Control of chronic infectious diseases in low resource settings

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In this thesis we examined how management of the three diseases could be further improved in three different settings. We have seen that for all three diseases and in all three settings a well functioning health system is of crucial importance, and we have identified ways to improve the synergies between disease control programs and general healthcare systems.

Tuberculosis in Uzbekistan

Though the DOTS strategy has been implemented in all districts of Uzbekistan since 2005, elements of the old Soviet system continue to exist in parallel. The Soviet approach to tuberculosis control was very much disease control oriented, which is understandable from a historic point of view. ‘Either the louse defeats socialism or the socialism defeats the louse’, Lenin stated in 1919. In those days the Soviet Union was emerging from the ruins of World War I and still engaged in a civil war; at the same time it was plagued by major epidemics. The epidemics were controlled and until the late 1960s great progress was made. The Soviet Union has to be credited for providing universal free access to primary healthcare services to all its citizens all over its vast territory. Much of these achievements is still in evidence today. Whereas for 2006 neighboring Afghanistan had an estimated under-five mortality rate of 235/1000 live births, for Uzbekistan the figure was 44/1000. Yet, starting in the 1970s, stagnation occurred and basic health indicators began to deteriorate. Already during the final years of the Soviet Union, hospitals were in a dilapidated state and there was lack of pharmaceuticals and medical equipment. Not only infrastructure became outdated, the knowledge and skills of providers also suffered. The gap between Soviet medicine and medicine in the western world became more pronounced with the advent of evidence based medicine; a new development to which the Soviet Union was neither willing nor, because of linguistic barriers, able to respond.

We conducted four studies on the management of tuberculosis in the healthcare system of Uzbekistan; one study on case finding, one study on prescribing practices and two studies on adherence to treatment. The current tuberculosis control system in Uzbekistan is based on the Stop TB strategy but still contains many elements of the old Soviet system. One of the elements of the old Soviet system still in place is active case finding based on mass X-ray screening. Annually in Uzbekistan over 3 million people are actively screened for tuberculosis but we found that such screening is poorly targeted. Although the official figures suggest otherwise, our study showed that the yield of active screening for tuberculosis in Uzbekistan is no higher than that reported in studies from Canada, Czechoslovakia and the Netherlands which led these countries to abandon mass radiography as a case finding tool.

Treatment for tuberculosis in Uzbekistan has traditionally been the domain of specialist physicians, who were prescribing individualized treatment regimens. The Stop TB strategy advocates standardized regimens, depending primarily on whether or not there is a history of previous treatment. Determining whether or not a patient has been treated before and prescribing a standard regimen to those without a
history of previous treatment does not require specialist knowledge. 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, apart from specific anti tuberculosis drugs, patients are also being prescribed a median of eight non-anti tuberculosis drugs. This is another remnant of the Soviet tradition where so-called ‘pathogenetic treatment’ was considered an essential component of tuberculosis treatment.\(^9\) We found that the rationale for prescribing these non-specific drugs is questionable. There is no apparent relation to concomitant diseases, some of the drugs prescribed are potentially dangerous and patients incur substantial costs when purchasing these drugs.

Our studies on adherence to treatment in the Uzbek capital Tashkent revealed various obstacles, most related to the healthcare system, at times in interaction with personal factors. In a quantitative study 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 were more at risk than others. Another notable finding was the fact that one third of defaulters did not really abandon treatment but rather abandoned the system under which treatment is provided. They did continue some form of treatment but preferred to pay for their drugs and organize treatment at their own convenience, rather than to receive drugs for free under program conditions.

In a subsequent qualitative study we found that 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. Though 75% of defaulters had been on treatment for at least 50 days, mainly as in-patients, they were poorly informed. Many did not know that tuberculosis is curable and for how long they were supposed to be treated. Also there were lots of irrational beliefs about side effects of tuberculosis treatment. Communication between patients and doctors is still very much underdeveloped in Uzbekistan; moreover there are conflicting patient management guidelines because of the Stop TB strategy being implemented in parallel with remnants of the old Soviet system. Fear of being stigmatized was 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 opportunity costs related to it. Under the present economic circumstances in Uzbekistan, pensioners and unemployed need to engage in informal daily labor to make ends meet. Only those employed by the government will not loose their income while on admission. As we also saw in our study on prescribing practices, being on admission in a tuberculosis hospital has substantial direct costs as well.

