Tuberculosis case finding in a population with high HIV prevalence in western Kenya
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Chapter 1
General Introduction
1.1 TUBERCULOSIS DISEASE AND BURDEN

Tuberculosis (TB) is a treatable disease that ranks among the top ten causes of death worldwide\(^1\), and is a leading cause of death in people in the most economically productive age groups.\(^2\) TB disproportionately affects populations in low and middle income countries and people living with the human immunodeficiency virus (HIV). In 2009, 30% of the estimated 9.4 million incident cases were in Africa, where 12% of the global population lives. Twelve percent of new TB cases were HIV-infected of whom 80% were in Africa. Of the estimated 1.7 million deaths from tuberculosis 0.38 million (22%) were among HIV-infected people.\(^3\) Tuberculosis is rooted in poverty and inequity, and the disease itself has an impoverishing effect.\(^4\), \(^5\) Controlling the tuberculosis pandemic is among the Millennium Development Goals (MDGs) that were set to eradicate poverty.\(^2\), \(^6\)

TB was an epidemic disease in western Europe and North America during the crowded conditions of the Industrial Revolution, where case rates reached over 1000 per 100 000 population per year in the late 1700s and early 1800s. Between 1600 and 1800 most people were infected, and up to 25% of deaths were caused by TB. The epidemic reached eastern Europe about a century later and the disease travelled along with European exploration and colonization of Asia, Africa and South America.\(^7\) In western Europe and North America improved living conditions, better nutrition, removal of infectious individuals to treatment facilities, and genetic herd immunity likely contributed to the decline, which was followed by antibiotic chemotherapy.\(^7\)

Tuberculosis is a bacterial infectious disease. The pathogens causing disease in humans are part of the *Mycobacterium tuberculosis* complex of organisms (comprising *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. microti* and *M. canetti*), of which *M. tuberculosis* is responsible for most of the disease.\(^8\) Phylogenetic studies suggest that mycobacteria were contemporaneous with early hominids in East Africa 3 million years ago\(^9\), and have since been shaped by human demographic and migratory events and evolved into a genetically diverse pathogen that is transmitted efficiently and is capable of causing disease.\(^10\), \(^11\) Members of the *M. tuberculosis* complex likely developed 20,000–35,000 years ago from ancestral strain that underwent an evolutionary bottleneck.\(^9\) Robert Koch first identified *M. tuberculosis* in 1882.\(^7\)

*M. tuberculosis* is a non-motile, non-encapsulated, non-spore forming obligate intracellular pathogen, with an acid-fast lipid-rich wall, that can infect several animal species, although human beings are the principal hosts. The bacillus replicates slowly, and grows most successfully in tissues with high oxygen content, such as the lungs.\(^8\)
Introduction

*M. tuberculosis* is transmitted through inhalation of infectious droplet nuclei that are projected in the environment by infectious persons through coughing, sneezing, talking, and singing. The bacteria are able to withstand drying and remain buoyant in ambient air or house dust for prolonged periods of time, which can be interrupted by ventilation and ultraviolet irradiation.\textsuperscript{12, 13} The major factors that determine the risk of becoming exposed to tubercle bacilli include the number of incident infectious cases in the community, the extent and duration of their infectiousness, and the number and nature of interactions between a case and a susceptible contact per unit of time of infectiousness.\textsuperscript{12, 13}

