Tuberculosis case finding in a population with high HIV prevalence in western Kenya
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Citation for published version (APA):
van 't Hoog, A. H. (2012). Tuberculosis case finding in a population with high HIV prevalence in western Kenya
Chapter 7

Discussion
The main aim of this thesis was to evaluate tuberculosis (TB) case finding in the Health and Demographic Surveillance (HDSS) population in western Kenya. We found a high prevalence of infectious pulmonary tuberculosis (PTB) in the study population and estimated that of all prevalent infectious PTB 48% was attributable to human immunodeficiency virus (HIV) infection. The proportion of PTB cases detected, expressed as the case detection rate (CDR), was below the Kenya national estimate and the World Health Organization (WHO) target at the time. HIV-infected TB patients were detected at a higher rate compared to HIV-uninfected, but the proportion of HIV-infected PTB cases detected was lower (chapter 2). Among HIV-uninfected TB patients, case detection through self report was less successful among women and older persons (chapter 3). Among TB patients on treatment mortality and excess mortality were high, although declining since the introduction of TB-HIV interventions. Complete uptake of these interventions could further reduce mortality during treatment by at least one third (chapter 4). Chest radiograph (CXR) reading for any abnormality by clinical officers had higher sensitivity than expert reading in the identification of bacteriologically confirmed TB cases (chapter 5). In combination with symptom screening chest radiography was the most sensitive screening tool among currently available screening tests to select suspects for further bacteriological testing in prevalence surveys (chapter 6).

The high prevalence of infectious PTB of which almost half was attributable to HIV infection, suggests insufficient TB control and continued transmission in the study population, from HIV-uninfected and HIV-infected persons with TB. Some studies in high HIV populations have suggested that although HIV greatly increased TB case notifications, the contribution of HIV to TB prevalence and thus to transmission may be limited, due to a shorter duration of infectiousness in HIV-infected compared to HIV-uninfected TB patients, and to lower transmission from HIV-infected TB cases who have a lower bacterial load, although in a meta-analysis the effect of HIV-infection on reducing transmission of drug-susceptible TB did not reach statistical significance. A shorter duration of infectiousness in HIV-infected persons with TB is the result of faster progression of \emph{M tuberculosis} infection to severe disease in the presence of HIV co-infection, resulting in more rapid TB diagnosis or death. Undiagnosed TB is a well described frequent cause of death in HIV-infected persons. The contribution of HIV-attributable TB to transmission was found to be low in some populations, judged by stable incidence rates of TB among the HIV-negative population, or stable annual risk of tuberculosis infection (ARTI). Studies in other high HIV prevalence populations found increased TB incidence rates in the HIV-infected and uninfected population,
and the majority of person-years of undiagnosed smear-positive TB in the community to be among HIV-infected individuals. The net effect of HIV on TB transmission is unpredictable, and its determinants are not fully understood, but HIV-prevalence and poor access to and quality of health care will play a role. In settings where TB diagnosis is not readily available, time to diagnosis will be longer, resulting in a longer period of infectiousness in HIV-infected persons who survive until TB diagnosis, while due to high mortality and rapid progression to death in HIV infected TB patients who are not promptly diagnosed, the proportion of TB case detected will be low. The faster rate of detection in HIV-infected TB patients in western Kenya is consistent with a shorter disease duration in HIV-infected compared to HIV-uninfected persons with TB. The low CDR in HIV-infected persons with TB and high mortality among HIV-infected TB patients on treatment, suggest high mortality prior to diagnosis and insufficient case detection.