Based on our findings, some concrete recommendations can be made to improve the tuberculosis control system in Uzbekistan. Screening over three million persons a year by mass radiography is not a cost-effective strategy. The findings in studies from Canada, Czechoslovakia and the Netherlands led to the recommendation in the ninth report of the WHO expert committee on tuberculosis that the policy of indiscriminate
tuberculosis case-finding by mobile mass radiography should now be abandoned.\(^8\) This does not mean that radiography no longer has a role to play in screening or individual case management; it just means that blanket population screening is ineffective and has a too high opportunity cost. Under the current policy more than half of the population of Uzbekistan is eligible for X-ray screening. The program policy of assigning targets on the actual numbers of people to be screened, results in arbitrary screening of those that are easiest to reach. Restricting screening efforts to known high risk groups such as contacts of tuberculosis patients, people living with HIV, and inmates of prisons and pre-trial detention centers could be much more effective and far less costly.\(^10\)

Irrational prescribing practices that became apparent in our second study have been reported also from the general health services in Uzbekistan\(^11\). Such practices will be difficult to correct since linguistic barriers and the absence of a tradition of evidence-based medicine prevent doctors from accessing the mainly English language peer-reviewed medical literature. A recent Russian-language textbook on tuberculosis, published in 2004 and written by the leading specialist of the Russian Federation, still advocates pathogenetic treatment but does not provide any references to evidence in favor of this approach.\(^12\) The quickest way to achieve a change in prescribing practices for tuberculosis would be for the management of the national tuberculosis control program (DOTS Center) to provide clear guidelines on rational prescription of additional non-tuberculosis drugs. Unfortunately such efforts are bound to meet with much resistance from the National Research Institute for Pulmonology and Phthisiatry (NRIPP), the management of which still adheres to the Russian tradition.

The adherence studies highlighted the need for a much more client-oriented approach to tuberculosis control. The system is still too much focused on disease control; a tuberculosis patient is seen as a potential source of infection and therefore needs to be isolated in a tuberculosis hospital. Under the current conditions of economic hardship in Uzbekistan, with a large proportion of the population living below the poverty line, tuberculosis patients cannot afford to be hospitalized and the system cannot afford to properly maintain tuberculosis hospitals.\(^13\) Moreover it has been shown that infection of contacts usually occurs before patients are diagnosed and started on treatment.\(^14\) A further shift towards ambulatory treatment seems a logical step.

There has been some degree of integration of tuberculosis control into general primary healthcare services but more is required. In their study on effectiveness of integration into health systems of targeted interventions, Atun et al. describe 5 critical health system functions: ‘Stewardship and governance’, ‘Financing’, ‘Service delivery’, ‘Monitoring and evaluation’ and ‘Demand generation’; demand generation includes advocacy and social mobilization.\(^15\) Although in Uzbekistan service delivery for tuberculosis has been integrated to some extent, patients are still confronted with two different sets of service providers. Part of their treatment is provided by the tuberculosis system; part of it is provided by the general primary healthcare system. Within the general primary healthcare system, tuberculosis patients are set apart from other patients and meet with reluctance of health care providers. The problem of fragmentation of service delivery could be overcome if the tuberculosis program would progressively restrict its role to the other core functions i.e. ‘stewardship and governance’, ‘financing’, ‘monitoring and evaluation’ and ‘demand generation’, and
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leave routine service delivery in the hands of the general primary healthcare system. Experience from all over the world has shown that routine tuberculosis treatment according to standardized guidelines does not require specialist doctors. Organizing treatment services within the primary health care system is therefore part of the key operations for DOTS implementation advocated by WHO. There will still be a role though for specialists in diagnosing and treating complicated cases, such as cases of multi drug resistant tuberculosis.

Another important obstacle to adherence that became apparent from the studies is the inadequate communication between providers and patients. In the Soviet era the medical profession generally assumed a rather parental role towards its patients and did not see the need to inform patients on their condition, its prognosis and treatment. Patient centeredness is a relatively recent invention and came at a time when the Soviet medical system was already in decline. Current provider attitudes will not change overnight but designing standard sets of messages to be communicated to patients and assigning the task of communicating these messages to certain categories of health workers may help to bridge the gap. Obviously this is still far removed from the shift from a paternalistic biomedical model to a model of shared decision-making advocated by Vermeire et al.

