Title

High Prevalence of Pulmonary Tuberculosis and Inadequate Case Finding in Rural Western Kenya

Authors

Anna H van't Hoog (1,2), Kayla F Laserson (1,3), Willie A Githui (4), Helen K Meme (4), Janet A Agaya (1), Lazarus O Odeny (1), Benson G Muchiri (1), Barbara J Marston (3), Kevin M DeCock (3,5), Martien W Borgdorff (2).

Affiliations:
(1) Kenya Medical Research Institute, KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya
(2) Academic Medical Centre, University of Amsterdam, The Netherlands
(3) Centers for Disease Control and Prevention, Center for Global Health, Atlanta, USA
(4) Kenya Medical Research Institute, Centre for Respiratory Diseases Research (CRDR), Nairobi, Kenya
(5) Centers for Disease Control and Prevention, Nairobi, Kenya

Corresponding author:

Anna H van't Hoog,

Academic Medical Center, University of Amsterdam,

Dept of Clinical Epidemiology (KEBB) J1B.207-1,

PO Box 22660, 1100 DD Amsterdam, The Netherlands

Tel: +3120 566 2349 Fax: +3120 691 2683

Email: a.h.vanthoog@amc.uva.nl ; avanthoog@ke.cdc.gov

Sources of support: PEPFAR.USAID through John's Hopkins University. Protocol development was also supported by the Gates Foundation.

Running head: TB Prevalence Western Kenya

Descriptor number: 11.2 Epidemiology of Tuberculosis

Word count for the body of the manuscript, excluding abstract, references and online supplementary information for the Online Repository: 3844

At a Glance Commentary:

Previous studies have suggested that passive case finding might be adequate for TB control. However TB epidemiology has changed dramatically as a result of the HIV epidemic, and information is limited on the prevalence of tuberculosis and adequacy of case finding in African populations with high rates of TB and HIV. This study identified a considerable prevalence of infectious and largely undiagnosed pulmonary tuberculosis in western Kenya, where rates of HIV infection are high. Most persons with active TB had not sought treatment. Passive TB case finding is inadequate, particularly in those who are HIV-infected. Intensified case finding is required to control TB in this resource-limited, high HIV prevalence setting.

Title page

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Author contributions:

Study conception: KDC, BJM, MWB, and AHH

Study design: MWB, KDC, BJM, AHH and WAG

Study planning and conduct: AHH, WAG. HKM, JAA, LOO, BGM, KL.

Data analysis and drafting of manuscript: AHH

Revision of manuscript for important intellectual content: all authors.

ABSTRACT

Rationale: Limited information exists on the prevalence of tuberculosis and adequacy of case finding in African populations with high rates of HIV.

Objective: To estimate the prevalence of bacteriologically confirmed pulmonary tuberculosis (PTB) and the fraction attributable to HIV, and to evaluate case detection.

Methods: Residents ≥15 years old, from 40 randomly sampled clusters, provided two sputum samples for microscopy; those with chest radiograph abnormalities or symptoms suggestive of PTB provided one additional sputum for culture.

Measurements: PTB was defined by a culture positive for *M.tuberculosis* or 2 positive smears. Persons with PTB were offered HIV testing, and interviewed on care seeking behavior. We estimated the population attributable fraction of HIV on prevalent and notified PTB, the patient diagnostic rate (PDR), and case detection rate (CDR), using provincial TB notification data.

Main Results: Among 20,566 participants, 123 had PTB. TB prevalence was 6.0/1000 (95% CI 4.6-7.4) for all PTB and 2.5/1000 (1.6-3.4) for smear-positive PTB. Of 101 prevalent TB cases tested, 52 (51%) were HIV-infected, and 58 (64%) of 91 cases who were not on treatment and were interviewed had not sought care. Forty-eight percent of prevalent and 65% of notified PTB cases were attributable to HIV. For smear-positive and smear-negative PTB combined, the PDR was 1.4 cases detected per person-year among HIV-infected persons having PTB and 0.6 for HIV-uninfected, corresponding to CDRs of 56% and 65%, respectively.

Conclusions: Undiagnosed PTB is common in this community. TB case finding needs improvement, for instance through intensified case finding with mobile smear microscopy services, rigorous HIV testing, and improved diagnosis of smear-negative TB.

Key words: *(MeSH))*

Tuberculosis, Pulmonary/*diagnosis/*epidemiology

HIV Infections/*complications/diagnosis/epidemiology

Population Surveillance/*methods

Kenya/epidemiology

Mass Screening/methods

INTRODUCTION

Case finding and treatment of symptomatic patients with infectious tuberculosis (TB) are the core elements of the global TB control strategy of the World Health Organization (WHO) (1). Estimates suggest low case finding in Africa (2), but data are limited. (3, 4) The HIV epidemic and – more recently- improved case finding have contributed to substantial increases in the notification rates in Africa over the past two decades. (5, 6) The complex interactions between HIV and TB, including the difficulty of diagnosing TB in HIV-infected patients, have increased the difficulties in assessing case detection. (6)

Case finding in countries with high TB burdens depends primarily on detecting TB among symptomatic patients who present to health services. This policy was based on results of active case finding studies in India and Kenya in the 1970's and 1980's (7-12), which found that most people with prevalent TB had sought care previously for their respiratory symptoms, suggesting that improved case detection in health facilities would effectively identify people with TB.

Modelling studies suggest that the goals for TB control are unlikely to be met without continued improvements in case detection to beyond the current global target of 70% (13), and that substantial improvement in TB control can be expected from improved case finding, including in populations with high HIV prevalence. (14, 15) Only few recent studies have investigated the prevalence of pulmonary TB (PTB) in Africa to evaluate case detection of PTB, in particular in populations with high HIV prevalence (16-21). We conducted a cross sectional study in a rural population of approximately 134,000 people in Nyanza Province in western Kenya (the Asembo area of Rarieda District, and Gem District) to determine: (i) the

prevalence of bacteriologically confirmed PTB; (ii) among PTB cases identified their HIV prevalence; and (iii) their contact with health providers. We used the survey results to evaluate case detection and the fraction of prevalent PTB attributable to HIV. The entire study population is monitored by a health and demographic surveillance system (HDSS) operated by the Kenya Medical Research Institute (KEMRI) and US Centers for Disease Control and Prevention (CDC) that captures vital events, migration and socioeconomic information.(22) The TB notification rate for the province (Nyanza) was 440/100,000 in 2006, approximately 1.5 times the Kenya average. HIV prevalence in the HDSS population was 16.8% in those aged 15-64 years (19.9% in females and 12.5% in males) in 2009 ((KEMRI/CDC, unpublished data). HIV prevalence was 7.1% among 15-64 year olds nationally in 2007. (23) Some of the results of this study have been previously reported in the form of abstracts. (24, 25)

METHODS

Sampling and study procedures

We randomly selected 40 of 105 clusters of 1-4 villages to obtain a sample of 20,000 participants[1], to measure a point prevalence between 0.5%-1% with a standard error ≤0.1%. Data collection took place from August 2006 through December 2007. All persons aged 15 years and above who resided in these clusters for at least one month were eligible. Individual written informed consent was obtained at the homes, followed by a questionnaire on the presence and duration of symptoms suggestive of TB (cough, hemoptysis, weight loss, fever, night sweats), history of TB treatment, household contact with TB patients, and smoking. All participants were instructed on how to give sputum, requested to provide two sputum samples

[1] Detailed methods are in the online data supplement.

(one spot, one overnight) for microscopic examination, and were invited to undergo chest radiography at a nearby mobile unit. Chest radiographs (CXRs) were classified onsite by a trained clinical officer as 'normal' or 'abnormal'. We requested an additional sputum sample for culture if a participant had symptoms defined as suggestive of TB or any abnormality on CXR or a positive sputum on smear microscopy (Figure 1). Participants who were ill with any illness were treated or referred as appropriate.

Laboratory methods

Sputum samples for microscopy were transported daily to the KEMRI/CDC laboratory in Kisumu, decontaminated with 4% NaOH-NALC, stained with Auramine O, and examined by fluorescence microscopy (FM). (26) If ≥1 acid fast bacilli (AFB) per equivalent of 100 immersion fields was observed, and confirmed by a second reader, the slide was considered positive. Sputum samples for culture were transported to the KEMRI Centre for Respiratory Diseases Research laboratory in Nairobi within 1-4 days for culture on two Löwenstein-Jensen (LJ) slants (27), and one 8ml Mycobacteria Growth Indicator Tube (MGIT™ Manual Mycobacterial Growth System, Becton Dickinson, Franklin Lakes, USA). LJ slants were considered positive for *M.tuberculosis* complex by conventional phenotypic identification tests (27) or the Capilia test, an immunochromatographic assay (FIND and Tauns Co. Ltd). (28) MGIT tubes with indication of bacterial growth were examined by Ziehl-Neelsen (ZN) microscopy (29) and species identification was confirmed by the Capilia test.

Case definitions

Smear-positive prevalent PTB was defined as one positive smear and a positive culture, or two or more smears positive for AFB, unless positive on culture for nontuberculous mycobacteria and not for *M.tuberculosis* complex. Culture-positive, smear-negative prevalent

PTB was defined as culture positive for *M.tuberculosis* complex without a positive smear. A positive culture was defined as: (i) growth of ≥ 5 colonies on LJ medium with AFB confirmation by ZN smear, a positive Capilia test or a standard identification profile (27); or (ii) a MGIT culture with growth, showing AFBs on ZN microscopy and a positive Capilia test.

Data collection among TB cases

Participants with PTB were interviewed about duration of symptoms and contact with health providers and referred for TB treatment. After consenting, HIV testing and CD4 cell count (FacsCalibur® Becton Dickinson, San Jose, CA) were performed. HIV infection was defined as a positive test result using standard ELISA tests in parallel (Enzygnost anti HIV-1/HIV-2 Plus®; Dade Behring Diagnostics, Marburg, Germany, and Vironostika HIV Uni-Form II Ag/Ab® Biomerieux, Boxtel, The Netherlands) and a third ELISA test (BioRad HIV-1/2 Plus O EIA®, Bio-Rad Laboratories, Redmond, WA) if discordant. HIV-infected TB patients were offered HIV care and treatment in line with national guidelines.

Data processing and statistical analysis

Data entry procedures are described in the online supplement. Survey data were linked to HDSS data, to determine education level, socio-economic status (SES) (30), recent in-migration, distance to health facilities, and the number of persons sleeping in a house. Reported prevalence estimates, odds ratios and 95% confidence intervals were adjusted for cluster sampling using SAS 9.1 survey procedures (SAS Institute Inc., Cary, North Carolina, USA). Risk factors for prevalent PTB were analyzed using logistic regression. Missing values of explanatory variables were multiply imputed.

Population attributable fraction

We estimated the population attributable fraction (PAF) (31) of prevalent PTB due to HIV, in the population aged 15 years and older. For comparison we also estimated the PAF of PTB notified to the provincial TB control program attributable to HIV. For the former we extrapolated age- and gender-specific HIV prevalence rates from home-based HIV testing and counselling in the HDSS area (KEMRI/CDC, unpublished data) to estimate the number of HIV-infected survey participants. To estimate the PAF of HIV on notified PTB, we obtained age- and gender-specific HIV prevalence in the provincial population from a national HIV survey (23), and used the Nyanza Province (2007) reports of TB notifications and HIV prevalence among notified PTB patients. (32) We standardized age- and gender-specific PTB prevalence, PTB notification (both stratified by HIV status), and HIV prevalence rates to the 2006 HDSS population structure.