Our findings seem to contrast with the high CDR in Kenya overall, which had reached 70% in 2006 (57% in HIV-infected and 79% in HIV-uninfected persons with TB), and the stable ARTI in Kenya over the last decade, despite increases in the notification rate. In the study area and Nyanza province as a whole, HIV prevalence is considerably higher than in other parts of Kenya. Possibly TB control is less successful in this region with a greater burden of HIV-attributable TB, compared to rural areas with lower HIV prevalence. A tuberculin survey conducted in Kenya between 1994-1996 showed an increased annual risk of TB infection during the period since the prior survey conducted in 1986-1990, and mostly in the districts with high HIV prevalence. The latest tuberculin survey (2004-2007) found that the national ARTI had remained stable, with increases and decreases varying between the sampled areas, which may be due to sampling error. However in all three districts in Nyanza province, ARTI’s had increased again, again suggesting increasing transmission in this region. The CDR for HIV-infected persons with TB in our study and for Kenya overall were similar, but in HIV-uninfected persons with TB the CDR in our study was lower (65-71%) than the Kenya-estimate. The difference in CDRs may be explained in part by differences in estimation methods and uncertainties in the assumptions. A national TB prevalence survey is therefore important.

The limitations of passive case detection contribute to insufficient case detection, since the approach relies on patients’ decisions to seek care and on recognition of suspects by health workers. In addition the shortcomings of sputum microscopy and clinical diagnosis substantially contribute to diagnostic delays and drop-out. Study results in
this thesis suggest considerable delays prior to TB diagnosis in the study population, in HIV-infected and -uninfected, smear-positive and smear-negative patients, and a long period of infectiousness. Efforts to seek care at a facility presumed to be capable of (referring for) diagnosis of TB were low among the prevalent cases identified in the survey, of whom 95% were not (yet) on treatment at the time of survey. Although in a cross-sectional survey some cases of infectious TB are identified in an early stage\textsuperscript{37, 38} and would not yet be considered a suspect by the health service according to the guidelines for passive case detection\textsuperscript{39, 40}, provider contact was also low among patients who reported symptoms of longer duration.\textsuperscript{1} One third of patients who had sought care had only consulted an informal provider\textsuperscript{22}, which contributed to diagnostic delay in other studies.\textsuperscript{30, 41, 42} The self-reported durations of cough reported by TB patients identified through passive case detection, were considerably longer than the average delay of 68 days in low income countries, found in a systematic review.\textsuperscript{30, 43} Delays beyond thirty days have been associated with significantly increased transmission.\textsuperscript{44} The probability of case detection through self-report strongly depended on the presence of prolonged cough and increased illness\textsuperscript{22}, which likely prompts care-seeking and diagnosis. Self-reported duration of symptoms are however a poor indicator for the duration of infectiousness\textsuperscript{45} and are affected by increased symptoms in patients with co-morbidities.\textsuperscript{46} The patient diagnostic rate (PDR) would reflect the inverse of the duration of illness before diagnosis if all TB cases were notified and mortality was negligible.\textsuperscript{47} The PDR’s in the study population were low in the presence of treatment\textsuperscript{47}, which combined with high mortality\textsuperscript{23}, also suggests slow case detection through the passive approach, leaving a pool of infectious TB in the community.

A high burden of HIV-attributable TB may negatively affect passive case finding in HIV-uninfected and HIV-infected persons for several reasons: increased missed diagnoses, since the sensitivity of direct sputum smear tends to decrease with high workload\textsuperscript{48}; stigma related to HIV-associated TB and fear to be diagnosed with HIV, or to be considered HIV-infected once diagnosed with TB resulting in reluctance and delay to seek care\textsuperscript{30, 42, 49-51}; and possibly the high burden of HIV-associated TB may also reduce the suspicion of TB both by patients themselves and by health workers in people with less severe illness\textsuperscript{50}, or at ages at which HIV-attributable TB is less common, like in the elderly.

The observational studies in this thesis had various limitations which have been discussed in the chapters. An important limitation was that the available laboratory capacity allowed for one sputum culture on suspects from the prevalence survey only. Multiple
cultures, and cultures on all participants would have identified more prevalent cases\textsuperscript{52}, and possibly subclinical cases, which are more common in HIV-infected individuals.\textsuperscript{53} The high prevalence reported here is therefore a minimum estimate, while the accuracy of screening strategies has been somewhat overestimated.