Following exposure to *M. tuberculosis*, most immunocompetent individuals either eliminate the infection by their innate immune response or an acquired mediated immune response, or develop so-called latent tuberculosis, a clinical disorder in which the host immune system retains sufficient control over replication of the bacterium such that the individual remains free of tissue damage and symptoms.\textsuperscript{8, 14} Approximately one third of the global population has latent *M. tuberculosis* infection\textsuperscript{15}, with great variations between the proportion infected between different parts of the world. The interactions of *M tuberculosis* with the human host that mediate clinical latency are largely unknown.\textsuperscript{8} Clinical disease develops in approximately 10% of immunocompetent infected individuals.\textsuperscript{16, 17} Nearly all pathology and disease is a consequence of the cell mediated immune response, and has traditionally been classified according to the pattern of progression. Progressive primary disease is severe acute disease resulting from a primary infection, usually in childhood or in immunocompromised individuals. Manifestations include meningitis and miliary (disseminated) tuberculosis.\textsuperscript{18} In reactivation, pre-existing infection emerges from its otherwise quiescent state causing disease.\textsuperscript{18} Incidence is highest within the first few years after infection, and then rapidly falls off.\textsuperscript{16} Post-primary disease is for practical purposes defined as disease that occurs more than five years after primary infection.\textsuperscript{18} The binary concept of latent infection and active disease is increasingly considered over-simplistic and replaced by the concept of a more dynamic spectrum of immune responses, mycobacterial metabolic activity and organism load.\textsuperscript{14} Important risk factors for progression to disease given that infection has occurred are HIV infection and the degree of immunosuppression, under nutrition, smoking, diabetes, alcohol misuse and possibly indoor air pollution. Age and sex are strong determinants, with highest risks in elderly people, those who are very young, and in men older than 20 years.\textsuperscript{2, 16} Genetic factors are also important determinants of the host defense but in the presence of chemotherapy their contribution to TB epidemiology is unclear.\textsuperscript{19}
Diagnosis
Respiratory symptoms like persistent cough and haemoptysis, and systemic symptoms like weight loss, fever, night sweats and fatigue are suggestive of active tuberculosis, but have low predictive values. Microscopic examination of a smear of sputum stained by Ziehl-Neelsen’s method (ZN) or by auramine to identify acid-fast rods is most widely used for a bacteriological diagnosis. It is a sensitive test for identifying the most infectious cases, but not for diagnosing all tuberculosis, since patients with bacterial loads below 10,000 bacilli per ml of sputum and extrapulmonary tuberculosis are missed. Smear examination is laborious and requires collection of multiple samples.

Mycobacterial culture followed by species identification is the most sensitive method for detecting TB, but it can take several weeks to yield results, and demands advanced technical infrastructure that is not widely accessible in many countries. Radiographic examination, together with a trial of antibiotics, is the prevailing procedure to diagnose smear-negative pulmonary tuberculosis. Although certain abnormalities are highly suggestive of pulmonary tuberculosis, the radiographic appearance of TB is not uniform, and interpretation is subject to observer error, which limit the sensitivity and specificity of chest radiography.

Nucleic acid amplification tests have high specificity, and their sensitivity in respiratory samples is better than that of sputum smear microscopy, but lower than culture. The technology is still expensive but provides rapid results, and is promising in the rapid detection of drug resistance.

So far there is little or no role for immunological tests in the diagnosis of pulmonary tuberculosis. Serological tests to detect the antibody response to one or more mycobacterial antigens have shown variable performance. Positive tuberculin skin test (TST) responses, or interferon-gamma release assays incorporating species-specific mycobacterial proteins provide evidence of prior M. tuberculosis infection, but are unable to distinguish latent infection from active disease.

Treatment
Mycobacteria are innately resistant to most antibacterial agents. Standardized short-course chemotherapy – rifampicin (R) and isoniazid (H) for 6 months, supplemented with pyrazinamide (Z) and ethambutol (E) in the first 2 months - is effective against drug-susceptible tuberculosis, but the long treatment necessitates structured programmes to
improve adherence. Effective treatment reduces infectiousness even of sputum smear-positive cases within a few weeks. The emergence of multidrug-resistant (MDR) TB, caused by *M. tuberculosis* that is resistant at least to isoniazid and rifampicin, and of extensively resistant (XDR) TB, resistant to multiple second line drugs, is an increasing global problem. MDR and XDR TB greatly challenge TB control in Eastern Europe, Asia and South Africa, but are still less common in other African countries.

**HIV-TB**

Human immunodeficiency virus (HIV) is the most powerful known risk factor for progression from *M. tuberculosis* infection to active disease. The relative risk of TB among HIV-infected persons, compared with HIV-uninfected persons was estimated in 2007 to vary from the order of 20 times more in countries with a generalized HIV epidemic, to 37 times more in countries with low prevalence of HIV infection. The risk of tuberculosis strongly increases with declining CD4 cell counts. Within the first year after HIV infection, the risk of contracting TB is already increased, but the clinical presentation largely resembles that of TB in HIV-uninfected. With declining immunity more disseminated forms of TB are seen, and lack of typical features like cavitations. The overlap of the TB and HIV epidemics have increased the burden of HIV-associated tuberculosis and resulted in rising TB case notifications from the mid-1980s. Of the 33.2 million persons infected with HIV globally, one-third is estimated to also be infected with *M. tuberculosis*. Two-thirds of HIV-infected persons live in sub-Saharan Africa. HIV alters the epidemiology of tuberculosis through endogenous reactivation of pre-existing infection with *M. tuberculosis* in persons who become infected with HIV, and through increased progression from new infection or re-infection with *M. tuberculosis* to active disease in persons with pre-existing HIV infection. Finally, increased TB incidence in HIV infected individuals may lead to increased transmission of tubercle bacilli to the general population.