Case detection

We used the same data on provincial TB notifications, HIV prevalence, and standardization approach to estimate HIV-specific patient diagnostic rates (PDR) and case detection rates (CDR) for new PTB cases. The PDR is the rate at which prevalent cases are detected by control programs and is calculated as the number of reported cases per 100,000 persons per year divided by the prevalence per 100,000. (33) The case detection rate was calculated as proposed by Dye et al (2, 34), and expresses the proportion of new PTB cases detected during the reported year.

We also calculated the number of persons with prevalent PTB who would have been detected by improved TB case finding approaches that are currently not in place: improved case detection of self-reporting patients at health facilities, an intervention providing smear

microscopy on a regular basis to everyone in the community with cough ≥ 2 weeks, and intensified case finding in HIV-infected (ICF). This analysis utilized data on 91 of 117 (78%) participants with prevalent PTB who were not on TB treatment at the time of the survey and had complete data on HIV status and contact with care providers.

The study was approved by the scientific and ethical steering committees of the Kenya Medical Research Institute (protocol number 943) and the institutional review board of the US Centers for Disease Control and Prevention (protocol number 4712).

RESULTS

Participation

According to the 2006 HDSS database that was used for sampling, 30,759 eligible residents were registered in the sampled clusters, and 22,656 (74%) eligible persons were present in the home during initial or repeat study visits. Presence in the home was significantly lower in men (62%) than women (83%), significantly lower than the average in men aged 15-44 years and in women aged 15-24 years (Annex Table 1). Of those present, 20,710 (91%) consented to participate (range by age and sex group 86-94% (Annex Table 1)). After exclusion of 144 (0.7%) records with missing interview data, the analysis included 20,566 participants, of whom 63% were female (Figure 2). The median number of participants per cluster was 541 (inter-quartile range 436-607, annex Table 2). During the interview, 3,490 persons (17%) reported symptoms suggestive of PTB (Figure 3, Annex Table 2). Of the 19,216 (93%) participants who underwent chest radiography, 5,342 (28%) had an abnormal CXR as judged by the clinical officer, 20,409 (99%) participants provided a spot sputum sample and 19,788 (96%) an overnight sample. Of the 7,346 (36%) participants with suggestive symptoms or

CXR abnormality, 6,808 (93%) had a culture result, of which 162 (2%) were contaminated on both media. Sputum results of persons who were unable to provide a sputum sample for microscopy or culture, and of contaminated cultures, were considered negative.

Prevalence

In total, 123 persons with pulmonary TB were identified: 47 (38%) smear-positive, culture-positive, 72 (59%) culture-positive, smear-negative, and 4 (3%) culture negative, smear-positive (Figure 3). Eighty-six persons reported being on TB treatment at the time of the survey of whom 80 did not have bacteriologically confirmed PTB by study definitions and were therefore not classified as prevalent PTB in further analyses. The prevalence of bacteriologically confirmed PTB in the study population was 6.0/1000 (95% confidence interval (CI) 4.6-7.4), and the prevalence of smear-positive PTB 2.5/1000 (95% CI 1.6-3.4).

The prevalence of PTB was higher in men than women (crude OR 1.5; 95% CI 1.1-2.2). The age distribution differed by gender (Table 1): in women, prevalence was highest in the age group 25-34 year, and in men, in those aged 35-54 years. Other risk factors for prevalent TB included previous TB treatment (adjusted OR (aOR) 2.7; 95% CI 1.4-5.1), recent in-migration (aOR 2.9; 95% CI 2.0-4.1), and lowest socio economic asset score quartile (aOR 1.5; 95% CI 1.0-2.1). Tuberculosis prevalence was highest in participants living at 2-2.9 km from a health facility providing TB treatment, compared to those who lived either nearer or further away. Education level, the number of persons sleeping in the house, and having lived with a TB patient in the previous 2 years were not significantly associated with prevalent TB (Table 1).

HIV

HIV status was available for 101 (82%) prevalent cases. Fifty-two (51%) were HIV-infected and had a median CD4 cell count of 196 cells per µl (interquartile range (IQR) 126-282). Thirteen (25%) reported knowing their HIV-positive status prior to TB diagnosis. Smear results were not significantly associated with HIV status and CD4 cell count. HIV-infected cases were younger (median age 35 years, IQR 28-47) than HIV-uninfected (median 53 years, IQR 28-71, p=0.0025 Wilcoxon rank sum test), but did not differ by gender. HIV prevalence was 1/19 (5%) among cases 65 years and older. Among the cases, recent in-migrants had a higher HIV prevalence (27/32, 84%) than those known to the HDSS for longer than 6-12 months (25/69 (36%), p<0.001, Annex Table 4).

We estimated that 48% of prevalent TB (both smear positive and all bacteriologically confirmed) in the study population was attributable to HIV (Table 2). Among notified new PTB cases in Nyanza Province, the PAF of HIV was 58% for smear-positive and 65% for all PTB. The rate at which new PTB cases were detected, expressed as the PDR, was higher for HIV-infected (1.4 cases detected per person-year among persons having all PTB) than for HIV-uninfected PTB cases (0.6 cases detected per person-year for all PTB), but the proportion of HIV-infected PTB cases detected, expressed as the CDR, was lower: 56% compared to 65% in HIV-uninfected (Table 3).

Case finding

A cough for three or more weeks, the main indication for initiation of diagnostic investigations in the health facilities at the time this study was conducted, was reported by 48 (39%) of 123 PTB cases, 29 (57%) of 51 smear-positive and 19 (26%) of 72 smear-negative cases (p<0.001). Half (52%) of the cases reported a cough for 2 or more weeks, and a quarter

reported no cough at all. Cough was more common in HIV-infected cases: a cough for three or more weeks was reported by 26 of 52 (50%) HIV-infected and by 15 of 49 (31%) HIV-uninfected cases (p=0.05), and cough of any duration by 49 of 52 (94%) and 30/49 (61%) respectively (p=<0.001). CXRs, also used in the health facilities to diagnose PTB, showed abnormalities in 113 (94%) of the 120 persons with PTB who had a CXR.

Of the 123 prevalent cases, 6 (5%) reported taking anti-TB treatment at the time of survey (1 smear-positive), and 9 (7%) reported prior treatment (6 smear-positive). Of the prevalent cases not currently on treatment, 91 (78%) were interviewed about contact with health providers. In the previous year, 22 of 45 (49%) smear-positive versus 11 of 46 (24%) smear-negative cases had sought care at a public health facility (p=0.017). Cases who reported a cough for 3 or more weeks reported seeking care significantly more often in the previous year than those with cough for a shorter duration or no cough (19/38 (50%) versus 14/53 (26%) p=0.028). However, among those with 3 or more weeks of cough, only 12/38 (32%) had sought care in the previous 3 months. Health provider contact did not differ by HIV status.

Among the 91 prevalent cases who were diagnosed by the survey, 15 (16%) who had consulted a public health provider in the previous 6 months would possibly have been diagnosed earlier if case detection at health facilities were more successful and high quality smear microscopy were offered to all patients self-presenting with prolonged cough for ≥ 2 weeks (Figure 4). An additional intervention providing smear microscopy on a regular basis to everyone in the community with cough ≥ 2 weeks would have identified 34 (37%) cases. Intensified case finding in HIV-infected (ICF) alone, assuming the entire population knew their HIV status and attendance at HIV care services was high, could have identified 45 (49%) of prevalent cases if smear-positive and smear-negative cases were adequately

diagnosed. Combining all three interventions would have identified 63% of the prevalent cases.

DISCUSSION

We found a high prevalence of bacteriologically confirmed PTB. The estimated proportion of PTB attributable to HIV infection was 48% for prevalent, and 58-65% for notified PTB. While the patient diagnostic rate was higher in HIV-infected than HIV-uninfected TB patients, the proportion of cases detected was estimated to be lower among HIV-infected TB patients, presumably because of greater mortality in persons with HIV. (2, 35) Most of the identified prevalent cases would not have been identified by the current case detection approach based on smear-microscopy in self-reporting patients with prolonged cough. Improved case finding strategies with the potentially highest impact on TB prevalence suggested by this study were, in addition to improving case finding at health facilities, active case finding of smear-positive cases with a cough for 2 or more weeks, combined with ICF in HIV-infected persons, assuming the entire population knew their HIV status and high attendance at HIV-services. The latter would be expected to also lower TB incidence through increased ART uptake. (20)

A high prevalence of TB in populations with high HIV prevalence has been reported in several sub-Saharan African settings (17, 18, 20, 36), but this study is one of the first comprehensive surveys in a rural African population. Earlier studies including from Kenya had suggested that most TB cases could be identified by decentralized health services (10, 37), but these studies were conducted in populations with low HIV prevalence, and had restricted bacteriological examination to persons with a cough over 3-4 weeks identified by household heads. Our survey applied a more comprehensive symptom algorithm and obtained

CXRs from all adult community members, identifying a considerable burden of undiagnosed infectious TB. Our estimated case detection rate for all PTB (56% in HIV-infected and 65% in HIV-uninfected) was in the same range but somewhat lower than the CDR reported for Kenya, which was 71% (59-88) for all TB cases in 2005 and 79% (66-98) in 2008. Achieving the STOP-TB partnership 2015 target CDR of 84% (38) poses substantial challenges. The differences between the CDR estimate we found and those reported for Kenya may be explained by regional differences and less successful TB control in the study region, by a higher proportion of HIV-infected in whom case detection has been reported to be lower (6, 20), and/or by different methods used to estimate CDRs and uncertainties in the assumptions. (2, 6) Data from our and other TB prevalence surveys may contribute to validation of the CDR estimation methods. National TB prevalence surveys have resulted in upward CDR adjustment in Eritrea (39) and downward adjustment in Viet Nam.(2) A national survey is therefore highly recommended in Kenya, to better assess case detection and also as a step towards direct measurement of the impact of the overall control program. (3)

The estimated PAF of HIV on prevalent TB (48%) was lower than on notified PTB, but higher than reported in high HIV prevalence populations in Zambia (36%) (18), and Zimbabwe (33%).(36) Consequently a large burden of unrecognized PTB in HIV-infected is also contributing to community transmission,(40, 41) and to mortality in the studied population.(35) Intensified case finding among HIV-infected is WHO policy, but not implemented widely (2). Aside from barriers to effective screening, impact is limited by low knowledge of HIV status (36), which was below 20% among HIV-infected in Kenya in 2007 (23), and among persons with TB-HIV identified in the survey only 25% knew their HIV status prior to TB diagnosis. Interventions to improve uptake of HIV testing have been well received in this region. (42) Widespread knowledge of HIV status, high attendance at HIV

services, and better algorithms and diagnostic services to rapidly diagnose smear-negative TB (43), would reduce HIV-attributable TB prevalence by ICF, as well as by the effect of anti-retroviral treatment (ART) on TB prevalence. (20) In the study area availability of ART gradually increased from 2004. At the time of survey less than 10% of HIV-infected had started ART.(44)

This study also shows the importance of improving case finding of HIV-uninfected persons with TB, who were detected at a low rate and comprised half the TB prevalence, although they represented only 29% of notified cases. Improving TB case detection by enhancing the current passive case finding strategy alone would be expected to have limited success, with the reported low contact with TB care providers and known shortcomings of conventional smear microscopy.(45) Improving passive case finding by the health service, using sputum culture, CXR and additional staffing increased case detection in some high HIV prevalence urban occupational settings. (17) Health-system strengthening to this level may also enhance early care seeking by persons with TB, but is far from available in a rural African setting. In the meantime the feasibility of a mobile van to collect sputum for microscopy would be worth exploring. This approach was successful in Harare in an urban slum setting in reducing prevalence, more so than door-to-door case finding. (21) Mobile services may be appealing to mobile or migrant populations, who had high TB and TB-HIV prevalence in this study. Additional efforts may be needed to include housebound elderly. TB diagnostic services could be combined with HIV-counselling and testing. The feasibility and costs of these interventions require further study.