Resistance from the established order is a well documented obstacle to reforms in tuberculosis control in former Soviet countries and is further compounded by the absence of a tradition of evidence based medicine. Much more progress could be achieved if the Uzbek health authorities would further reform the governance structures for tuberculosis control, i.e. further reinforcing DOTS Center in its role of National Tuberculosis Program. When DOTS was first introduced, creating a parallel management structure involving both DOTS Center and NRIPP was a necessary compromise. In the meantime DOTS Center has a proven track record by developing policies that are fully in line with the Stop TB strategy and successfully managing the implementation of two grants from the Global Fund to combat AIDS, Tuberculosis and Malaria, which provide a substantial part of the running costs for tuberculosis control in Uzbekistan. Time has come to abandon the dual management structure and limit the role of NRIPP to that of a research institute. Problems such as the high recurrence rates among successfully treated TB patients documented by Cox et al. in the Karakalpakstan region definitely warrant further scientific investigation.

Visceral leishmaniasis in India

Within the framework of this thesis we conducted two studies on visceral leishmaniasis in Bihar State, India. We conducted a study into the association between visceral leishmaniasis and keeping domestic animals inside the house because earlier studies had provided conflicting results and given the important place of cattle in the local sociocultural context. Our study revealed no additional risk (nor benefit) from ownership of animals or keeping animals inside the house. We were able to exclude potential sources of bias that may have been present in earlier studies by carefully documenting potential confounders such as socio-economic status and type of housing. Housing conditions rather than the keeping of animals were found to be significant risk factors for visceral leishmaniasis.
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Of all the risk factors identified in previous studies, many are related to socio-economic conditions and few are amenable to change.\textsuperscript{22-27} We investigated the role of animals not just because of conflicting results from earlier studies but also because if keeping animals indoor would be a significant risk factor, this would be one that can be addressed. Bovines in particular were of interest because the vector for visceral leishmaniasis in the area, \textit{Phlebotomus argentipes}, is known to have a preference for feeding on bovines and because soil conditions in bovine cattle sheds are known to provide good breeding sites for this particular sandfly species.\textsuperscript{28,29,30,31} With only about 6\% of visceral leishmaniasis cases interviewed reporting to keep bovines indoor, the impact at population level (population attributable risk) could be marginal at most. Moreover we found that the proportion of non-cases keeping animals indoor was almost identical, resulting in an odds ratio of 0.88 (95\% CI 0.37-2.08). Based on this study, there is no rationale for recommendations on changing animal husbandry practices. However our study used a matched design in which cases and controls were matched by neighborhood; thus we could only assess associations at the individual or household level. There may still be an effect at a higher level as was shown by Bern \textit{et al.} in Bangladesh.\textsuperscript{23}

The fact that housing conditions came out as strong determinants, even after controlling for socio-economic status warrants further investigation. Damp floors measured by palpation were a significant risk factor in our study as well as in an earlier study by Bern \textit{et al.} in Nepal.\textsuperscript{22} In both studies damp floors were a very common exposure with 83\% of the population in our study and 52\% of the population in the study of Bern \textit{et al.} exposed. We also found a strong association between non-cemented floors and dampness. Though much is still unknown about the breeding sites of phlebotomine sandflies, it is known that they require moist soil rich in organic and nitrogenous matter, it seems therefore biologically plausible that a cemented floor can have a protective effect.\textsuperscript{30} Cementing floors could be a useful intervention but further evidence using more objective measurements of humidity is required.

An aspect that is not captured by any cross sectional risk factor study is temporal variation. As Bucheton \textit{et al.} demonstrated in a study in Sudan over a 4-year period, factors that were significantly associated with visceral leishmaniasis in the early years were no longer found to be associated in later years.\textsuperscript{32} Visceral leishmaniasis typically affects a village until saturation has been achieved; only a minority of those infected actually develop clinical disease.\textsuperscript{33} Host factors related to zinc, retinol, and other micronutrients known to modulate immunological status may be important in whether or not an infected person falls ill.\textsuperscript{26} Once the pool of susceptible persons in a village has been exhausted the incidence will drop again.\textsuperscript{22} The outcomes of any cross sectional study will therefore very much be determined by the phase of the epidemic at the time of the study. Bern \textit{et al.} appeal for adequately powered integrated demonstration projects to provide proof of principle for visceral leishmaniasis elimination. Such projects in carefully chosen sites should ensure that strategies chosen are appropriate to the ecological and epidemiological characteristics of each location.\textsuperscript{27} Given the highly clustered distribution of visceral leishmaniasis both in space and in time and the relatively low overall incidence of clinical disease, achieving an adequate power might prove problematic though.

