spring and autumn. As long as the patient was admitted and/or not able to work; (s)he was provided with an income substitution. Treatment and hospitalization were entirely free of charge.

This was the tuberculosis control system that Uzbekistan inherited when the Soviet Union fell apart in 1991. Due to economic difficulties during the years following independence, the system could no longer be maintained; at the same time there was a steep increase in tuberculosis case notification rates from the early 1990s. Faced with this situation, Uzbekistan decided to reform its tuberculosis control system according to the principles of the internationally recommended DOTS strategy. Under the new system, case finding is mainly passive and decentralized to general health facilities. Treatment regimens have been standardized. New patients are treated for 6 months; patients with a history of previous treatment are treated for 8 months. Patients are still admitted to specialized hospitals but only for the first 2-3 months, the so-called intensive phase. For the remaining 4-5 months, treatment is provided on an outpatient basis, drugs are provided three times weekly under supervision of a health worker from specially designated rooms in general policlinics (DOTS corners). The reforms were implemented in a phased manner; by 2005 all districts of Uzbekistan had been covered.

Although the DOTS strategy is now officially implemented in all districts of Uzbekistan, many elements of the former system are still in place. These include annual chest X-ray screening of a large part of the population and mandatory hospitalization during the first 2-3 months of treatment. Also the practice of keeping
patients on register after completion of treatment and prescribing additional treatment courses in spring and autumn has been maintained. This is the result of compromises that were necessary to overcome initial resistance to the DOTS strategy from tuberculosis specialists. A national tuberculosis program was created, directly answerable to the minister of health, under the name ‘DOTS Center’.\textsuperscript{32} Traditionally policies in tuberculosis control were decided upon by the National Research Institute for Pulmonology and Phthisiatry (NRIPP). When DOTS Center was created, the two structures continued to exist in parallel and as a result there is still no uniform national tuberculosis policy as both institutions issue their own specific guidelines. Over the years DOTS Center has become firmly established and has been the principle recipient of two grants from the Global Fund to fight Aids, Tuberculosis and Malaria. These grants provide a substantial part of the running costs for tuberculosis control in Uzbekistan. While the second grant is currently only in its first phase, the first grant has been very successfully implemented.\textsuperscript{33}

The studies on tuberculosis included in this thesis relate to the specific context of Uzbekistan. The fact that two systems of tuberculosis control exist in parallel has resulted in a number of inconsistencies in policies and practices related to case finding and treatment. These inconsistencies are causing confusion among patients as well as staff. Our studies on tuberculosis explored case finding, prescribing practices and problems related to adherence to treatment with the aim of informing policy reform.

**Visceral Leishmaniasis in India**

*Visceral leishmaniasis*, also known as *Kala-azar* is a vector-borne parasitic disease which is nearly always fatal if left untreated.\textsuperscript{34,35} Protozoa of the *leishmania* complex cause an obligate intra-macrophage infection. The clinical syndrome is characterized by fever, weight loss, splenomegaly, hepatomegaly, and anemia, but, as in tuberculosis, only a fraction of those infected develop clinical disease.\textsuperscript{36} Though visceral leishmaniasis is endemic in over 60 countries, 90% of all reported cases occur in just 6 countries: Bangladesh, Brazil, Ethiopia, India, Nepal and Sudan.\textsuperscript{9} The disease is transmitted through the bite of an infected phlebotomine sandfly. The host reservoir is different in different parts of the world, reflecting a difference in parasite strains. Whereas in Europe and Latin America the causative organism is *Leishmania infantum*, which has the domestic dog as its main reservoir, on the Indian subcontinent (Bangladesh, India, Nepal) the causative organism is *Leishmania donovani*, which is essentially a parasite of humans.\textsuperscript{8} A skin condition, called post-*kala azar dermal leishmaniasis* (PKDL), can occur after a patient has been treated for and apparently cured from visceral leishmaniasis. PKDL is not a serious clinical condition but PKDL patients are very infectious and may form a reservoir of the parasite.\textsuperscript{37}

Parasitological confirmation remains the reference standard for diagnosis but is not very sensitive unless a spleen puncture is performed. Because this is a risky procedure, several serological tests have been developed. Some of these tests are highly sensitive and have a high positive predictive value when used in endemic areas among clinical visceral leishmaniasis suspects. One test format in particular, the rK-39 dipstick, has proven very useful under field conditions.\textsuperscript{38,39} Though these serological tests do have a high positive predictive value when used in a population
Chapter 1. General Introduction

of clinical visceral leishmaniasis suspects, substantial proportions of asymptomatic persons in endemic areas will also test positive. This is assumed to be a reflection of the existence of sub clinical infections; it is unclear which proportions of these sub clinical infections progress to clinical infections.\textsuperscript{36,40}