The presence HIV infection complicates the clinical presentation through its effect on the immune system, resulting in changes in the presentation of active TB disease. This makes the diagnosis of active TB more difficult. Prolonged cough is not sensitive enough on its own as a symptom of TB in HIV-infected persons. Patients may have few symptoms or have symptoms that are very non-specific. Individuals with HIV-associated TB have fewer bacilli in their sputum than do HIV-uninfected persons with pulmonary TB, resulting in lower sensitivity of ZN smear microscopy, and thus more smear-negative pulmonary disease. Subclinical disease, and extrapulmonary disease are also
more common. In addition, HIV infection compromises the validity and effectiveness of chest radiography in the diagnosis of pulmonary TB, and the findings are more often normal in HIV-infected persons who have culture-confirmed pulmonary TB. The diagnostic difficulties contribute to a longer duration of the diagnostic process, and to increased mortality from undiagnosed TB.

Although standard first-line therapy for TB is effective in HIV-infected patients with drug susceptible TB, the treatment of M tuberculosis and HIV co-infection is complicated by increased toxicities and interactions between standardized short-course chemotherapy and antiretroviral drugs (ART) when administered together, and may result in reduced adherence. Immune reconstitution inflammatory syndrome (IRIS) is an additional complication, either from paradoxical worsening or recurrence of TB manifestations during immune recovery, or unmasking IRIS in HIV-infected patients who have unrecognized TB when they begin receiving ART. This issue underlies the recommendation to delay ART until TB treatment has been completed in patients with well-preserved immunity, or until completion of the 2-month intensive phase of TB treatment for patients with CD4 cell counts between 50 and 200 cells/mm³. There is however increasing evidence that ART initiation early in TB treatment greatly improves survival. Outbreaks of MDR-TB in settings with high HIV prevalence suggest that HIV infection is associated with primary MDR-TB.

1.2 TUBERCULOSIS CONTROL

The main focus of tuberculosis control has been on cutting transmission from infectious TB cases through early detection and effective treatment, which also reduces the duration of illness and the risk of death. The contribution of vaccination has been limited so far. The BCG vaccine, although widely used has low, variable and waning efficacy and little effect on the transmission of tuberculosis infection. Better vaccines could potentially have a large impact with time, but are still in pre-clinical and clinical development stages. Reducing the impact of social determinants could also reduce TB, as happened in Europe and North America where improved social conditions at the beginning of the 20th century contributed to a decline in TB incidence. For high burden countries, this goal depends on long term development. However, it has been suggested that TB can be controlled in almost any socioeconomic circumstances. Prompt case detection and treatment of infectious individuals will in the next decades remain important pillars towards TB elimination.
The DOTS strategy has been the mainstay of the TB control strategy recommended by the WHO since TB was declared a global emergency in 1993, and includes 5 elements: political commitment, reliance on passive case detection and diagnosis by direct smear microscopy, a mechanism to secure drug supplies, standardized recording and reporting, and use of standardized short-course chemotherapy with direct observation of treatment.\(^{70, 74}\) The challenges\(^{75}\) due to the increasing burden of HIV-associated tuberculosis\(^{17}\), MDR, and too slow decline (or rises) in the global TB burden, led to The Stop TB Strategy. It aims at reducing the burden of TB in line with global targets set for 2015.\(^{76}\) The six major components of the strategy are: (i) pursue high-quality DOTS expansion and enhancement; (ii) address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations; (iii) contribute to health-system strengthening based on primary health care; (iv) engage all care providers; (v) empower people with TB, and communities through partnership; and (vi) enable and promote research.\(^{76}\) The TB/HIV interventions include the ‘3I’s’: Intensified case finding in HIV-infected (ICF), Isoniazid preventive therapy (IPT) and Infection control.\(^{77}\)