Insecticide spraying during the malaria eradication campaigns of the 1950s did for some years suppress the incidence of visceral leishmaniasis below detectable levels,
which provides strong evidence that vector control can be an effective strategy. Further elucidating the breeding sites of *Phlebotomus argentipes* could be another important step in controlling the disease by improving the effectiveness of current insecticide spraying campaigns. Among all possible research topics related to visceral leishmaniasis, this is probably one of the most relevant.

In our second study we explored health care seeking behavior and management of visceral leishmaniasis in the government primary healthcare system in Muzaffarpur district of Bihar State. Patients presented to the community health centers with a delay of one to two months, the vast majority first presented to unqualified local practitioners. Delay was not much different for those who first presented to the outreach workers of the primary healthcare system, the auxiliary midwives/nurses (ANM) and ‘accredited social health activists’ (ASHA). Though diagnosis and treatment of visceral leishmaniasis are supposed to be free, we found that patients interviewed had incurred substantial direct costs. The median expenditure was equivalent to nearly 2 months of household income. When assessing treatment outcomes we found differences between the official reports and the outcomes documented at the community health centers; differences between official reports and information obtained through patient interviews were even more outspoken. We found out that 48% of patients were still treated on antimonials and that 40% of those had required a second course of treatment; overall 27.5% of patients treated had required a second treatment course. The recording and reporting system in use did not register these problems.

Although India has a well designed primary healthcare system with outreach workers at village level (ASHAs), supervised by auxiliary nurses/midwives (ANMs), these outreach workers are so far not involved in diagnosis and treatment of visceral leishmaniasis. Diagnostic and treatment facilities are available only at community health center level, to which patients present with considerable delay. Since visceral leishmaniasis on the Indian subcontinent is assumed to be an anthroponosis, early case detection and treatment are of key importance in controlling the disease. The rK39 dipstick test has shown high sensitivity on the Indian subcontinent, combined with good specificity when used on clinical visceral leishmaniasis suspects. Moreover the test is easy to perform, a village health worker can be trained in just a few hours; the kit requires no additional equipment, it is smaller in size than a mobile phone and can be stored at ambient temperature. A diagnostic test of this type is highly suited for use by outreach workers, such as the ANMs in India. The ANM may take the history, check some basic signs such as temperature and spleen enlargement, and perform a rapid test to exclude malaria. In case the malaria test turns out negative, an rK39 dipstick test is done to confirm the diagnosis of visceral leishmaniasis. If the diagnosis is not in doubt and the clinical condition of the patient is not too serious, the current standard treatment regimen using oral miltefosine could be provided at this level. In case of difficulties in diagnosis or clinical complications, the patient could be referred to the community health center. Thus diagnosis and treatment of VL can be brought closer to the patient without much additional investment. This would also reduce the direct and indirect costs to patients who no longer need to travel to the community health center.

With involvement of ANMs and ASHAs, it is also possible to explore the feasibility and cost-effectiveness of active case finding among high risk populations. Since
Visceral leishmaniasis is known to have a very focal distribution, all those living in the same hamlet as a known case could be considered at high risk.\textsuperscript{42,43} An ASHA could visit the households and enquire about cases of chronic fever not responding to anti-malaria treatment. Any suspect case identified could be tested on the spot with an rK-39 dipstick test and referred to the ANM in case of a positive result. Households not having any suspect cases at the time of visit can be informed and explained where to report if anyone develops a chronic fever later on. This approach would need to be field tested to assess its feasibility and effectiveness.