A number of new treatments have become available since 1990; at that time the only treatment in use was 20 to 28 days of daily injections of pentavalent antimony. Pentavalent antimony is still widely used but there have been several reports of high rates of resistance to the drug from Bihar, India.\textsuperscript{41} Three additional, highly effective parenteral drugs are now available: amphotericin B, lipid formulations of amphotericin B and aminosidine (paromomycin).\textsuperscript{42} More recently an oral drug, miltefosine, has been added to the armamentarium.\textsuperscript{43}

On the Indian subcontinent the estimated population at risk for visceral leishmaniasis is around 200 million, the estimated annual incidence about 420,000. The disease affects mainly poor rural communities; 50% of all reported cases are from the state of Bihar in India\textsuperscript{44}. As a result of intensive dichlorodiphenyltrichloroethane (DDT) spraying during the malaria eradication campaigns of the 1950s and 1960s, the reported incidence of visceral leishmaniasis on the Indian subcontinent decreased to zero levels. However a few years after the spraying campaigns were abandoned there was a strong resurgence, starting in the state of Bihar in the 1970s and peaking in the 1990s.\textsuperscript{34} Though vector control can apparently be effectively used to control visceral leishmaniasis, resistance to DDT and the high cost of alternatives such as pyrethroid insecticides pose challenges. Bearing this in mind; the governments of Nepal, India and Bangladesh developed a ‘Regional strategic framework for elimination of Kala-azar from the South-East Asia region’ which envisions five main strategies:

1. Early diagnosis and complete case management
2. Integrated vector management and vector surveillance
3. Effective disease surveillance through passive and active case detection and vector surveillance
4. Social mobilization and building partnerships
5. Clinical and operational research

To achieve early diagnosis and complete case management, rK-39 dipstick tests are to be made available in all public health facilities in endemic areas. Treatment regimen of choice is miltefosine, an oral drug. Treatment is provided preferably under direct supervision of a health worker. Amphotericin B and lipid formulations of amphotericin B are kept as 2\textsuperscript{nd} line treatment; aminosidine is a possible alternative.\textsuperscript{45}

The mainstay of vector management is indoor residual insecticide spraying. In India DDT is the insecticide of choice even though there have been a number of reports about DDT resistance in sandflies\textsuperscript{46}. To ensure efficient use of insecticide, areas of high transmission are to be determined. Insecticide treated bednets are the second component of the vector management strategy. The sandfly vector on the Indian subcontinent, \textit{Phlebotomus argentipes}, prefers to feed around midnight. Several observational studies have shown a protective effect of bednet use against visceral leishmaniasis however a recent intervention trial in the region was inconclusive (A.Picado, personal communication).\textsuperscript{38,47}
Chapter 1. General Introduction

The remaining three components of the strategy, disease surveillance, social mobilization and research are mainly aimed at supporting the first two components. Disease surveillance includes surveillance of PKDL because of the role of PKDL patients as a reservoir of the parasite. Social mobilization is important to reduce patient’s delay, to promote adherence to treatment and to generate support for vector control activities. The main research objectives are the identification of additional drugs and diagnostics and monitoring of drug resistance. Identifying an appropriate treatment regimen for PKDL is an important aspect.

The health care system in India is a classical district health system, though the term ‘district’ can be misleading as an Indian district with a population size averaging 2 to 3 million is comparable to a province/region in other countries. The equivalent of the ‘health district’ in those other countries is called a ‘block’ in India, with an average population size of around 200,000 to 300,000. Since visceral leishmaniasis in India is a disease of rural areas, I will focus here on the rural health care system. Primary health care in rural blocks of India has been organized as a 3-tier system. At the top of the pyramid is the Community Health Center, in theory catering for a block population of 120,000. This Community Health Center is staffed with physicians and has a limited number of beds; the next level of referral is the district hospital. By design each Community Health Center should support 4 Primary Health Centers. The Primary Health Center is the lowest level of the system at which physicians are available. A primary health center in its turn supports 6 Health Sub-centers, run by auxiliary nurses/ midwives (ANM). In addition, at village level there are volunteer outreach workers known as ‘accredited social health activists’ or ASHA’s. They are supervised by the ANMs and constitute the link between the community and the health system. The system is well organized with all ASHA’s attending meetings at the Community Health Center once every four weeks; ANMs meet twice a month. Though according to the norms there should be one Community Health Center per 120,000 population and one Primary Health Center per 30,000 population, the actual population numbers to cover are much higher. The rural areas of Muzaffarpur district in Bihar State in which we conducted our studies have a population of almost four million but altogether there are only 14 Community Health Centers and 4 Primary Health Centers (S.P. Singh, personal communication).