The disease, transmission, and movement patterns of the population classified as recent in-migrants requires further study. This predominantly young population did not (yet) meet the HDSS resident definition requiring residency in the area for at least 4 months at the HDSS enumeration round prior to the time of our survey. Although illness related migration is common in Africa (46), only 2% of the prevalent cases reported to have moved into the area because of illness (data not shown).

The maximum possible benefit from any case finding interventions would only be reached if a simple highly sensitive test for all bacteriologically active PTB were available. In our setting, this would reach approximately 1/3 of prevalent cases if applied to suspects visiting health facilities, 2/3 if applied in a community based case finding strategy in combination with the symptom algorithm used in our study and 100% if applied based on symptoms and CXR abnormalities as done in this survey, or offered to the total population. The development of such tests deserves a high priority on the global TB research and development agenda.

The design and logistical challenges of the study may have affected the reported prevalence. We observed participation bias, however a weighted prevalence estimate, adjusting for differential non-participation, was only 3-5% lower (data not shown). Laboratory cross-contamination could account for some false-positive cases. (47) HIV-infected persons may have been more likely to report symptoms suggestive of TB (48), but less likely to have CXR abnormalities. This could potentially bias the PAF estimate but a sensitivity analysis showed no significant effect (data not shown). A number of smear-negative cases may have been missed among participants who did not have or did not report symptoms suggestive of TB (18, 49), and in whom CXR abnormalities were absent (49) or misclassified, since sputum

was not cultured from all participants, and we only cultured one sputum sample. (50) Overall, we consider the reported prevalence to be minimum estimate. An additional limitation of our study is that HIV status was not obtained from all participants, only from identified cases, and was unavailable for 22 (18%) of those, in 15 (68%) because the patient had died by the time of follow up, possibly due to HIV infection.

In conclusion, we found a high burden of prevalent and predominantly undiagnosed PTB in this rural community, in HIV-infected and uninfected. There is a need to improve TB case finding. The approaches with the highest potential yield include a combination of ICF with rigorous HIV testing and improved diagnosis of smear-negative PTB, together with mobile smear microscopy services; such interventions and their evaluation should be operations research priorities.

Acknowledgements

We acknowledge the KEMRI/CDC Research and Public Health Collaboration staff , the study team, the TB and HIV laboratories, the KEMRI CRDR staff, the TB clinics, the Asembo and Gem communities, and the study participants and the CDC-Kenya Global AIDS Program. We thank Richard Chaisson for his facilitative role, and John Williamson for statistical advice. This paper is published with the approval of the Director KEMRI. The KEMRI/CDC HDSS is a member of the INDEPTH Network.

Disclaimer

The views expressed in this manuscript do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices or organizations imply endorsement by the US government.

Author contributions:

Study conception: KDC, BJM, MWB, and AHH

Study design: MWB, KDC, BJM, AHH and WAG

Study planning and conduct: AHH, WAG. HKM, JAA, LOO, BGM, KL.

Data analysis and drafting of manuscript: AHH

Revision of manuscript for important intellectual content: all authors.

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Figure legends and footnotes

Figure 2. Selection of Study Participants from the Population in the HDSS* Area

*HDSS=Health and Demographic Surveillance System

†Of the eligible population expected according to the HDSS registration at the time of sampling, 3,314 (11%) had moved, 337 (1%) had died, 418(1%) were unable to consent, and 7,760 (26%) were not available at the time of survey. 3,726 persons were eligible, but not yet registered by the HDSS.

‡Includes 1 smear negative (MGIT) culture positive case.

Figure 3. Distribution of PTB Cases by Symptoms and Chest Radiograph Abnormality

PTB=Pulmonary Tuberculosis, CXR=Chest Radiograph, Smear=Sputum smear microscopy, + = Positive, - = Negative

* The denominators for the percentages are in the box one level upward.

† 1 participant had not provided a sample, 3 samples were contaminated on MGIT and negative on LJ.

‡Participants who did not provide any sputum sample (n=157) are considered smear-negative culture-negative

Table 1. Prevalence of Bacteriologically Confirmed PTB, and Risk Factors

PTB=Pulmonary Tuberculosis CI=Confidence Interval HDSS=Health and Demographic Surveillance System

* p ≤0.05

§Missing values of explanatory variables were multiply imputed for the multivariate analysis; 88% of records had complete data for all variables listed in the table.

†Adjusted for cluster sampling

‡A hospital, health centre or dispensary where TB drugs are dispensed under supervision of the national TB program, and staff are expected to have been trained on TB. Calculated as the absolute distance based on geographic coordinates.

Table2. Gender and Age Standardized Estimates to Determine the Population Attributable Fraction (PAF) of HIV for Prevalent PTB in the Study Area and for Notified PTB in the Province.

PTB=Pulmonary Tuberculosis; PAF=Population Attributable Fraction;

*The study population and prevalent TB cases were standardized for age and gender to the population in the Health and Demographic Surveillance system (HDSS). Home based Voluntary HIV counseling and testing data from 32.000 persons aged 15 years and above were used to estimate the number of HIV-infected persons in HDSS population (KEMRI/CDC unpublished data).

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PTB+=Smear-positive Pulmonary Tuberculosis. 15+ = aged 15 years and above

*Expressed as the number of cases detected per-person year among persons having PTB.

We assumed HIV results in persons with missing results to be similar to those not missing.

Of 22 missing results, 15 were due to death before follow up and 7 were not found, refused or not tested.

Tables and Figures

Figure 1: Screening Procedures to Select Participants Eligible for Sputum Culture

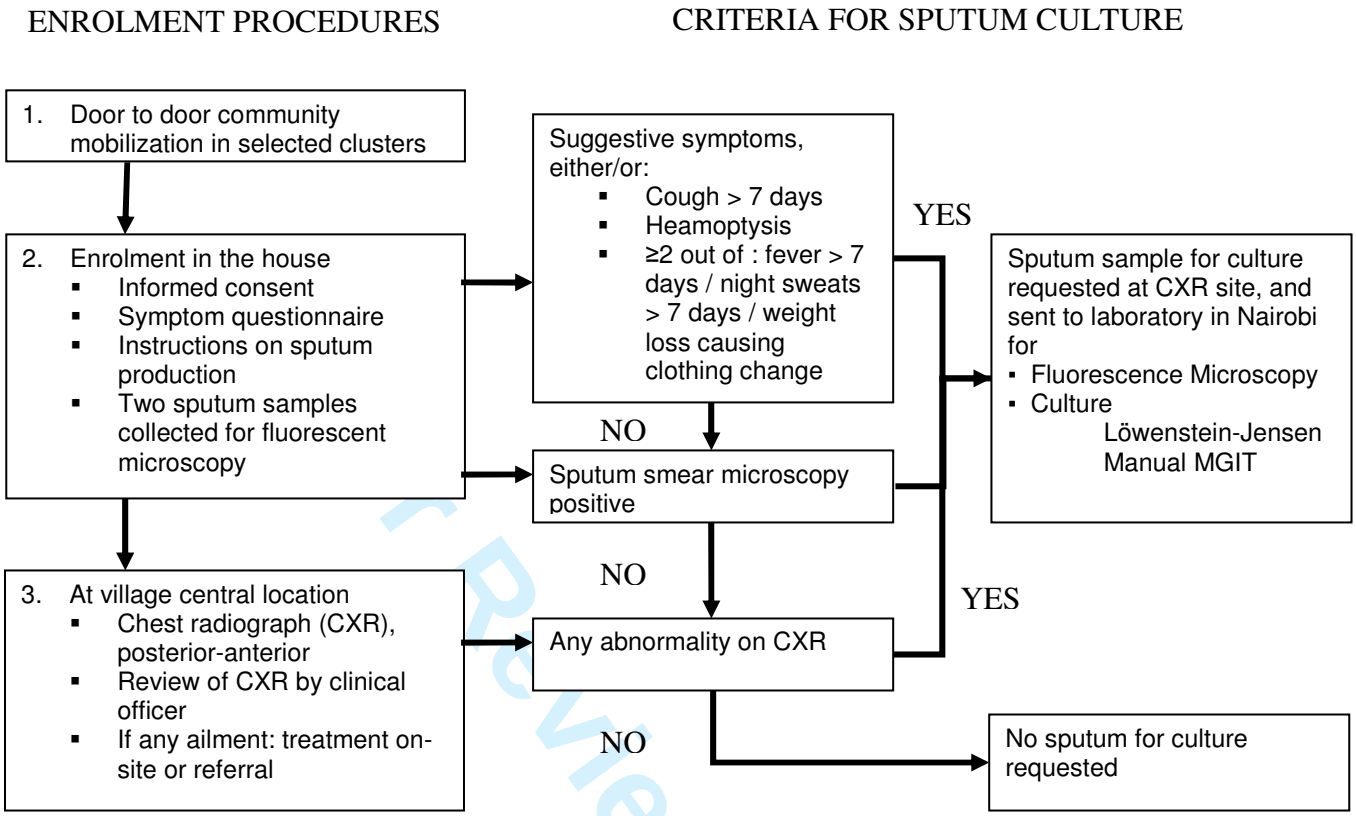
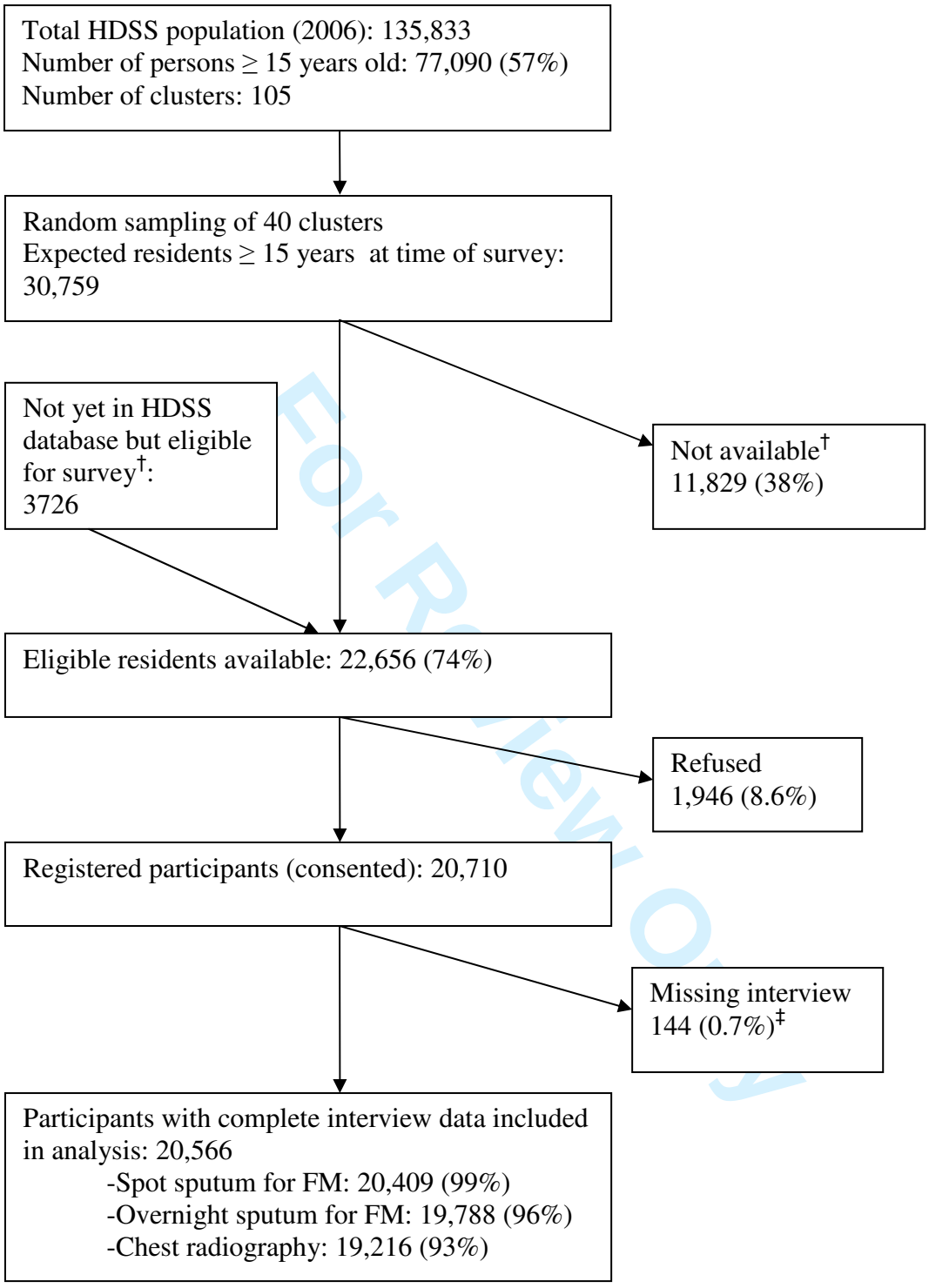