An aspect that became apparent from our second study is the lack of appropriate recording and reporting system to monitor clinical outcomes of visceral leishmaniasis treatment. As Styblo pointed out more than 30 years ago, there is a need to monitor not only the disease but also the effect of the control measures implemented.\textsuperscript{44} Since then he has stood at the cradle of the recording and reporting system now in use for tuberculosis all over the world. The system generates two main types of reports, a report on case registration and, with a delay of 12-15 months, a quarterly report on treatment outcomes of these same cases.\textsuperscript{45,46} Whenever a patient is started on a treatment course, (s)he will be registered either as a ‘new’ case or as a case with a history of previous treatment; the latter is broken down into categories which include ‘Relapse’, ‘Treatment after default’ and ‘Treatment after failure’. In the standard case registration report a breakdown is provided between new cases and the different categories of patients with a history of previous treatment; thus one can get at first glance an indication of whether the program is successful. A high proportion of relapses in the case registration report would be a clear indication of poor treatment outcomes in the recent past. The report on treatment outcomes shows which proportion of cases started on treatment have actually been cured, thus providing information on current effectiveness of the program. High proportions of treatment failures would prompt further investigation into the possible causes, such as drug resistance.

Visceral leishmaniasis is different from tuberculosis because it requires a 6 months follow-up after treatment and because there is no easy way to document cure. When considering the combined duration of treatment and follow-up for visceral leishmaniasis and tuberculosis they are not that much different though, seven months and six months respectively. Whereas in tuberculosis a negative sputum smear at the end of treatment is considered evidence of cure, in visceral leishmaniasis this would theoretically require a negative splenic puncture. Obtaining a splenic puncture is not possible in many cured patients because the spleen has regressed, and poses clear practical and ethical problems in the others. A clinical assessment of the general condition of the patient six months after the end of treatment is therefore advocated by most programs but in reality not many patients show up spontaneously for this follow-up visit. Here again the network of ANMs and ASHAs is a resource that should be used. They can visit the patient, take his history, check his temperature and possibly also record spleen size, and report back to the community health center.

In our study, among 131 patients without a history of previous treatment interviewed 36 (27.5\%) had required a second treatment. Part of this information could be derived from the routine records kept at the community health center but none of it was reported to the district level. Even the fact that 48\% of patients were still treated
on antimonials was not known at district level, neither was it known that 40% of these patients had required a second course of treatment. When tuberculosis control programs were upscaled in resource limited settings, Styblo was very much aware of the risks involved. He realized that a poor quality disease control program might actually do more harm than good. The drug resistance problem that has been so prominent in tuberculosis control could also compromise control of visceral leishmaniasis. Miltefosine has a long half-life and resistance can develop from a single point mutation. It is therefore of utmost importance to closely monitor treatment outcomes and switch to combination regimens as soon as clinical evidence on their effectiveness and safety becomes available. Partly in response to the outcomes of our study, a recording and reporting system based on the formats of the tuberculosis system has been developed and is currently being piloted in community health centers in Muzaffarpur district.

As our study on healthcare seeking behaviour showed, most visceral leishmaniasis patients first report to private practitioners, either qualified or unqualified. The private sector cannot be ignored and efforts should be made to involve the qualified private practitioners in the disease control efforts. This has also been done in the tuberculosis control programs and has become one of the pillars of the Stop TB Strategy. Private practitioners involved in the system will have to adhere to standards of diagnosis and treatment of visceral leishmaniasis that are in accordance with the national guidelines. This should include reporting on a regular basis to the block health coordination all cases registered for treatment and their treatment outcomes.

For visceral leishmaniasis control to properly function requires supervising the activities of ANMs and ASHAs and maintaining a good recording and reporting system. Also a regular supply of diagnostics and drugs needs to be ensured. In endemic districts this requires a visceral leishmaniasis coordinator at block level. Such a coordinator should conduct regular meetings with ANMs and ASHAs and visit on a regular basis not only the government health care facilities but also the qualified general practitioners in the block. Appointing a full time visceral leishmaniasis coordinator at block level would not be very efficient; the task could however be assigned to the tuberculosis coordinator who needs to visit the same health facilities and interact with the same village health workers while performing his tuberculosis related tasks. Such an approach needs to be field tested before more specific recommendations can be made.

**Human African Trypanosomiasis in the DRC**

Integration of HAT control into primary healthcare is a necessity when considering the declining incidence trends. This has been recognized by the management of the national HAT control program (PNLTHA) which has made integration one of the main objectives in the implementation plan of the fourth phase of support from its principal donor, the Belgian Technical Cooperation. Sub objectives are to have responsibility for planning of HAT control handed over to the ‘zone de santé’, the health district; to increase effectiveness of the activities of mobile screening teams; to have case finding, treatment and follow-up of HAT included in the package of services provided through the district health system; and to have epidemiological data used for follow-
up of patients and monitoring of disease control. Obviously our two studies on HAT fit in well with these objectives.