In the prevalence survey HIV-status was obtained on identified TB cases only. HIV-status on all participants, or a random sample, would have allowed for a more precise estimate of the population attributable fraction (PAF) of HIV, for adjustment of confounding by HIV of the risk factors for prevalent TB, and for calculation of specificity and predictive values of symptoms and CXR screening by HIV status. We did not collect information on antiretroviral treatment (ART) and HIV care enrolment, which was very low at the time we designed the study.\textsuperscript{54} In future studies this information and knowledge of HIV status would be important to better identify the contributions to prevalence, insufficient case finding and mortality. The limitations do not invalidate the overall conclusion that TB control in this area is insufficient and interventions to improve TB control are needed.

The studies in this thesis suggest that priorities for TB control would be to improve case detection as a way to reduce prevalence. Improved case finding is also expected to reduce mortality from undiagnosed TB. To reduce mortality in patients diagnosed with TB, scaling up existing TB-HIV interventions should be a priority, since mortality was high in TB patients whose HIV status was unknown, or if HIV-infected, not on or not known to be on ART.\textsuperscript{23}

The need for improved case finding is increasingly recognized internationally.\textsuperscript{55} An important goal of improved case finding is to shorten the time between onset of the disease and diagnosis or death. This will reduce the prevalence of infectious TB and by implication transmission, resulting in a reduction of secondary cases.\textsuperscript{56-58} Mathematical modelling studies have suggested that substantial improvement in TB control can be expected from improved case finding, including in populations with high HIV prevalence.\textsuperscript{59-61} Active case finding interventions (ACF) have demonstrated impact on TB control. Repeated mass radiography campaigns with mobile equipment in the US and Europe between the 1930s and the 1960s, were (not necessarily causally) associated with reductions in TB death rates, notifications, and were successful in detecting previously unknown TB cases and diagnosing TB cases earlier.\textsuperscript{62} In Harare in an urban population with high HIV prevalence, populations were randomised to receive either 6-monthly rounds of door-to-door enquiry for persons with chronic cough or neighbourhood visits.
by mobile sputum collection vans, in order to find individuals with smear-positive TB using fluorescence microscopy. Both approaches reduced the prevalence of infectious TB by over 40% in three years. Prevalence reduced in the population with and without HIV infection, but most strongly in the HIV-negative population. The mobile van had a significantly higher yield, but possibly identified cases at a later stage than the door-to-door approach. Whether a similar intervention would be effective in rural populations is unknown. In rural Southern Ethiopia the introduction of TB education and sputum collection by extension workers at village health posts increased the identification of smear-positive cases compared to control villages, but the study did not provide a reliable impact measure and HIV prevalence was low. Results are awaited of a large study investigating whether enhanced case finding through better access to smear microscopy and community education reduces TB prevalence in populations with high HIV prevalence in South Africa and rural Zambia. Further studies should focus on which interventions can be effective and practical in rural populations with high HIV prevalence, on whether the effects of active case finding for a defined period can be sustained with less intensive interventions, and on how new rapid but still expensive diagnostic tests could be utilized for active case finding in a cost effective way.

New TB diagnostics are expected to substantially improve TB control. Recent developments that are relevant for resource limited settings include LED (light emitting diode) fluorescence microscopy to improve the quality and efficiency of smear microscopy and an automated rapid nucleic acid amplification test, the Xpert MTB-RIF. The latter has demonstrated a simplification and greater accuracy of clinic based TB diagnosis, within acceptable ranges of cost effectiveness, and is being introduced for TB diagnosis in health facilities at an increasing number of locations. However high test cost, technical requirements and restrictions in throughput are potential limitations for its utility in large scale ACF, and require further evaluation. A highly sensitive point of care (POC) test that can be carried out at the location at which care is provided, giving immediate results without referral to a specialist laboratory, is most desired but currently not available. The Xpert MTB-RIF does not meet the minimum POC specifications.