1.3 ROLE OF IMPROVED CASE DETECTION

The WHO estimated that in 2009 approximately 63\% of all new cases of TB were notified globally, and approximately 50\% in the African region.\(^3\) Although the estimates are imprecise due to limited data\(^3, 78, 79,\) and some TB patients may have been diagnosed and treated but not been captured by surveillance\(^80,\) many TB patients remained untreated because they either did not seek care, or sought care but were not diagnosed.\(^3\)

Case finding in most high TB burden countries depends primarily on detecting TB among symptomatic patients who self-present to health services, also called ‘passive case finding’\(^81,\) with ZN sputum smear microscopy for bacteriological confirmation.\(^82\) Active and enhanced case finding (ACF and ECF) require a special effort by the health care system, to identify and bring into treatment people with TB who have not sought diagnostic services on their own initiative. ECF makes a population aware of TB symptoms and encourages self-presentation, while ACF involves face-to-face contact and immediate onsite evaluation.\(^81\) ACF has been successful in Europe and North America, mainly through mass radiography campaigns, although their yield decreased with declining TB rates.\(^81\) In developing countries ACF was explored in studies from India\(^83\) and Kenya.\(^84-89\) Nsanzumuhire, Aluoch and colleagues conducted a series of studies in eastern Kenya between 1974 and 1983 and explored different strategies to identify TB suspects, i.e. persons with a chronic cough, who were then further examined by sputum smear and
Chapter 1

The strategies included questioning village elders for community members with a chronic cough, questioning pregnant women attending antenatal care for household members with a chronic cough, identification of suspects among outpatients attending local health units, or examination of previously registered TB patients and their close contacts. They compared the yield with the number of cases identified through a household survey, during which household heads were requested to identify persons with chronic cough for at least one month. House to house visits revealed by far the most TB cases, but were considered too cumbersome and costly for scaling up. Moreover, 75% of suspects identified in the case finding studies had consulted a health facility for their respiratory symptoms, and for persons living within 9 miles of a district hospital, a similar yield was obtained by examination of outpatients. At the time, TB diagnostic services were centralized at district hospitals, suggesting that improved case detection in decentralized health facilities would effectively identify people with TB, rather than needing mass active case finding.

In areas with high HIV prevalence, the DOTS strategy failed to control TB. Modeling studies suggest that substantial improvement in TB control can be expected from improved case finding, including in populations with high HIV prevalence. Improving case detection in combination with improving cure rates are considered the most cost-effective strategies to reduce the burden of TB in high HIV prevalence settings.

1.4 MEASUREMENT OF TB BURDEN AND MDG GOALS

In the assessment of DOTS implementation, key elements are the case detection of smear-positive TB and their treatment success. In the Stop TB Strategy, the targets set for tuberculosis control are that by 2015 the incidence of tuberculosis needs to be falling, and the 1990 prevalence and mortality are halved. By 2050, TB should be eliminated as a public health problem, which will be achieved if incidence has fallen to <1 case per million population per year. Incidence, prevalence and mortality are important measures to describe tuberculosis epidemiology, and have become the main indicators to monitor impact of control strategies. If surveillance systems are optimal, the tuberculosis incidence rate, the number of new and relapse tuberculosis cases (all forms) arising per 100 000 population per year, can directly be measured from the case notification rate, i.e., the number of cases (new and relapse) notified to national TB programs per 100 000 population per year. Direct measurement of incidence in population based cohort studies is laborious and rarely done. Indirect incidence estimates, from measures of the prevalence of infection or active disease, or estimates of tuberculosis deaths, suffer from bias and imprecision.
The prevalence of active tuberculosis is defined as the number of cases of TB disease in a specified population at a given point in time, is a direct measure of illness caused by tuberculosis, and an indicator of transmission in the population. Prevalence is the product of incidence and duration of illness and responds more rapidly than incidence to improved case finding and drug treatment (which shorten the duration). Prevalence is measured directly through surveys. Indirect estimates have a considerable level of uncertainty.

Mortality, the number of deaths caused by TB, can be counted directly from vital registration, provided vital registration systems have adequate quality and coverage, or can be assessed from verbal autopsy, or estimated indirectly from the product of incidence and case fatality (the risk of death from TB among people with active TB disease). TB mortality statistics often exclude TB deaths in HIV-infected, since HIV is then recorded as the underlying cause of death, according to the International Classification of Diseases.