Both studies were related to screening tests with the aim of evaluating diagnostics that can be used for diagnosis and/or surveillance by the primary health care system. We validated the CATT-D10, a new format of the CATT-test, and tested its thermo-stability. We found that the CATT-D10 performed equally well as the classical format; moreover 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 fact that it is packaged in 10-dose vials rather than the 50-dose vials in which the classical CATT is packaged is another major advantage when used at the level of a peripheral health center since utilization rates of such facilities are generally low.\textsuperscript{53}

If made available to health facilities in endemic areas, the test can be used to rapidly identify patients with a high likelihood of suffering from HAT. In centers that have a microscope and microscopist trained for malaria, lymph node puncture and thick film can be examined on the spot. If these tests turn out negative or if microscopy is not available, the patient can be referred to the zonal hospital where also the more sensitive tests such as CTC and mAECT can be performed. Low positive predictive value of the CATT test is a problem when the test is used with asymptomatic persons but will be far less of a problem when symptomatic persons are tested. Thus peripheral health facilities will be able to offer a good service to persons presenting with symptoms that could be related to HAT.

In the meantime another test is being developed which might on the long run replace the CATT-D10. The test is being developed under the auspices of the ‘Foundation for Innovative Diagnostics’ (FIND). It will come in the format of a lateral flow test and will be easier to perform than the CATT which still requires a rotator.\textsuperscript{54} At the moment of writing this thesis it is not clear though exactly when this test will become available and whether it will be easily affordable.

Surveillance for sleeping sickness has hardly changed since colonial times. Still it is based on mobile teams going from village to village and screening entire populations. The only innovation has been the introduction of the CATT test as screening tool in the 1980s. It is beyond doubt that the current efforts cannot be maintained once the external funding ends, moreover even with the resources currently available the surveillance can never be exhaustive.\textsuperscript{55} There is an urgent need for an alternative strategy that is less costly and less labor intensive.

In our second study on HAT we validated two screening tests which can be performed on filter paper samples, MicroCATT and ELISA/T.\textit{b. gambiense} ; we also assessed their potential for use in a surveillance system. The samples were collected and stored under otherwise routine program conditions and processed in research laboratories in Kinshasa and Antwerp. Both test formats had an acceptable sensitivity and a very high specificity, which makes them suitable for use in an early warning system based on lot quality assurance sampling (LQAS). If on a village population of 1000, a sample size of at least 600 can be achieved, both tests can reliably distinguish a 2% prevalence from a zero prevalence. The 2% cut off at village level
was chosen because HAT tends to have a very focalized distribution; the prevalence may be very low at regional level but much higher in the individual affected villages. Lutumba et al. describe an outbreak in a village affecting 47 out of 224 households over a 3-year period; Chappuis et al. found prevalences of above 3% in areas that had not been under regular surveillance for a while.\textsuperscript{56,57} We do make the assumption of a random sample, which remains to be verified. There doesn’t seem to be much reason though to assume a directional bias leading to undersampling of cases. The fact that, in comparison to the mobile team approach, the samples can be collected over a longer period makes it less likely that those who are exposed because of activities outside the village are missed.

A sampling fraction of 60% is possible to achieve, considering the fact that mobile teams are able to sample 70-80% when screening village populations.\textsuperscript{55} However requiring a sample size of 60% is somewhat contradictory to the principle of LQAS which is to arrive at a conclusion based on a very small sample. The absence of a 100% sensitive and specific test means that a certain amount of misclassification of cases and non-cases occurs, which reduces the efficiency of the procedure.

As an alternative to a LQAS approach that aims to detect signals at village-level, a filter paper based surveillance system could also be worked out to identify individual HAT suspects. This requires that every individual with a positive serological test would be individually invited for a confirmation procedure. For this purpose MicroCATT would be the test of choice because this requires a higher sensitivity; ELISA/\textit{T.b.gambiense} could also be used but at a lower cut off point.