The HDSS where the studies in this thesis were conducted would be well placed to pilot and evaluate active TB case finding interventions. ACF has recently been included in the Asembo morbidity surveillance area within the HDSS, where 25 000 residents are visited at home every 2 weeks. During the home visit persons with symptoms suggestive of respiratory or diarrheal diseases are referred for further diagnosis to a nearby health
centre. Suspects identified by a screening algorithm composed of symptoms, HIV-status and CXR will receive sputum diagnosis by Xpert MTB-RIF. The pilot will allow an assessment of the maximum yield in notified TB cases that could be expected from intensive repeated door to door case finding in combination with a more sensitive diagnostic test. However, this approach is unlikely to be feasible for scale up.

From the study described in chapter 2 approaches with a high potential to diagnose TB cases earlier include provision of smear microscopy on a regular basis to everyone in the community with cough ≥ 2 weeks, and a combination of intensified TB case finding (ICF) in HIV-infected individuals with improved diagnosis of smear-negative PTB. The latter would require rigorous HIV testing to enhance early diagnosis of HIV-infection. Both mobile and home based HIV counselling and testing (HBCT) programs have been well received in western Kenya. A possible intervention may be to hold 6-monthly mobile camps offering HIV testing to everyone and sputum smear microscopy (using LED microscopy) to persons with a cough for 2 or more weeks. Sputum microscopy examination aims to reduce transmission from the most infectious individuals. Persons with HIV infection would be referred for further care, which would allow for ICF with sensitive algorithms and improved diagnostics to diagnose smear-negative TB, isoniazid preventive therapy, and early initiation of ART. ART is increasingly recognized as an important strategy in reducing transmission and mortality from both HIV and TB, and the mobile service would provide a synergistic contribution to the control of both diseases.

One of the prerequisites for success of mobile services will be the ability to attract persons at increased risk for prevalent TB and/or slow case finding. Mobile services may be attractive to mobile persons. Persons who had recently moved into the HDSS had high prevalence of TB and HIV compared to the population that was known to HDSS for longer. Among the HDSS population migration is very high and mostly driven by economic and social factors. Migration is often not permanent and most commonly to or from urban areas, where TB rates are generally higher in the crowded urban slums. Possibly in this community migration to and from high TB transmission areas contributes to the spread of infectious diseases to rural areas as has been described in Southern Africa. Since mobile services would reduce some of the needs for transport cost and other private health expenditure, the services could attract the least wealthy part of population who have a higher prevalence of PTB.
Mobile services may however not reach the elderly, in whom TB prevalence was also high\(^1\), likely due to poor case detection\(^{22}\) and increased incidence rates due to reactivation.\(^{88}\) The elderly may be a source of *M. tuberculosis* transmission in the community that remains relatively unnoticed, and possibly additional outreach to target this group may be required. In addition, mobile services are vulnerable to break-down and require additional resources to sustain the service. It is therefore important to not only evaluate whether mobile services could reduce TB and HIV transmission in rural areas, but also whether the reductions in prevalence can be sustained by less intensive interventions.

The evaluation of strategies to increase case detection should be priorities for operations research, and include an assessment of the feasibility, impact on TB control, and cost-effectiveness. The most important outcome of improved case finding would be reduction in tuberculosis transmission rates and declines in incidence.\(^{62, 89}\) Since no diagnostic test is available for recent tuberculosis infection, and incidence estimates are uncertain if case finding is incomplete, the closest proxy outcome is the prevalence of infectious tuberculosis in the community.\(^{89}\) Prevalence surveys are however large, logistically challenging, and expensive undertakings.\(^{1, 90-93}\) Screening is important to increase the efficiency.\(^{94}\) The currently available diagnostics, sputum smear microscopy and especially culture, prohibit bacteriological examination of tens of thousands survey participants in many high TB burden countries, and require selection of suspects with a greater pre-test probability of TB.