Figure 2. Selection of Study Participants from the Population in the HDSS* Area



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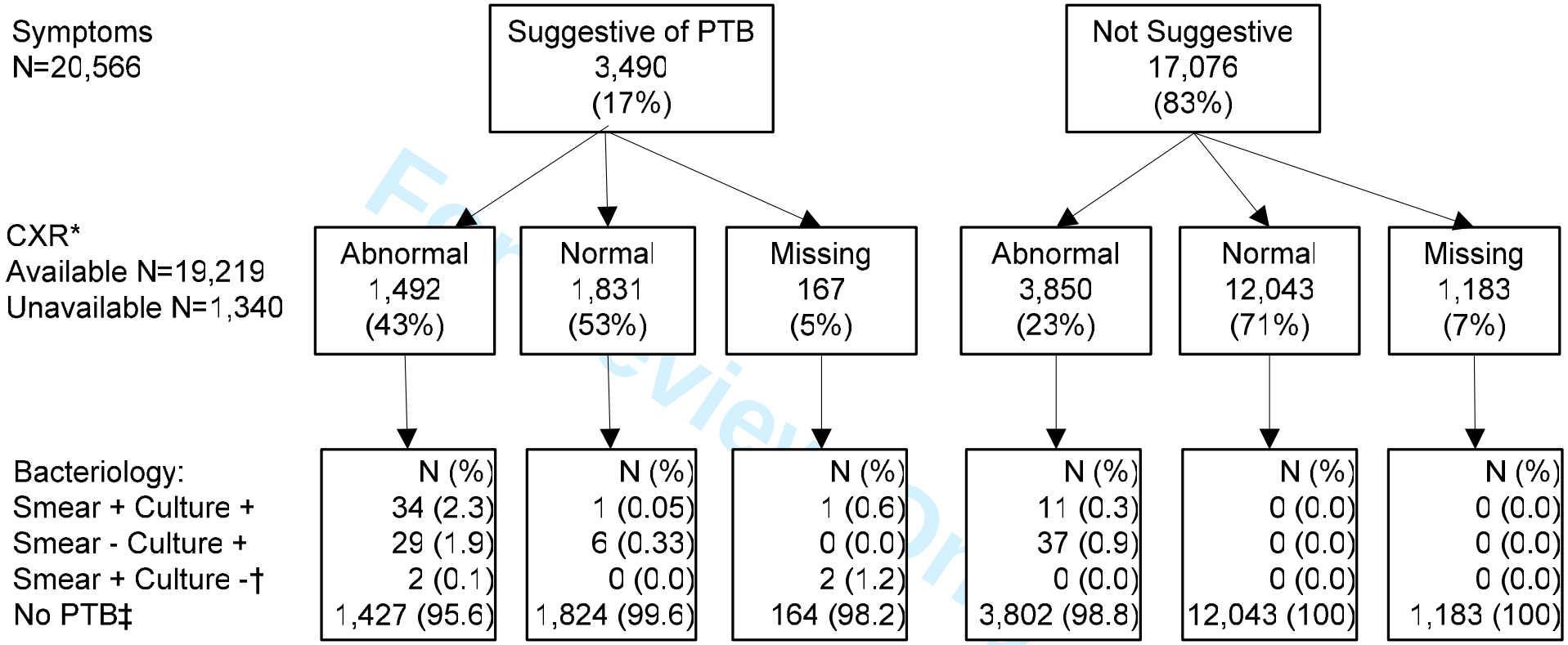
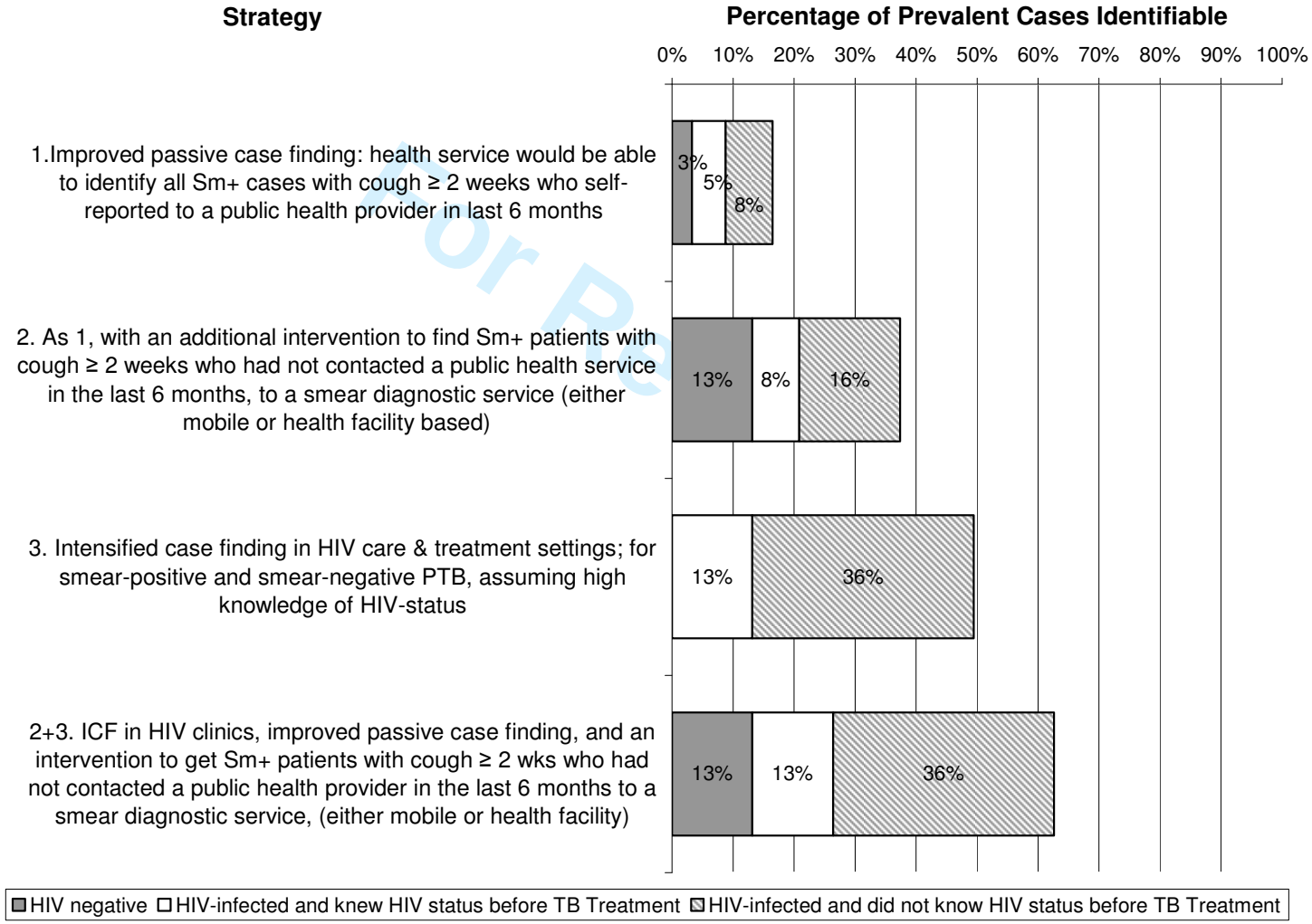


Figure 4 – Potential Yield of Applying different Case Finding Strategies on Prevalence of Pulmonary TB, and Potential Overlap with Strategies targeting HIV-infected Populations.