In a next phase of the study we now need to find out more about the feasibility and costs of filterpaper based screening, using either LQAS or the individual approach. A typical health zone in the DRC has a population of 120,000; screening all villages every 2 years while enrolling 75% would result in a workload at the district laboratory of 45,000 samples per year or 200 per working day. This will require an additional staff member but it is feasible, certainly when taking into account the fact that mobile teams are currently screening up to 60,000 persons per year.\textsuperscript{55} Apart from the costs of performing the laboratory tests, a small incentive will probably be necessary for the health workers to actually collect the samples. Also the costs of providing a further diagnostic workup for those testing positive on the screening tests need to be taken into account. However the annual costs of operations of a mobile team were estimated at 54,342 USD in 2007 by Lutumba et al., making it very probable that a filter paper based system will turn out to be cost-effective.\textsuperscript{58}

Even if the costs would not be reduced, filter paper based surveillance can still be beneficial if it is implemented by general health services staff. Currently cases diagnosed by the mobile screening teams are referred to fixed general health facilities for treatment. Robays et al. estimate that 90% of cases detected this way are actually started on treatment.\textsuperscript{55} Though this is definitely not a bad result, things could be further improved if screening, diagnosis and treatment were all performed at the same fixed location. This would definitely go a long way towards realizing the objective of integration of HAT service delivery into primary healthcare.

Finally a filter paper based screening system needs to be linked to a geographical information system. Cattand describes a system whereby based on surveillance...
results villages are classified into four groups: endemic, suspect, free of sleeping sickness, and of unknown epidemiological status. Suspect villages are villages in which a known HAT case used to reside or in which a serological survey disclosed seropositive individuals but without parasitological confirmation. This information is plotted on a map which can be used to guide surveillance efforts.

Such a system can easily be created; it just requires villages to be geo-referenced and survey data to be entered into a table. Plotting on a map all villages according to their epidemiological status can be done using free software such as EpiMap. The map thus created can be used to guide the screening activities of mobile teams and to identify villages in need of filter paper based screening. Such a map would be useful not just for HAT but for other healthcare programs as well, thus further contributing to the objective of integration.

**Overall conclusion**

We have studied three chronic infectious diseases in three different health systems contexts and found some common ground and scope for cross-fertilisation with regard to organisation of disease control measures.

We learned that in all three settings and for all three diseases – but for different reasons – there is a need for more involvement of first line health services in disease control measures.
control activities. Service delivery for tuberculosis control worldwide has to a large extent been integrated into general healthcare but as a former Soviet country Uzbekistan is lagging behind. Abandoning the current dual governance structure and fully embracing the Stop TB strategy would almost certainly save money and increase effectiveness. Visceral leishmaniasis control in India has progressed far in integration of service delivery but could still make further gains by making better use of the available networks of village health workers. Control of HAT in the DRC is still very much a vertical program. The program is very much donor dependent; in view of declining incidence trends and therefore diminishing efficiency of blanket population screening, there is a high likelihood that sooner or later this international aid will stop. There is therefore an urgent need to explore alternative strategies for HAT surveillance and control that prove to be more cost-effective and appropriate for implementation by regular health services.

The tuberculosis control programs have over the past 30 years developed a very elaborate program management system including elements such as regular supervision of health services staff, well organized supply systems and a standardized output based recording and reporting system. The recording and reporting system seems to be much weaker, definitely when it comes to monitoring clinical outcomes, both for visceral leishmaniasis and HAT. The visceral leishmaniasis control program in India would greatly benefit from adopting a recording and reporting system based on the tuberculosis formats. Though this was not within the scope of this thesis, the same applies to HAT control in the DRC where a major drug resistance problem went unnoticed for years. Rather than to reinvent the wheel, visceral leishmaniasis and HAT control programs should learn from the success stories of the tuberculosis control programs.

For the three diseases in the three settings, a number of research questions remain to be addressed. The main research questions for tuberculosis control are enshrined in the Stop TB strategy and are related to development of new diagnostics, drugs and vaccines. In the specific context of Uzbekistan further studies on the long term effectiveness of standardized treatment regimens in an environment of high initial drug resistance would be another research priority. Studies by Cox et al. have indicated that there may be amplification of drug resistance and increased recurrence rates when standardized regimens are used without taking into account the initial drug resistance patterns. In visceral leishmaniasis control in India there is an urgent need to evaluate safety and effectiveness of combined treatment regimens to prevent development of resistance against the new drugs; also there is a need to gather more information on the breeding sites of phlebotomine sandflies to improve vector control efforts. For HAT control in the DRC pilot projects on integration and further studies into the feasibility of alternative surveillance systems are urgently needed.
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