The study in this thesis reinforces the current recommendation to apply a combination of CXR and symptom screening.\(^{92}\) Symptom screening for ‘any TB symptom’ has high but variable sensitivity, but very low specificity\(^{46, 91, 95, 96}\) (chapter 5), which limits the use of screening for ‘any TB symptom’ alone in prevalence surveys. CXR screening alone had higher sensitivity and overall accuracy in our study and varied less in other studies (chapter 5), but the lower sensitivity of CXR in HIV-infected\(^{11, 97}\) is a concern. The current recommendations on prevalence survey design advise CXR reading by medical officers and experts.\(^{92}\) However, we found that clinical officers, who have a lower medical training level but are more available in African countries, were able to classify CXRs of confirmed TB cases as abnormal with high sensitivity and similar levels of inter-reader agreement as reported in other studies.\(^{98, 99}\) This example can be followed in other surveys. From our data, CXR screening by experts would have increased specificity above 90% if only abnormalities consistent with TB would be considered, but this would have resulted in a larger underestimation of prevalence.\(^{100}\)
A screening test with high sensitivity and reasonable specificity for bacteriologically confirmed TB, of which the accuracy is not affected by HIV status, and which is suitable for high throughput under survey field conditions, would eliminate the need for symptom or CXR screening in prevalence surveys. If screening tests were developed for this purpose, cost considerations may differ from clinical settings or when used in ACF. A sensitive test that allows simplification of survey procedures and elimination of the need for mobile radiography could be cost saving for prevalence surveys. On the contrary, for ACF, modeling suggests that a less sensitive but more frequently used case finding tool may be more effective in reducing transmission than a less frequently used highly sensitive tool, and symptom screening may thus be applicable for active case finding. The utility of screening tools for active case finding versus for prevalence surveys requires separate evaluation.

For national TB prevalence surveys there is currently not a strong recommendation to include HIV testing other than among identified TB cases. Collection of information on HIV status, use of ART and IPT is optional and should not compromise the primary survey objectives by lowering the survey participation rate. However, the increasing acceptance of HIV testing, knowledge of HIV status, and access to ART alter the impact of HIV on TB epidemics over time. In populations with high HIV prevalence information on HIV status, ART and IPT would allow further analysis of trends in TB prevalence and access to care in HIV-negative and HIV-positive people, specifically in HIV-infected persons who are not on ART, and would be useful if the decline in prevalence over time is less then expected.

The effectiveness of case finding interventions should ideally be assessed as TB cases averted or reduction in prevalence. Evaluating all efforts for active case finding interventions with TB prevalence surveys would however be unrealistic, while programmatic indicators (uptake, notification rates, mortality among TB and HIV treatment cohorts) alone are usually insufficient to measure impact. The HDSS in western Kenya would be well placed to evaluate the impact of a TB and HIV early case finding intervention, if prospective linkage between HDSS demographic and HIV status databases, and TB and HIV clinical records is established. This would allow monitoring of trends in TB case notification rates and all-cause mortality in the same population, stratified by HIV status and the use of ART. Since trends in case notifications are easily affected by changes in TB incidence from other causes including changes in HIV epidemiology, and by changes in the quality of surveillance, they could be combined with clustering
measured through genotyping as an indicator for decreased transmission,\textsuperscript{106-108} and with the proportions of cases identified in an early disease stage as indication of early TB case detection.\textsuperscript{62} Measurement of TB-specific mortality is unavailable in this population\textsuperscript{23, 109}, but adjusted trends in excess mortality would, among persons diagnosed with TB, capture the benefits of improved TB control on mortality, and among HIV-infected persons\textsuperscript{110}, the impact of early HIV and TB case finding, which includes reductions in death from undiagnosed TB. Other suggested or reported indicators to assess TB case detection are less preferred. Self-reported treatment delay\textsuperscript{111} is subjective and affected by increased symptoms in patients with co-morbidities.\textsuperscript{46} Ratios that include cases detected through surveys or active case finding and notifications, but either depend on duration of treatment\textsuperscript{17, 112}, which may change with new drugs\textsuperscript{113}, or on immeasurable estimates of incidence\textsuperscript{63} or other assumptions have limitations when used to compare the effect of interventions. The latter also applies to the CDR. The information collected in the HDSS would provide a validation of simultaneously collected programmatic indicators.

In conclusion, high prevalence, and poor case detection denote insufficient TB control in a rural population in western Kenya with high HIV prevalence. The effect of active TB and HIV case detection on decreasing TB transmission and mortality requires further evaluation.
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