Tables

Table 1. Prevalence of Bacteriologically Confirmed PTB, and Risk Factors

		Cases (all PTB)	Participants	Prevalence per 1000†	Crude OR (95% CI)	Adjusted OR (95% CI)§
Total		123	20,566	6.0		
95% CI				4.6 ; 7.4		
Design effect				1.62		
Gender and Age					p=0.05	p=0.17
Females	15-24	14	3,752	3.7	0.53 (0.22-1.30)	0.47 (0.19-1.16)
(age in years)	25-34	17	2,426	7.0	1	1
	35-44	12	1,932	6.2	0.89 (0.40-1.97)	1.04 (0.47-2.28)
	45-54	7	1,844	3.8	0.54 (0.20-1.45)	0.63 (0.25-1.59)
	55-64	5	1,246	4.0	0.57 (0.24-1.34)	0.64 (0.27-1.54)
	65+	10	1,771	5.7	0.80 (0.41-1.58)	0.82 (0.34-2.02)
Males	15-24	5	2,810	1.8	0.25 (0.08-0.81)	0.25 (0.08-0.78)
	25-34	13	1,240	10.5	1.50 (0.68-3.33)	1.09 (0.46-2.59)
	35-44	12	881	13.6	1.96 (0.95-4.05)	1.49 (0.70-3.18)
	45-54	11	820	13.4	1.93 (0.91-4.07)	1.57 (0.73-3.40)
	55-64	7	801	8.7	1.25 (0.52-2.99)	1.25 (0.51-3.05)
	65+	10	1,043	9.6	1.37 (0.57-3.28)	1.42 (0.61-3.33)
Reported history of TB treatment					p<0.001	p=0.002
None reported		114	20,115	5.7	1	1
Previously treated		9	440	20.5	3.67 (1.95-6.88)	2.70 (1.42-5.13)
Missing§		-	11			
TB contact in the house in previous 2 years					p=0.07	
Yes		18	2,013	8.9	1.58 (0.97-2.56)	
None reported		105	18,461	5.7	1	
Missing§		-	92			
Education					p=0.37	
None		18	2,709	6.7	1	
Some primary		82	13,981	5.9	0.88 (0.58-1.34)	
More than primary		15	3,112	4.8	0.72 (0.37-1.41)	
Missing§		8	764	10.5		
Smoking					p<0.001	p=0.16
Current Smoker		27	2,129	12.7	2.66 (1.66-4.26)	1.79 (0.96-3.34)
Past smoker		21	2,846	7.4	1.54 (0.87-2.70)	1.25 (0.61-2.53)
Never smoked		75	15,583	4.8	1	1
Missing§		-	8			
Recent in migrant					p<0.001	p<0.001
Known to HDSS for > 6-12 months		82	16,914	4.9	1	1
Recent In-Migrant		41	3,652	11.2	2.33 (1.67-3.26)	2.85 (1.97-4.13)
Socio Economic Asset Score					p=0.01	p=0.05
<25%		34	4,122	8.3	1.68 (1.16-2.45)	1.45 (1.00-2.09)
≥25%		73	14,883	4.9	1	1
Missing§		16	1,561	10.3		
Number of persons sleeping in same house					p=0.52	
1-2		60	10,057	6.0	1	
3-4		33	5,884	5.6	1.12 (0.72-1.75)	

5+	16	3,701	4.3	0.82	(0.48-1.39)		
Missing[§]	14	924	15.2				
Distance to a TB treatment facility‡					p=0.02		p=0.005
< 1 km	10	3,043	3.3	0.41	(0.22-0.75)	0.37	(0.20-0.66)
1- < 2 km	30	5,251	5.7	0.71	(0.48-1.05)	0.71	(0.48-1.05)
2- < 3 km	50	6,229	8.0	1		1	
3- < 4 km	27	4,662	5.8	0.72	(0.48-1.08)	0.69	(0.46-1.03)
4+ km	6	1,381	4.4	0.54	(0.28-1.03)	0.55	(0.29-1.05)

PTB=Pulmonary Tuberculosis CI=Confidence Interval HDSS=Health and Demographic Surveillance System[§]Missing values of explanatory variables were multiply imputed for the multivariate analysis; 88% of records had complete data for all variables listed in the table.

[†]Adjusted for cluster sampling

‡A hospital, health centre or dispensary where TB drugs are dispensed under supervision of the national TB program, and staff are expected to have been trained on TB. Calculated as the absolute distance based on geographic coordinates.

Table 2. Gender and Age Standardized Estimates to Determine the Population Attributable Fraction (PAF) of HIV for Prevalent PTB in the Study Area and for Notified PTB in the Province.

	Prevalent PTB from Survey					**Notified PTB in Nyanza Province (32)**				
Population	Cases*	Population Size*	Prevalence per 1000	PAF (c-b)/c	Prevalence Rate Ratio (a/b)	Cases	Population Size	Notification per 1000	PAF (c-b)/c	Notification Rate Ratio (a/b)
	Culture and/or Smear-positive					All New PTB (Smear-positive, negative and smear not done)				
HIV+ (a)	250.3	11,799	21.22	48%	7.0	11589.7	418,235	27.71	65%	14.7
HIV- (b)	199.1	65,291	3.05			5081.3	2,689,114	1.89		
All (c)	449.4	77,090	5.83			16671.0	3,107,349	5.37		
	Smear-positive					Smear-positive				
HIV+ (a)	102.5	11,799	8.69	48%	7.1	110.8	9,748	11.37	58%	11.9
HIV- (b)	80.2	65,291	1.23			64.2	67,342	0.95		
All (c)	182.7	77,090	2.37			175.1	77,090	2.27		

PTB=Pulmonary Tuberculosis; PAF=Population Attributable Fraction;

*The study population and prevalent TB cases were standardized for age and gender to the population in the Health and Demographic Surveillance system (HDSS). Home based Voluntary HIV counseling and testing data from 32.000 persons aged 15 years and above were used to estimate the number of HIV-infected persons in HDSS population (KEMRI/CDC unpublished data).

Table 3: Estimates of Patient Diagnostic Rate (PDR) and Case Detection Rate (CDR) for new PTB (Smear-positive and Smear-negative combined) in HIV-infected and uninfected.

Population		(a) Notification rate of new PTB per 1000 population 15+	(b) Prevalence of new PTB per 1000 population 15+	(a)/(b) Patient Diagnostic Rate*	(d) Duration of disease (years) (2)	Case Detection Rate
	HIV+	27.71	20.60	1.34	0.93	56%
	HIV-	1.89	3.12	0.61	3	65%
	Total	5.37	5.79	0.93		

PTB=Smear-positive Pulmonary Tuberculosis. 15+ = aged 15 years and above

*Expressed as the number of cases detected per-person year among persons having PTB.

We assumed HIV results in persons with missing results to be similar to those not missing. Of 22 missing results, 15 were due to death before follow up and 7 were not found, refused or not tested.

Online Data Supplement

High Prevalence of Pulmonary Tuberculosis and Inadequate Case Finding in Rural Western Kenya

Anna H van't Hoog (1,2), Kayla F Laserson (1,3), Willie A Githui (4), Helen K Meme (4), Janet A Agaya (1), Lazarus O Odeny (1), Benson G Muchiri (1), Barbara J Marston (3), Kevin M DeCock (3,5), Martien W Borgdorff (2).

DETAILED METHODS

Sampling and Study Population

We randomly selected 40 of 105 clusters of 1-4 villages to obtain a sample of 20.000 participants[1], to measure a point prevalence between 0.5%-1% with a standard error ≤0.1%. Data collection took place from August 2006 through December 2007.

We grouped 217 villages in the study area in 105 clusters of 1-4 villages, with an average population size of 1279 (range 752-1959), expected to yield on average 500 study participants per cluster. We selected 40 clusters through simple random sampling. All persons aged 15 years and above who resided in these clusters for at least one month and were able to provide informed consent were eligible to participate in the study.

Study Procedures

Data collection took place between 31 July 2006 and 20 December 2007. After door to door community mobilization, a study worker visited all compounds in the sampled clusters,

accompanied by a village informant. Persons not at home were reminded and 2 revisit attempts were made. Individual written informed consent was obtained at the homes, followed by a questionnaire with questions on the presence and duration of symptoms suggestive of TB (cough, hemoptysis, weight loss, fever, night sweats, see Figure 1), history of TB treatment, household contact with TB patients, and smoking. The unique Health and Demographic Surveillance System (HDSS) identifiers of participants were confirmed or updated to allow data linkage.

We requested all participants to provide two sputum samples for microscopic examination. The study workers gave instructions on sputum collection aided by simple breathing techniques {E1} and observed the production of one spot sample. An unobserved early morning sample was collected the next day.

We requested all participants to undergo chest radiography at a mobile unit located at a nearby location. We provided transport if walking was not feasible. One chest radiograph (CXR), posterior-anterior view, 35 by 43 cm, was made using a 40 KW radiography machine, and developed in an automatic high speed film processor. CXRs were reviewed –independent of participant information- the same day onsite by a trained clinical officer, and classified as either 'normal' or 'abnormal', in case of any abnormality. At a later time, a radiologist reviewed all CXRs using a chest radiograph recording and reporting system described elsewhere. {E2} At the CXR location, we requested an additional sputum sample for culture if a participant had either symptoms defined as suggestive of TB (cough for more than 1 week and/or hemoptysis and/or two or more of the following: weight loss that led to a change in fit of clothes, fever for the last 2 weeks or more, night sweats for the last 2 weeks or more), or any abnormality on CXR or a positive sputum smear microscopy. Figure 1). Abnormalities

were not restricted to the lungs or being suggestive for PTB. Participants with any illness were treated or referred as appropriate.

Laboratory methods

Sputum samples were collected in 50 ml plastic centrifuge tubes, and kept cool before and during (daily) transportation to the KEMRI/CDC laboratory in Kisumu (±50-100 km away from the study area), where the samples for microscopy were processed. Sputum samples were liquefied and decontaminated with 4% NaOH-NALC, concentrated, stained with Auramine O and examined by fluorescence microscopy (FM). Each smear was scored by one reader in accordance with standard methods. {E3} If one or more acid fast bacilli (AFB) per equivalent of 100 immersion fields were observed (adjusted for the magnification), a second reader reviewed the slide. If the second review was also positive, the result was confirmed. A blinded independent reader also examined a random 10% sample of negative smears (mixed with positives).

Sputum samples collected for culture were transported by road to the laboratory at the KEMRI Centre for Respiratory Disease Research laboratory (CRDR) in Nairobi, at ±400 km distance within 1-4 days after collection. Sputum was processed as described above. After decontamination we incoculated each sample on two Löwenstein-Jensen (LJ) slants {E4,E5} and one 8ml Mycobacteria Growth Indicator Tube (MGIT^{TM} Manual Mycobacterial Growth System, Becton Dickinson, Franklin Lakes, USA) {E6}, using separate sterile Pasteur pipettes and pipette tips, respectively, for each sample. A slide for FM was made from the concentrate prior to culture. LJ slants and MGIT tubes were incubated at 37^{o}C and read weekly for 8 and 6 weeks respectively. Löwenstein-Jensen slants were considered positive for *M.tuberculosis* complex by conventional phenotypic identification tests {E4,E5}or

Capilia test, an immunochromatographic assay (FIND and Tauns Co. Ltd). {E6} Mycobacterial growth in the MGIT tubes was determined by a 365 nm UV transilluminator manual reader, followed by Ziehl-Neelsen microscopy and species identification was confirmed by Capilia. {E7} To monitor laboratory cross-contamination, simulated specimens {E8} were included in every batch of media as negative and positive (H37Rv strain) controls. All negative and positive controls were negative and positive on microscopy and culture, respectively. Negative controls following positive samples were negative.

Case definitions

Smear-positive prevalent PTB was defined as two or more smears positive for AFB, unless positive on culture for nontuberculous mycobacteria and not for *M.tuberculosis* complex), or one positive smear and a positive culture. Culture-positive, smear-negative prevalent PTB was defined as a culture positive for *M.tuberculosis* complex without a positive smear. A positive culture was defined as (i) growth of ≥ 5 colonies on LJ medium with AFB confirmation by ZN smear, a positive Capilia test or a standard identification profile {E4, E8}, or (ii) a MGIT culture with growth, showing AFBs on ZN microscopy and a positive Capilia test.

Data collection among TB cases

Participants with PTB were interviewed about presence and duration of symptoms and contact with health providers and referred for TB treatment. HIV testing and CD4 cell count (FacsCalibur® Becton Dickinson, San Jose, CA) were performed.were done, after consenting and counseling. HIV infection was defined as presence of antibodies against HIV on standard ELISA tests in parallel (Enzygnost anti HIV-1/HIV-2 Plus®; Dade Behring Diagnostics, Marburg, Germany, and Vironostika HIV Uni-Form II Ag/Ab® Biomerieux, Boxtel, The

Netherlands) and a third ELISA test (BioRad HIV-1/2 Plus O EIA®, Bio-Rad Laboratories, Redmond, WA) if discordant.