The case detection rate (CDR) expresses the number of new infectious cases detected as a percentage of expected incident cases (i.e. the notification rate divided by the incidence rate). In the absence of direct measures of incidence, the CDR is assessed from completeness of case notifications in combination with expert opinion, from a combination of time trends in tuberculosis case notification rates, HIV infection prevalence in adults and in TB patients, or by using prevalence measures from surveys. Then, the CDR is derived at by calculation of the patient diagnostic rate (PDR), which is the notification rate divided by the prevalence rate, taking into account an estimate of the duration of illness in untreated patients. On its own, the PDR provides a measurable indicator of the rate at which prevalent cases are detected by the health service. The complex interactions between HIV and TB have increased the difficulties in assessing case detection. The importance of CDR estimates in monitoring TB control is decreasing, and from 2010 only the CDRs for all TB cases are still reported in global reports, while the CDR for smear-positive TB is phased out.

The prevalence of *M. tuberculosis* infection, measured through TST surveys, provides - if repeated - supporting information about trends in transmission. The use of single TST surveys for estimating disease burden has lost importance.

The cure rate is the proportion of patients cured out of those diagnosed, analyzed in cohorts of patients. The goal is at least 85%, in the assumption that, based on
observations from Europe and North America, achieving a CDR of 70% and cure rate of 85% will reduce the prevalence of infectious TB cases, the number of infected contacts, and hence the burden of illness and mortality due to TB.\textsuperscript{69, 95}

**1.5 TUBERCULOSIS PREVALENCE SURVEYS**

In addition to providing a direct measure of the burden of infectious tuberculosis, prevalence surveys provide an opportunity to characterize prevalent cases who were not yet on TB treatment, explore the reasons why some patients are diagnosed and treated for TB while others are not, and explore associations between TB and other social and economic factors (potential determinants of health).\textsuperscript{93, 104} If repeated, prevalence surveys allow assessment of TB disease prevalence over time, and thereby the evaluation of the impact of TB control interventions on reducing disease burden.\textsuperscript{78, 105, 106} A number of Asian countries have demonstrated declining prevalence at national or regional level.\textsuperscript{107-109} National TB prevalence surveys are conducted, planned or recommended (between 2008 and 2015) in 21 global focus countries,\textsuperscript{3} where notification data obtained through routine surveillance are incomplete or of unproven accuracy, and estimated TB prevalence is more than 100 per 100,000 population.\textsuperscript{78, 93} Of those, 12 are in Africa,\textsuperscript{3} where national surveys have rarely been conducted, and even less so during the HIV-era. Because TB is a relatively rare disease, TB prevalence surveys require large sample sizes to accurately identify pulmonary tuberculosis (PTB) cases in the study population, as only a relatively low number of TB cases (50 to several hundred cases) can be identified even in a large study population (50-100,000 individuals). To ensure that the number of TB cases missed is kept to a minimum, one would ideally perform bacteriological testing on the full study population. To limit the cost of the survey and the burden to the study population, screening is often performed, to select participants with relatively high risk, i.e. suspects, of whom sputum samples are collected.\textsuperscript{110} Reported screening tools include symptom questionnaires,\textsuperscript{109, 111, 112} chest radiography,\textsuperscript{113} sputum culture,\textsuperscript{21} sputum microscopy and combinations of these.\textsuperscript{114} The experience with screening from Asia may not be fully applicable to Africa, because HIV has complicated the diagnosis of TB disease in Africa, and there are greater limitations in the availability of highly specialized personnel to read and interpret chest radiographs, and in the laboratory capacity to perform large numbers of sputum cultures. The implications of these differences on screening and missed cases in prevalence surveys have not been fully evaluated.

**1.6 TUBERCULOSIS IN KENYA**

Kenya is a low income country with - in 2008 - a population of 38.8 million. Gross national income per capita was $730 and health expenditure per capita $33. Approximately 46%
of the population lives below the national poverty line and 78% lives in rural areas. Life expectancy at birth was 53 years (Table 1). Kenya is one of the 22 high TB burden countries that together account for approximately 80% of all new TB cases arising globally each year. In 2009, a total of 110,065 TB cases (all forms of tuberculosis) were reported. In the 1960-ies and 70-ies TB rates were falling, but they have increased exponentially in the last 2 decades (Figure 1), largely attributed to the HIV epidemic. HIV prevalence in Kenya reached it’s peak in 2005, and was 7.1% in adults aged 15-64 years at the Kenya AIDS Indicator Survey in 2007, 8.4% in women and 5.4% in men. In Nyanza province, a predominantly rural area bordering lake Victoria, HIV prevalence was 14.9%, 17.2% in females and 11.6% in males, with the highest prevalence rates in 30-34 years old women and 40-44 year old men. In Nyanza province, TB case notification peaked at 440/100 000 in 2006, (431/100 000 in 2007) and was 400/100 000 in 2009 for all types of TB, and 130/100 000 for smear-positive TB. In Nyanza province, the prevalence of HIV in TB patients was 70%, while this was 44% nationally.