In addition to the public system there is a substantial network of private practitioners, both qualified and unqualified. In the private sector as well as in the public sector, different traditions of medicine co-exist. Apart from classical allopathic medicine, there are also the ancient Indian systems such as Ayurveda, Siddha, Unani and homeopathy. These systems of alternative medicine have officially been recognized, including training and certification of providers.

In endemic areas, diagnosis and treatment of visceral leishmaniasis are available at Community Health Center level. Case finding is passive; any patient with a history of fever of more than 2 weeks, not responding to anti-malarials, has to be subjected to an rK-39 dipstick test according to instructions of the VL elimination program. Those testing positive receive free treatment, provided on an out-patient basis. Outreach workers are not systematically involved in case finding and treatment.

In this thesis we explored health care seeking behavior and treatment outcomes for visceral leishmaniasis under routine conditions in government primary healthcare
facilities in Bihar State. We also examined factors associated with transmission of visceral leishmaniasis as such information can be used to mitigate risk either directly by addressing risk factors or indirectly though improved targeting of indoor residual insecticide spraying.

**Human African Trypanosomiasis in the Democratic Republic of the Congo**

West African HAT, caused by the parasite *Trypanosoma brucei gambiense*, is transmitted by tsetse flies in a man-fly-man cycle. Unlike East African HAT, caused by *Trypanosoma brucei rhodesiense*, which has cattle and some wild animals as a reservoir, West African HAT is essentially a disease of humans. In the absence of appropriate treatment, HAT infection inevitably leads to death. West African HAT has two stages, the hemolymphatic stage with no or few specific symptoms, followed by the meningoencephalitic stage when the causative parasite has crossed the blood/brain barrier. The second stage is characterized by neurological signs and personality changes. Damage to the hypothalamus may lead to disturbance of the normal sleep pattern which has led to the disease being called ‘sleeping sickness’.

About 60% of all cases of West African HAT reported worldwide are from the DRC, which has seen a surge in cases during the second half of the 1990s. The highest peak was observed in 1998, when 26,318 cases were reported; by 2008 the reported annual incidence was down to 7,326 cases. (Un-published data, Programme Nationale de Lutte contre la Trypanosomiase Humaine Africaine)

In diagnosis of HAT there are three steps, screening, confirmation tests and staging. Screening is mostly done on the basis of a serological test called the card agglutination test for trypanosomiasis (CATT). The CATT test is a test on capillary blood that can easily be performed under field conditions but does require a cold chain. It has a specificity of around 95% and a sensitivity ranging from 87-98%. The CATT test can also be performed on blood samples collected on filter paper. A few alternative screening tests exist, some of which can also be performed on samples collected on filter paper. These include micro-CATT, LATEX/*T.b.gambiense* and ELISA/*T.b.gambiense*.

Individuals testing positive on screening tests are subjected to a number of parasitological confirmation tests. The routine confirmation tests used are microscopic examination of a lymph node aspirate and the thick blood film. A wet preparation from a lymph node aspirate is examined at a magnification of 400x to identify the presence of motile Trypanosomes. In thick film examination, 20 µl of stained blood is examined for the presence of Trypanosomes at 1000x magnification; the technique is basically the same as used for diagnosis of malaria. Both methods are highly specific but have poor sensitivity; Miézan et al estimate their combined sensitivity at 70% but Lutumba et al estimate it much lower (44.8 %, 95% CI 36.8–53.0). To overcome the problem of low sensitivity, a number of concentration techniques have been developed. These include the capillary tube centrifugation test (CTC), the quantitative buffy coat (QBC) and the mini-anion-exchange centrifugation technique (mAECT). The first two methods are based on concentration of trypanosomes through centrifugation; mAECT is based on anion exchange chromatography to separate the trypanosomes, which are less negatively charged than blood cells, from venous blood. In all three techniques the final product
is examined by microscopy; in QBC trypanosomes are stained with acridine orange and examined in a dark room under ultraviolet illumination, in CTC and mAECT, tubes are examined directly at low magnification. These techniques are more sensitive but still far from perfect, reported sensitivity estimates range from 95% for QBC to 56.5% (95% CI 48.3–64.5%) for CTC and 75.3% (95% CI 67.7–81.9%) for mAECT. Though they are more sensitive than the traditional confirmation tests, the technical requirements have been an obstacle to their routine use under field conditions. Production of the QBC test kit has been interrupted.