HIV-infected TB patients were offered HIV care and treatment in line with national guidelines.

Data processing and statistical analyses

Every participant was assigned a unique study number that was bar-coded to link the study forms, samples and radiographs. Questionnaire data were collected on handheld computers (PDA). Data on household registration, radiography reporting and culture results were entered on scannable forms (Cardiff Teleforms®, Autonomy Cardiff, San Diego, California, USA). Responses to questionnaires addressing care seeking behaviors and the results of AFB smear testing were entered manually, the latter double, and discrepancies resolved from the original forms. Different data sources were cross-checked for validity.

Survey data were linked to the HDSS, to determine: (i) education level; (ii) recent in-migration, defined as a person who did not meet HDSS residency criteria at the time of collection of the HDSS data available to the survey (approximately 6-12 months previous), either due to recent in-migration or extreme mobility. For the HDSS, a minimum residency period of 4 months is required; (iii) to compute the absolute distance to health facilities, based on geographic coordinates; (iv) the number of persons registered as sleeping in a house; and (v) socio-economic status, which was based on an asset ranking score. Principal component analysis (PCA) method was used to generate weights for the following broad household characteristics: occupation of participant and spouse, source and quality of water, source of fuel for cooking, livestock and asset ownership. {E9} The scores were used to rank the study participants in socio-economic status quartiles.

Statistical analyses were done using SAS 9.1 survey procedures (SAS Institute Inc., Cary, North Carolina, USA) for crude, stratified and multivariable analyses, which takes correlation within the cluster into account using the Taylor series (linearization) method to estimate the covariance of the regression coefficients.

The reported risk factors for prevalent PTB were examined in a univariate logistic regression model, then stratified for gender and added (forward selection) to a logistic regression model based on known (biological) plausibility, statistical significance in univariate analysis ($p<0.20$) and contribution to the model. Missing values of explanatory variables were multiply imputed. {E10}

Differences in proportions were tested with chi-square test, or Fisher's exact test if the sample was small. All reported prevalence estimates, odds ratios and 95% confidence intervals were adjusted for cluster sampling.

Population attributable fraction and case finding

In order to assess the population impact of HIV, we estimated the population attributable fraction (PAF) of prevalent PTB due to HIV in the population aged 15 years and older, and on notified PTB for comparison. For the former, since HIV status was only available for PTB cases, we extrapolated age- and gender-specific HIV prevalence rates from home based HIV testing and counselling of 32,000 persons aged 15 years and older in the HDSS area (KEMRI/CDC, unpublished data) to estimate the number of HIV-infected study participants. To estimate the PAF of HIV on notified PTB, we obtained age- and gender-specific HIV prevalence in the provincial population from a national HIV survey {E11}, and used the Nyanza Province (2007) reports of TB notifications and HIV prevalence among notified PTB patients: in adult TB patients (≥15 years), 62% of new notified smear-positive, and 70% of all new notified PTB patients (new smear-positive and negative combined) were HIV-

infected.{E12} For smear-positive PTB we standardized age- and gender-specific PTB prevalence, PTB notification (both stratified by HIV status), and HIV prevalence rates to the 2006 HDSS population structure. For smear-positive and smear-negative notified PTB combined the same standardization was not applied, since smear-negative PTB notifications and HIV prevalence in smear-negative PTB patients are not routinely reported by age group. We used the same data on provincial TB notifications, HIV prevalence, and standardization approach to estimate HIV-specific patient diagnostic rates (PDR) and case detection rates (CDR) for new PTB cases. The PDR is the rate at which prevalent cases are detected by control programs and can be measured as the number of reported cases per 100,000 persons per year divided by the prevalence per 100,000 {E13}. The case detection rate was calculated as proposed by Dye et al {E14}, and expresses the proportion of new PTB cases detected during the reported year, derived from the PDR and the rates (obtained from other reports {E15} at which patients die or self-cure:

$$CDR = \frac{PDR\ pyr^{-1}}{\left(PDR + \frac{1}{d}\right) pyr^{-1}} \qquad \{E15\}$$

The duration of disease (d) was assumed to be about 3 years in HIV-uninfected and the disease duration ratio of 0.31 in HIV-positive people as compared with HIV-negative people.{E15} For the estimation of the PDR and CDR re-treatment cases (i.e. treated within previous 2 years) were excluded from the prevalent cases, to be consistent with notifications of new PTB.

We also calculated the number of persons with prevalent PTB who would have been detected by approaches to improve TB case finding that are currently not in place: improved case detection at health facilities, an intervention providing smear microscopy on a regularly basis to everyone in the community with cough ≥ 2 weeks, and intensified case finding in HIV-

infected (ICF). This analysis was restricted to 91 of 117 (78%) participants with prevalent PTB who were not on TB treatment at the time of survey, and had complete data on HIV status and contact with care providers.

The study protocol was approved by the scientific and ethical steering committees of the Kenya Medical Research Institute (protocol number 943) and the institutional review board of the US Centers for Disease Control and Prevention (protocol number 4712).

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Online Data Supplement

High Prevalence of Pulmonary Tuberculosis and Inadequate Case Finding in Rural Western Kenya

Anna H van't Hoog (1,2), Kayla F Laserson (1,3), Willie A Githui (4), Helen K Meme (4), Janet A Agaya (1), Lazarus O Odeny (1), Benson G Muchiri (1), Barbara J Marston (3), Kevin M DeCock (3,5), Martien W Borgdorff (2).

ADDITIONAL TABLES

Table E1: Distribution of gender and age of the number of eligible persons expected according to the HDSS* database, the number of eligible persons found and the number who agreed to participate.

		Registered in HDSS	Eligible persons found	% of Registered†	Participants	% of Found‡
Female		17,030	14,123	83%	13,055	92%
Age group (yrs)	15-24	6,012	4,146	69%	3,776	91%
	25-34	3,022	2,666	88%	2,451	92%
	35-44	2,303	2,094	91%	1,939	93%
	45-54	2,142	1,974	92%	1,854	94%
	55-64	1,441	1,345	93%	1,252	93%
	65+	2,110	1,898	90%	1,783	94%
Male		13,729	8,532	62%	7,655	90%
Age group (yrs)	15-24	6,087	3,135	52%	2,832	90%
	25-34	2,453	1,456	59%	1,256	86%
	35-44	1,532	1,001	65%	889	89%
	45-54	1,247	915	73%	827	90%
	55-64	1,060	877	83%	804	92%
	65+	1,350	1,148	85%	1,047	91%
Total		30,759	22,655	74%	20,710	91%

*HDSS = Health and Demographic Surveillance System.
†p<0.001 for the trend by age group in males and in females, and for the difference by gender.
‡p=0.04 for the trend by age group in males, and <0.001 in females.

Table E2. Participation, suggestive symptoms, chest radiograph abnormalities and bacteriologically confirmed cases by cluster

Cluster Number	Eligible persons found	Participants in Analysis	Suggestive Symptoms	CXR available	CXR Abnormality	Smear+ cases	Smear- culture+ cases
		n	n	n	n	n	n
39	694	615	231	587	264	1	7
44	705	579	104	521	174	2	1
43	554	490	67	459	100	2	0
35	708	670	126	648	143	2	0
21	313	242	23	214	34	0	0
31	559	487	59	458	81	0	1
19	577	536	82	519	94	4	4
10	514	445	70	426	101	2	0
5	527	481	109	471	199	4	0
36	366	332	78	325	105	0	1
24	601	547	134	514	93	1	5
23	380	322	73	285	37	0	1
26	614	564	126	523	80	0	2
27	446	426	69	408	27	1	0
29	650	620	92	596	41	1	2
33	615	574	84	551	63	2	0
13	530	454	55	407	51	2	4
1	753	645	102	581	53	1	0
8	741	674	97	599	131	1	5
97	600	560	85	541	91	0	4
60	458	399	79	362	68	1	1
55	677	617	76	596	96	1	2
73	365	333	30	319	66	2	1
56	592	552	92	516	140	2	1
57	730	683	125	649	166	1	4
61	696	647	124	598	209	1	4
64	608	578	99	542	174	0	1
65	482	453	69	424	120	0	1
102	415	364	76	335	165	2	2
69	529	478	96	433	131	7	3
76	412	365	56	334	108	2	0
82	666	628	100	601	243	0	3
104	406	367	57	344	207	0	1
88	548	505	79	486	174	0	4
84	545	509	80	482	220	3	2
85	760	694	97	621	244	0	0
79	449	403	50	373	154	1	1
93	624	599	76	550	229	1	2
96	625	547	57	489	244	1	1
95	622	582	106	529	222	0	1
Total	22,656	20,566	3,490	19,216	5,342	51	72

CXR=Chest Radiograph +=positive

Table E3. Prevalence of Smear-Positive Pulmonary TB, by possibly associated factors

		No. of Participants in the Survey	Smear-Positive PTB cases	Prevalence per 1000[†]
Total		20,566	51	2.5
95% CL				1.6 ; 3.4
Design effect				1.66
Gender and Age group (years)				*
Females	15-24	3,752	7	1.9
	25-34	2,426	8	3.3
	35-44	1,932	4	2.1
	45-54	1,844	5	2.7
	55-64	1,246	1	0.8
	65+	1,771	3	1.7
Males	15-24	2,810	1	0.4
	25-34	1,240	6	4.8
	35-44	881	6	6.8
	45-54	820	3	3.7
	55-64	801	5	6.2
	65+	1,043	2	1.9
Reported history of TB treatment				*
None reported		20,115	45	2.2
Previously treated		440	6	13.6
Missing		11	-	
TB contact in the house				
Yes		2,013	8	4.0
None reported		18,461	43	2.3
Missing		92	-	
Education				
None		2,709	5	1.9
Primary		13,981	38	2.7
Secondary/post secondary		3,112	4	1.3
Missing		764	4	5.2
Socio Economic Score				
<25%		4,122	12	2.9
≥25%		14,883	34	2.3
Missing		1,561	5	1.2
Smoking				*
Current Smoker		2,129	14	6.6
Past smoker		2,846	8	2.8
Never smoked		15,583	29	1.9
Missing		8	-	
Recent in migrant				*
Known to HDSS for > 6-12 months		16,914	33	2.0
Recent In-Migrant		3,652	18	4.9
Number of persons sleeping in same house				
1-2		10,057	20	2.0
3-4		5,884	18	3.1

5+	3,701	9	2.4
missing	924	4	4.3
Distance to a TB treatment‡ facility			
< 1 km	3,043	5	1.6
1- < 2 km	5,251	14	2.7
2- < 3 km	6,229	19	3.1
3- < 4 km	4,662	12	2.6
≥ 4 km	1,381	1	0.7

†Adjusted for cluster sampling
*Rao-Scott Chi-Square Test p ≤0.05.
‡A hospital, health centre or dispensary, where TB drugs are dispensed under supervision of the national TB program, and staff are expected to have been trained on TB treatment and diagnosis. Calculated as the absolute distance based on geographic coordinates.

E4. Characteristics and prevalence of bacteriologically confirmed PTB in study participants known to the HDSS for longer versus recent in-migrants.