Figure 1. The Case Notification Rate for all forms of TB and smear-positive PTB for the different Kenyan provinces between 1990 and 2008.

In Kenya, short course chemotherapy was initiated in 1993 as part of the DOTS strategy, and fully implemented in the whole country in 1998. New cases have been treated for 8 months (2RHZE/6HE) since DOTS and with the 6 month (2RHZE/4RH) regimen since 2009. Nationally, the treatment success rate of new smear-positive cases was 85%. In 2004, the case detection rate was estimated to be 53%, much lower than the WHO
target of 70%. After a revision of the estimation methods, the CDR was estimated to be 70% in 2006, 79% in HIV-negative adults and 57% in HIV-positive adults, and has further increased since. During the last national tuberculosis prevalence survey, done in 1958-59, the prevalence of TB disease prevalence was 0.6% (0.3%-0.9%) in the population of 10 years and older.

1.7 STUDY SITE

The studies described in this thesis were conducted in a rural part of Nyanza Province in western Kenya, that is included in the Health and Demographic Surveillance System (HDSS) of the Kenya Medical Research Institute (KEMRI) and US Centers for Disease Control and Prevention (CDC) Research and Public Health Collaboration. An HDSS is a longitudinal, population-based health and vital event registration system that monitors demographic (births, deaths, pregnancies, and migrations) and health (e.g., clinic attendance and hospital admission) events in a geographically defined population. The KEMRI/CDC HDSS was established as part of a randomized controlled trial of insecticide-treated bed nets from 1997 to 2004, and includes Asembo (Rarieda District) from 2001, and Yala and Wagai divisions of Gem District since 2002. Karemo division (Siaya District) was added from 2007 (Figure 3). The objectives are to provide an infrastructure for evaluation of population-based public health interventions, provide socio-demographic data to generate hypotheses and address the causes of morbidity and mortality in subgroups of the population, and serve as a sampling frame. Home visits are 4-monthly to record in-, out- and within- migration. Births and deaths are reported through a network of community based reporters and at 4-monthly visits.

Deaths are followed by a verbal autopsy diagnosis. Geographic information systems (GIS) coordinates are available for all households, and information on assets to determine socioeconomic status and on schooling is updated every 2 years.

By mid 2008 the total HDSS population of 225,061 persons (Asembo=64,509, Gem=83,059 and Karemo=77,496 people) lived in 54,367 households, distributed over 358 villages. Household size varied from 1 to 21 with a mean and median size of 4 individuals per household. The population is culturally homogeneous (more than 95% are of the Luo ethnic group) and lives in dispersed settlements. Population density is approximately 270 persons per km². Houses are made of mud, cement, or brick with roofs of iron...
Table 1 General statistics and health indicators for the population of Kenya, and of the KEMRI/CDC Health and Demographic Surveillance HDSS area

<table>
<thead>
<tr>
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<th>Kenya**</th>
<th>HDSS*</th>
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<tr>
<td>Population size</td>
<td>38.8 million</td>
<td>225,061</td>
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<tr>
<td>Crude birth rate (Life births per 1000 population)</td>
<td>39</td>
<td>37.5</td>
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<tr>
<td>Crude death rate (deaths per 1000 population)</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Infant mortality ratio (per 1000 live births)</td>
<td>56</td>
<td>107</td>
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<tr>
<td>Total fertility rate (children born alive per woman)</td>
<td>4.9</td>
<td>5.3</td>
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<tr>
<td>Life expectancy at birth</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>HIV prevalence in 15-64 yr olds§</td>
<td>7%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*HDSS=Health and Demographic Surveillance System
*2008 HDSS report122  **Worldbank115  §14.9% in Nyanza Province117