Once the causative micro organism has been demonstrated, staging of the disease is the next step. This requires a lumbar puncture because of the need to examine cerebrospinal fluid. Cerebrospinal fluid is examined for the presence of trypanosomes or a raised white blood cell count. If either of the two is present, the patient is assumed to be in the meningo-encephalitic stage. Staging is necessary because the treatment for the meningo-encephalitic stage is different from the treatment of the hemolymphatic stage and is highly toxic.

In the hemolymphatic stage, West African HAT is treated with daily intramuscular injections of pentamidine for 1 week. In the meningo-encephalitic stage the traditional treatment is with melarsoprol, a trivalent arsenic compound. It is given by slow intravenous injection either over a period of 10 consecutive days, or in 3-4 series spread out of over one month. The most serious side effect associated with melarsoprol is encephalopathy, which usually manifests itself during treatment as a sudden violent neurological deterioration. Lethal forms of encephalopathy can be expected in 3-5% of cases treated. Apart from these obvious toxicity problems, treatment with melarsoprol has also been shown to have high failure and relapse rates. More recently some less toxic treatments have become available. Di-fluoro-methyl-ornithine (DFMO) was first used for trypanosomiasis in 1985. The drug is administered by intravenous infusion four times a day for two weeks. During a trial that started in 2003, a combination of DFMO and nifurtimox (NECT) has been shown to be very effective and far less toxic than melarsoprol. The NECT schedule consists of twice daily administration of DFMO by intravenous infusion for 7 days, combined with daily oral administration of nifurtimox for 10 days. Though NECT has now been adopted as the first line treatment by most HAT control programs, including that of the DRC, melarsoprol is still widely used. Due to limited availability of nifurtimox, the actual choice is between melarsoprol administered once daily and DFMO administered four times daily. Health workers often opt for melarsoprol because it is less labor intensive to administer. Moreover melarsoprol treatment kits are less bulky, which is an important advantage in a country where paved roads are almost non-existent.

The backbone of HAT control remains active screening of the population at risk combined with free treatment for all cases identified. The aim is to achieve a reduction of transmission by eliminating the parasite from the human reservoir. Historically a number of West African HAT foci have been brought under control this way. Active case finding for HAT in the DRC is based on mobile teams visiting endemic villages and screening the entire population using the CATT test. Those testing positive are subjected to confirmation tests on the spot. Cases identified undergo a lumbar puncture for disease staging; they are then referred to fixed facilities for treatment. Difficulties in securing sufficient participation in the population
screening sessions, and the deficient sensitivity of screening algorithms, especially when it comes to the confirmation tests used, appear to be the main bottlenecks.\textsuperscript{63,71}

Vector control is another option, it can be based on area wide measures which include aerial spraying and sterile insect technique, or more localized measures such as the use of traps.\textsuperscript{72,73,74} Though vector control yielded good results in research settings, doubts remain about its feasibility and sustainability; it is expensive and requires active cooperation from the local population.

In 2001 the Pan African Tsetse and Trypanosomosis Eradication Campaign (PATTEC) was launched by the Organization of African Unity. The campaign aims at eradicating the disease as well as the \textit{Tse Tse} fly vector from the African continent.\textsuperscript{75} The regional committee of WHO in 2005 formulated a strategy with the aim of reducing the morbidity and mortality attributed to sleeping sickness in the African Region.\textsuperscript{76} By 2015, prevalence rates in all endemic areas should be below 1 per 10,000. Priority interventions include mapping disease distribution, case detection and treatment, setting up a surveillance system, and vector control. In the WHO strategy vector control is limited to areas of high transmission and based on trapping of \textit{Tse Tse} flies.