	Known to HDSS for > 6-12 months					Recent In-Migrant					p-value*
	Cases (all PTB)		Participants		Prevalence per 1000	Cases (all PTB)		Participants		Prevalence per 1000	
	n	%	n	%		n	%	n	%		
Total	82		16,832		4.9	41		3,611		11.4	
Gender											0.57
Female	45	54.9%	10,596	63.0%	4.2	20	48.8%	2,310	64.0%	8.7	
Male	37	45.1%	6,236	37.0%	5.9	21	51.2%	1,301	36.0%	16.1	
Age											0.0002
15-24	11	13.4%	4,601	27.3%	2.4	8	19.5%	1,935	53.6%	4.1	
25-34	13	15.9%	2,790	16.6%	4.7	17	41.5%	846	23.4%	20.1	
35-44	13	15.9%	2,424	14.4%	5.4	11	26.8%	365	10.1%	30.1	
45-54	16	19.5%	2,399	14.3%	6.7	2	4.9%	247	6.8%	8.1	
55-64	10	12.2%	1,910	11.3%	5.2	2	4.9%	125	3.5%	16.0	
65+	19	23.2%	2,701	16.0%	7.0	1	2.4%	93	2.6%	10.8	
Type of PTB by Sputum smear			n.a.					n.a.			0.70
negative	49	59.8%				23	56.1%				
positive	33	40.2%				18	43.9%				
HIV status			n.a .					n.a .			<0.0001
Pos	24	29.3%				27	65.9%				
Neg	44	53.7%				5	12.2%				
Unknown	13	15.9%				9	22.0%				
Suggestive symptoms by survey definition											0.33
Yes	47	57.3%	2,842	16.9%	16.5	28	68.3%	573	15.9%	48.9	
No	35	42.7%	13,990	83.1%	2.5	13	31.7%	3,038	84.1%	4.3	
Chest radiograph abnormal											0.74
Abnormal	74	90.2%	4,637	27.5%	16.0	39	95.1%	592	16.4%	65.9	
Normal	6	7.3%	11,199	66.5%	0.5	1	2.4%	2,668	73.9%	0.4	
missing	2	2.4%	996	5.9%	2.0	1	2.4%	351	9.7%	2.8	

HDSS= Health and Demographic Surveillance System PTB=Pulmonary Tuberculosis n.a.= not available.
*Fisher's exact test

Title

High Prevalence of Pulmonary Tuberculosis and Inadequate Case Finding in Rural Western Kenya

Authors

Anna H van't Hoog (1,2), Kayla F Laserson (1,3), Willie A Githui (4), Helen K Meme (4), Janet A Agaya (1), Lazarus O Odeny (1), Benson G Muchiri (1), Barbara J Marston (3), Kevin M DeCock (3,5), Martien W Borgdorff (2).

Affiliations:
(1) Kenya Medical Research Institute, KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya
(2) Academic Medical Centre, University of Amsterdam, The Netherlands
(3) Centers for Disease Control and Prevention, Center for Global Health, Atlanta, USA
(4) Kenya Medical Research Institute, Centre for Respiratory Diseases Research (CRDR), Nairobi, Kenya
(5) Centers for Disease Control and Prevention, Nairobi, Kenya

Corresponding author:

Anna H van't Hoog,

Academic Medical Center, University of Amsterdam,

Dept of Clinical Epidemiology (KEBB) J1B.207-1,

PO Box 22660, 1100 DD Amsterdam, The Netherlands

Tel: +3120 566 2349 Fax: +3120 691 2683

Email: a.h.vanthoog@amc.uva.nl ; avanthoog@ke.cdc.gov

Sources of support: PEPFAR.USAID through John's Hopkins University. Protocol development was also supported by the Gates Foundation.

Running head: TB Prevalence Western Kenya

Descriptor number: 11.2 Epidemiology of Tuberculosis

Word count for the body of the manuscript, excluding abstract, references and online supplementary information for the Online Repository: 3626

At a Glance Commentary:

Previous studies have suggested that passive case finding might be adequate for TB control. However TB epidemiology has changed dramatically as a result of the HIV epidemic, and information is limited on the prevalence of tuberculosis and adequacy of case finding in African populations with high rates of TB and HIV. This study identified a considerable prevalence of infectious and largely undiagnosed pulmonary tuberculosis in western Kenya, where rates of HIV infection are high. Most persons with active TB had not sought treatment. Passive TB case finding is inadequate, particularly in those who are HIV-infected. Intensified case finding is required to control TB in this resource-limited, high HIV prevalence setting.

Title page

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Author contributions:

Study conception: KDC, BJM, MWB, and AHH

Study design: MWB, KDC, BJM, AHH and WAG

Study planning and conduct: AHH, WAG. HKM, JAA, LOO, BGM, KL.

Data analysis and drafting of manuscript: AHH

Revision of manuscript for important intellectual content: all authors.

Title page

Title page

ABSTRACT

Rationale: Limited information exists on the prevalence of tuberculosis and adequacy of case finding in African populations with high rates of HIV.

Objective: To estimate the prevalence of bacteriologically confirmed pulmonary tuberculosis (PTB) and the fraction attributable to HIV, and to evaluate case detection.

Methods: Residents ≥15 years old, from 40 randomly sampled clusters, provided two sputum samples for microscopy; those with chest radiograph abnormalities or symptoms suggestive of PTB provided one additional sputum for culture.

Measurements: PTB was defined by a culture positive for *M.tuberculosis* or 2 positive smears. Persons with PTB were offered HIV testing, and interviewed on care seeking behavior. We estimated the population attributable fraction of HIV on prevalent and notified PTB, the patient diagnostic rate (PDR), and case detection rate (CDR), using provincial TB notification data.

Main Results: Among 20,566 participants, 123 had PTB. TB prevalence was 6.0/1000 (95% CI 4.6-7.4) for all PTB and 2.5/1000 (1.6-3.4) for smear-positive PTB. Of 101 prevalent TB cases tested, 52 (51%) were HIV-infected, and 58 (64%) of 91 cases who were not on treatment and were interviewed had not sought care. Forty-eight percent of prevalent and 65% of notified PTB cases were attributable to HIV. For smear-positive and smear-negative PTB combined, the PDR was 1.4 cases detected per person-year among HIV-infected persons having PTB and 0.6 for HIV-uninfected, corresponding to CDRs of 56% and 65%, respectively.

Conclusions: Undiagnosed PTB is common in this community. TB case finding needs improvement, for instance through intensified case finding with mobile smear microscopy services, rigorous HIV testing, and improved diagnosis of smear-negative TB.

Number of words abstract: 260

Key words: *(MeSH))*

Tuberculosis, Pulmonary/*diagnosis/*epidemiology

HIV Infections/*complications/diagnosis/epidemiology

Population Surveillance/*methods

Kenya/epidemiology

Mass Screening/methods

INTRODUCTION

Case finding and treatment of symptomatic patients with infectious tuberculosis (TB) are the core elements of the global TB control strategy of the World Health Organization (WHO) (1). Estimates suggest low case finding in Africa (2), but data are limited. (3, 4) The HIV epidemic and – more recently- improved case finding have contributed to substantial increases in the notification rates in Africa over the past two decades. (5, 6) The complex interactions between HIV and TB, including the difficulty of diagnosing TB in HIV-infected patients, have increased the difficulties in assessing case detection. (6)

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Case finding in countries with high TB burdens depends primarily on detecting TB among symptomatic patients who present to health services. This policy was based on results of active case finding studies in India and Kenya in the 1970's and 1980's (7-12), which found that most people with prevalent TB had sought care previously for their respiratory symptoms, suggesting that improved case detection in health facilities would effectively identify people with TB.

Modelling studies suggest that the goals for TB control are unlikely to be met without continued improvements in case detection to beyond the current global target of 70% (13), and that substantial improvement in TB control can be expected from improved case finding, including in populations with high HIV prevalence. (14, 15) Only few recent studies have investigated the prevalence of pulmonary TB (PTB) in Africa to evaluate case detection of PTB, in particular in populations with high HIV prevalence (16-21). We conducted a cross sectional study in a rural population of approximately 134,000 people in Nyanza Province in western Kenya (the Asembo area of Rarieda District, and Gem District) to determine: (i) the

prevalence of bacteriologically confirmed PTB; (ii) among PTB cases identified their HIV prevalence; and (iii) their contact with health providers. We used the survey results to evaluate case detection and the fraction of prevalent PTB attributable to HIV. The entire study population is monitored by a health and demographic surveillance system (HDSS) operated by the Kenya Medical Research Institute (KEMRI) and US Centers for Disease Control and Prevention (CDC) that captures vital events, migration and socioeconomic information.(22) The TB notification rate for the province (Nyanza) was 440/100,000 in 2006, approximately 1.5 times the Kenya average. HIV prevalence in the HDSS population was 16.8% in those aged 15-64 years (19.9% in females and 12.5% in males) in 2009 ((KEMRI/CDC, unpublished data). HIV prevalence was 7.1% among 15-64 year olds nationally in 2007. (23) Some of the results of this study have been previously reported in the form of abstracts. (24, 25)

METHODS

Sampling and study procedures

We randomly selected 40 of 105 clusters of 1-4 villages to obtain a sample of 20,000 participants[1], to measure a point prevalence between 0.5%-1% with a standard error ≤0.1%. Data collection took place from August 2006 through December 2007. All persons aged 15 years and above who resided in these clusters for at least one month were eligible. Individual written informed consent was obtained at the homes, followed by a questionnaire on the presence and duration of symptoms suggestive of TB (cough, hemoptysis, weight loss, fever, night sweats), history of TB treatment, household contact with TB patients, and smoking. All participants were instructed on how to give sputum, requested to provide two sputum samples

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[1] Detailed methods are in the online data supplement.

(one spot, one overnight) for microscopic examination, and were invited to undergo chest radiography at a nearby mobile unit. Chest radiographs (CXRs) were classified onsite by a trained clinical officer as 'normal' or 'abnormal'. We requested an additional sputum sample for culture if a participant had symptoms defined as suggestive of TB or any abnormality on CXR or a positive sputum on smear microscopy (Figure 1). Participants who were ill with any illness were treated or referred as appropriate.

Laboratory methods

Sputum samples for microscopy were transported daily to the KEMRI/CDC laboratory in Kisumu, decontaminated with 4% NaOH-NALC, stained with Auramine O, and examined by fluorescence microscopy (FM). (26) If ≥1 acid fast bacilli (AFB) per equivalent of 100 immersion fields was observed, and confirmed by a second reader, the slide was considered positive. Sputum samples for culture were transported to the KEMRI Centre for Respiratory Diseases Research laboratory in Nairobi within 1-4 days for culture on two Löwenstein-Jensen (LJ) slants (27), and one 8ml Mycobacteria Growth Indicator Tube (MGIT™ Manual Mycobacterial Growth System, Becton Dickinson, Franklin Lakes, USA). LJ slants were considered positive for *M.tuberculosis* complex by conventional phenotypic identification tests (27) or the Capilia test, an immunochromatographic assay (FIND and Tauns Co. Ltd). (28) MGIT tubes with indication of bacterial growth were examined by Ziehl-Neelsen (ZN) microscopy (29) and species identification was confirmed by the Capilia test.