sheets or thatch. They are predominantly clustered into compounds comprised of houses for the male head of household, his wives, and unmarried sons. Compounds are dispersed and lie adjacent to the households’ agricultural fields. Subsistence farming is the mainstay of the local economy. Rainfall is seasonal. Local crops include maize, sorghum, cassava, and millet. Because employment opportunities are limited, many young adults temporarily migrate to the urban areas to seek employment. Overall out-migration in 2008 was 127 moves per 1000 person years (py), and in-migration was 130/1000 py. The reasons for migration were socio-cultural and economic. The origins and destinations of the migrations are diverse with Nairobi being the most preferred urban destination, followed by Kisumu. More than half of the adult population had at least primary school education. In 2008, life expectancy at birth was 45 years. Of adult deaths, 61% were attributed to infectious diseases in 2008, with HIV/AIDS and TB as the major causes of death, and 78% of adult deaths took place at home. The high mortality and fertility rates (Table 1) result in a population pyramid (Figure 2) that is typical of a developing country population: a very broad base and slim top with each cohort being larger than the previous cohort, especially in the younger ages. Approximately 45% of the population is younger than 15 years of age and only 6% aged 65 years or older; 53% of the population are females.

Home based counseling and HIV testing was introduced in the area from 2008, and was received well. Among 32,000 persons tested by 2009, HIV prevalence in the HDSS population was 16.8% in those aged 15-64 years.19.9% in females and 12.5% in males (KEMRI/CDC, unpublished data).
Health care in the area is mostly provided by government dispensaries, health centres and (sub)-district hospitals, and a small number of not-for-profit or private facilities. In 2005, TB control was supervised by the division of leprosy, tuberculosis and lung diseases (DLTLD) of the ministry of health, and the area had approximately 2.5 TB diagnostic and 7.8 TB treatment facilities per 100 000 population. HIV prevention and treatment programs were initiated in the area from approximately 2003\textsuperscript{128}, but only gradually expanded. In Kenya, overall by 2008, ART coverage was approximately half of HIV-infected persons with CD4 cell counts below 200 cells/μl, and considerably less among persons with higher CD4 cell counts.\textsuperscript{116}

**Figure 2.** The 2008 mid-year study population pyramid by age and sex of Asembo, Gem and Karemo.\textsuperscript{122}

The HDSS forms part of the research program that was established in 1979, as a collaboration between KEMRI and CDC, initially with a focus on entomology and malaria epidemiology. Since the 2000’s, the research priorities expanded into demographic surveillance, malaria, HIV research and programs, emerging diseases, tuberculosis and other infectious diseases. Tuberculosis epidemiology studies were initiated in collaboration with the University of Amsterdam and results of the first studies are described in this thesis.
1.8 SCOPE AND OUTLINE OF THIS THESIS

The overall aim of this thesis is to evaluate TB case finding in the HDSS population in western Kenya and to evaluate the methods used in a TB prevalence survey.

The specific questions are:
- What is the prevalence of infectious pulmonary tuberculosis in the HDSS population?
- What proportion of prevalent PTB is attributable to HIV?
- What are risk factors for prevalent TB?
- What proportion of TB cases are found by the health service and at what rate?
- What are risk factors for slow/poor case finding?
- What are the all cause mortality rate and excess mortality among TB patients, during TB treatment?
- To what extent may chest radiograph reading by clinical officers rather than medical officers have resulted in underestimation of prevalence?
- Could the screening strategy used in the survey be modified to reduce the chest radiograph and culture requirements in similar surveys?

Chapter 2 describes the methods of the prevalence survey, the prevalence estimates, the proportion of the prevalent PTB attributable to HIV, risk factors for prevalent TB, and the proportion of and rate at which TB cases are found by the health service.

Chapter 3 describes risk factors for poor case finding obtained from a comparison between self reported TB cases and prevalent TB cases identified in the survey who were not (yet) on TB treatment.

Chapter 4 describes the all-cause mortality in a cohort of TB patients registered for TB treatment in excess of all-cause mortality in the HDSS population, and risk factors for death.

In Chapter 5, the chest radiograph field reading by clinical officers is compared with expert classifications on a sample of survey chest radiographs.

In Chapter 6, the screening methods applied in the survey are evaluated and compared with other surveys.

In the general discussion, the implications of the results for TB control and measuring of TB prevalence are discussed.
Figure 3. Map of the study area, distribution of TB treatment and diagnostic facilities, and clusters sampled in the prevalence survey.
REFERENCES