The history of \textit{HAT} in the DRC has been a vicious cycle of increasing prevalence, control measures being implemented, decreasing prevalence, control measures being neglected and again increasing prevalence. At the end of the colonial era in 1960 the disease was under control but gradually reemerged when control measures were abandoned. During the early 1990s control measures were completely and abruptly interrupted, resulting in a major resurgence going unnoticed for a long period; by the end of the 20\textsuperscript{th} century the reported incidence levels were almost back to those of the late 1920s and early 1930s (figure 4).

![Figure 4 Evolution in reported incidence of HAT in the DRC from 1926-2009](image)

When after 1998 control measures were restarted and intensified, the disease was rapidly brought under control again in most provinces affected. However, active case finding undertaken annually for more than 10 years did not bring the \textit{HAT} epidemic under control so far in two provinces, Bandundu and Kasai; those provinces now account for more than half the cases reported annually worldwide.\textsuperscript{77} Moreover recent
surveys conducted in areas where accessibility is problematic either due to remoteness or to conflict have revealed prevalence rates of 3% and above.\textsuperscript{78}

Once HAT prevalence is somewhat reduced, effectiveness and cost-effectiveness of active case finding becomes problematic. Participation rates in active screening drop because people no longer consider HAT a threat, at the same time the costs per case detected rise dramatically.\textsuperscript{63,71} Taking into account these constraints, the national HAT control programme, also known as Programme Nationale de Lutte contre la Trypanosomiase Humaine Africaine (PNLTHA) and its main donor, the Belgian Technical Cooperation, formulated a strategy in which integration of HAT control in the district health system is one of the key components.\textsuperscript{79} However it has been observed that patients presenting themselves to the health services at their own initiative are often misdiagnosed. This resulted in an average health systems delay of more than one year among 14 patients interviewed in Kinshasa in 2007 (Ehomba 2007, unpublished data).

The current health care system in the DRC was designed in 1984 and reformed in 2001. Its design was based on the Alma Ata declaration; the system aims at providing global, integrated and continuous care, with participation of the community.\textsuperscript{80} In the DRC the health district is called ‘zone de santé’; altogether there are 515 zones, with an average population of just above 120,000. In each zone there is a ‘general referral hospital’, run by the zonal health coordinator, who is a medical doctor. Each zonal health coordinator supervises a network of 5 or more health centres, run by nurses. Utilization rates of health care services are typically low with an estimated 0.15 consultations per inhabitant per year. In addition to the public system, a myriad of qualified and mostly unqualified private practitioners exists.

There are no less than 53 vertical disease control programs in the DRC, each having its own director. One of these programmes is the HAT control programme, the PNLTHA. The PNLTHA has its own staff and infrastructure; only recently the first steps towards integration of HAT case finding and treatment have been initiated. Case finding is traditionally active, involving mobile screening teams. Cases identified by mobile screening teams are referred for treatment to fixed facilities. Whereas previously these fixed facilities were also specialized HAT facilities, they have now been converted into general health centers. Increasingly HAT diagnostic and treatment services are also provided from other general health centers and hospitals.

In this thesis we focused on options for integration of HAT control in the DRC into the district health system and on how to keep HAT under control once the prevalence has been reduced. We validated a HAT screening test designed for use in peripheral health facilities and we explored alternative surveillance mechanisms.

**Outline of this thesis**

The remainder of this thesis is subdivided into three sections, one on each disease, followed by a general discussion. In section 1, made up of chapters 2-5, we present studies on tuberculosis in Uzbekistan. Chapter 2 presents an investigation into the yield of active case finding in two provinces of the country. Chapter 3 describes prescribing practices for tuberculosis in Uzbekistan. Chapters 4 and 5 describe the
problem of defaulting from tuberculosis treatment in Tashkent, the capital of Uzbekistan, using a quantitative and a qualitative approach, respectively.

Section 2 includes studies on visceral leishmaniasis in the endemic state of Bihar, India. Chapter 6 describes the management of visceral leishmaniasis in the primary health care system in a district of Bihar; chapter 7 explores risk factors associated with visceral leishmaniasis in a rural area of the same district.

Section 3 includes studies on human African trypanosomiasis in the Democratic Republic of the Congo. Chapter 8 describes the validation of a new format of a serological screening test for HAT, designed for use in peripheral primary health facilities. Chapter 9 presents an alternative method of HAT surveillance, designed in particular to continue monitoring endemic foci once the disease has been brought under control.

In Chapter 10 follows a general discussion of the studies included in this thesis.

References

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Chapter 1. General Introduction


Chapter 1. General Introduction