Case definitions

Smear-positive prevalent PTB was defined as one positive smear and a positive culture, or two or more smears positive for AFB, unless positive on culture for nontuberculous mycobacteria and not for *M.tuberculosis* complex. Culture-positive, smear-negative prevalent

PTB was defined as culture positive for *M.tuberculosis* complex without a positive smear. A positive culture was defined as: (i) growth of ≥ 5 colonies on LJ medium with AFB confirmation by ZN smear, a positive Capilia test or a standard identification profile (27); or (ii) a MGIT culture with growth, showing AFBs on ZN microscopy and a positive Capilia test.

Data collection among TB cases

Participants with PTB were interviewed about duration of symptoms and contact with health providers and referred for TB treatment. After consenting, HIV testing and CD4 cell count (FacsCalibur® Becton Dickinson, San Jose, CA) were performed. HIV infection was defined as a positive test result using standard ELISA tests in parallel (Enzygnost anti HIV-1/HIV-2 Plus®; Dade Behring Diagnostics, Marburg, Germany, and Vironostika HIV Uni-Form II Ag/Ab® Biomerieux, Boxtel, The Netherlands) and a third ELISA test (BioRad HIV-1/2 Plus O EIA®, Bio-Rad Laboratories, Redmond, WA) if discordant. HIV-infected TB patients were offered HIV care and treatment in line with national guidelines.

Data processing and statistical analysis

Data entry procedures are described in the online supplement. Survey data were linked to HDSS data, to determine education level, socio-economic status (SES) (30), recent in-migration, distance to health facilities, and the number of persons sleeping in a house. Reported prevalence estimates, odds ratios and 95% confidence intervals were adjusted for cluster sampling using SAS 9.1 survey procedures (SAS Institute Inc., Cary, North Carolina, USA). Risk factors for prevalent PTB were analyzed using logistic regression. Missing values of explanatory variables were multiply imputed.

Population attributable fraction

We estimated the population attributable fraction (PAF) (31) of prevalent PTB due to HIV, in the population aged 15 years and older. For comparison we also estimated the PAF of PTB notified to the provincial TB control program attributable to HIV. For the former we extrapolated age- and gender-specific HIV prevalence rates from home-based HIV testing and counselling in the HDSS area (KEMRI/CDC, unpublished data) to estimate the number of HIV-infected survey participants. To estimate the PAF of HIV on notified PTB, we obtained age- and gender-specific HIV prevalence in the provincial population from a national HIV survey (23), and used the Nyanza Province (2007) reports of TB notifications and HIV prevalence among notified PTB patients. (32) We standardized age- and gender-specific PTB prevalence, PTB notification (both stratified by HIV status), and HIV prevalence rates to the 2006 HDSS population structure.

Case detection

We used the same data on provincial TB notifications, HIV prevalence, and standardization approach to estimate HIV-specific patient diagnostic rates (PDR) and case detection rates (CDR) for new PTB cases. The PDR is the rate at which prevalent cases are detected by control programs and is calculated as the number of reported cases per 100,000 persons per year divided by the prevalence per 100,000. (33) The case detection rate was calculated as proposed by Dye et al (2, 34), and expresses the proportion of new PTB cases detected during the reported year.

We also calculated the number of persons with prevalent PTB who would have been detected by improved TB case finding approaches that are currently not in place: improved case detection of self-reporting patients at health facilities, an intervention providing smear

microscopy on a regular basis to everyone in the community with cough ≥ 2 weeks, and intensified case finding in HIV-infected (ICF). This analysis utilized data on 91 of 117 (78%) participants with prevalent PTB who were not on TB treatment at the time of the survey and had complete data on HIV status and contact with care providers.

The study was approved by the scientific and ethical steering committees of the Kenya Medical Research Institute (protocol number 943) and the institutional review board of the US Centers for Disease Control and Prevention (protocol number 4712).

RESULTS

Participation

According to the 2006 HDSS database that was used for sampling, 30,759 eligible residents were registered in the sampled clusters, and 22,656 (74%) eligible persons were present in the home during initial or repeat study visits. Presence in the home was significantly lower in men (62%) than women (83%), significantly lower than the average in men aged 15-44 years and in women aged 15-24 years (Annex Table 1). Of those present, 20,710 (91%) consented to participate (range by age and sex group 86-94% (Annex Table 1)). After exclusion of 144 (0.7%) records with missing interview data, the analysis included 20,566 participants, of whom 63% were female (Figure 2). The median number of participants per cluster was 541 (inter-quartile range 436-607, annex Table 2). During the interview, 3,490 persons (17%) reported symptoms suggestive of PTB (Figure 3, Annex Table 2). Of the 19,216 (93%) participants who underwent chest radiography, 5,342 (28%) had an abnormal CXR as judged by the clinical officer, 20,409 (99%) participants provided a spot sputum sample and 19,788 (96%) an overnight sample. Of the 7,346 (36%) participants with suggestive symptoms or

CXR abnormality, 6,808 (93%) had a culture result, of which 162 (2%) were contaminated on both media. Sputum results of persons who were unable to provide a sputum sample for microscopy or culture, and of contaminated cultures, were considered negative.

Prevalence

In total, 123 persons with pulmonary TB were identified: 47 (38%) smear-positive, culture-positive, 72 (59%) culture-positive, smear-negative, and 4 (3%) culture negative, smear-positive (Figure 3). Eighty-six persons reported being on TB treatment at the time of the survey of whom 80 did not have bacteriologically confirmed PTB by study definitions and were therefore not classified as prevalent PTB in further analyses. The prevalence of bacteriologically confirmed PTB in the study population was 6.0/1000 (95% confidence interval (CI) 4.6-7.4), and the prevalence of smear-positive PTB 2.5/1000 (95% CI 1.6-3.4).

The prevalence of PTB was higher in men than women (crude OR 1.5; 95% CI 1.1-2.2). The age distribution differed by gender (Table 1): in women, prevalence was highest in the age group 25-34 year, and in men, in those aged 35-54 years. Other risk factors for prevalent TB included previous TB treatment (adjusted OR (aOR) 2.7; 95% CI 1.4-5.1), recent in-migration (aOR 2.9; 95% CI 2.0-4.1), and lowest socio economic asset score quartile (aOR 1.5; 95% CI 1.0-2.1). Tuberculosis prevalence was highest in participants living at 2-2.9 km from a health facility providing TB treatment, compared to those who lived either nearer or further away. Education level, the number of persons sleeping in the house, and having lived with a TB patient in the previous 2 years were not significantly associated with prevalent TB (Table 1).

HIV

HIV status was available for 101 (82%) prevalent cases. Fifty-two (51%) were HIV-infected and had a median CD4 cell count of 196 cells per µl (interquartile range (IQR) 126-282). Thirteen (25%) reported knowing their HIV-positive status prior to TB diagnosis. Smear results were not significantly associated with HIV status and CD4 cell count. HIV-infected cases were younger (median age 35 years, IQR 28-47) than HIV-uninfected (median 53 years, IQR 28-71, p=0.0025 Wilcoxon rank sum test), but did not differ by gender. HIV prevalence was 1/19 (5%) among cases 65 years and older. Among the cases, recent in-migrants had a higher HIV prevalence (27/32, 84%) than those known to the HDSS for longer than 6-12 months (25/69 (36%), p<0.001, Annex Table 4).

We estimated that 48% of prevalent TB (both smear positive and all bacteriologically confirmed) in the study population was attributable to HIV (Table 2). Among notified new PTB cases in Nyanza Province, the PAF of HIV was 58% for smear-positive and 65% for all PTB. The rate at which new PTB cases were detected, expressed as the PDR, was higher for HIV-infected (1.4 cases detected per person-year among persons having all PTB) than for HIV-uninfected PTB cases (0.6 cases detected per person-year for all PTB), but the proportion of HIV-infected PTB cases detected, expressed as the CDR, was lower: 56% compared to 65% in HIV-uninfected (Table 3).

Case finding

A cough for three or more weeks, the main indication for initiation of diagnostic investigations in the health facilities at the time this study was conducted, was reported by 48 (39%) of 123 PTB cases, 29 (57%) of 51 smear-positive and 19 (26%) of 72 smear-negative cases (p<0.001). Half (52%) of the cases reported a cough for 2 or more weeks, and a quarter

reported no cough at all. Cough was more common in HIV-infected cases: a cough for three or more weeks was reported by 26 of 52 (50%) HIV-infected and by 15 of 49 (31%) HIV-uninfected cases (p=0.05), and cough of any duration by 49 of 52 (94%) and 30/49 (61%) respectively (p=<0.001). CXRs, also used in the health facilities to diagnose PTB, showed abnormalities in 113 (94%) of the 120 persons with PTB who had a CXR.

Of the 123 prevalent cases, 6 (5%) reported taking anti-TB treatment at the time of survey (1 smear-positive), and 9 (7%) reported prior treatment (6 smear-positive). Of the prevalent cases not currently on treatment, 91 (78%) were interviewed about contact with health providers. In the previous year, 22 of 45 (49%) smear-positive versus 11 of 46 (24%) smear-negative cases had sought care at a public health facility (p=0.017). Cases who reported a cough for 3 or more weeks reported seeking care significantly more often in the previous year than those with cough for a shorter duration or no cough (19/38 (50%) versus 14/53 (26%) p=0.028). However, among those with 3 or more weeks of cough, only 12/38 (32%) had sought care in the previous 3 months. Health provider contact did not differ by HIV status.

Among the 91 prevalent cases who were diagnosed by the survey, 15 (16%) who had consulted a public health provider in the previous 6 months would possibly have been diagnosed earlier if case detection at health facilities were more successful and high quality smear microscopy were offered to all patients self-presenting with prolonged cough for ≥ 2 weeks (Figure 4). An additional intervention providing smear microscopy on a regular basis to everyone in the community with cough ≥ 2 weeks would have identified 34 (37%) cases. Intensified case finding in HIV-infected (ICF) alone, assuming the entire population knew their HIV status and attendance at HIV care services was high, could have identified 45 (49%) of prevalent cases if smear-positive and smear-negative cases were adequately

diagnosed. Combining all three interventions would have identified 63% of the prevalent cases.

DISCUSSION

We found a high prevalence of bacteriologically confirmed PTB. The estimated proportion of PTB attributable to HIV infection was 48% for prevalent, and 58-65% for notified PTB. While the patient diagnostic rate was higher in HIV-infected than HIV-uninfected TB patients, the proportion of cases detected was estimated to be lower among HIV-infected TB patients, presumably because of greater mortality in persons with HIV. (2, 35) Most of the identified prevalent cases would not have been identified by the current case detection approach based on smear-microscopy in self-reporting patients with prolonged cough. Improved case finding strategies with the potentially highest impact on TB prevalence suggested by this study were, in addition to improving case finding at health facilities, active case finding of smear-positive cases with a cough for 2 or more weeks, combined with ICF in HIV-infected persons, assuming the entire population knew their HIV status and high attendance at HIV-services. The latter would be expected to also lower TB incidence through increased ART uptake. (20)

A high prevalence of TB in populations with high HIV prevalence has been reported in several sub-Saharan African settings (17, 18, 20, 36), but this study is one of the first comprehensive surveys in a rural African population. Earlier studies including from Kenya had suggested that most TB cases could be identified by decentralized health services (10, 37), but these studies were conducted in populations with low HIV prevalence, and had restricted bacteriological examination to persons with a cough over 3-4 weeks identified by household heads. Our survey applied a more comprehensive symptom algorithm and obtained

CXRs from all adult community members, identifying a considerable burden of undiagnosed infectious TB. Our estimated case detection rate for all PTB (56% in HIV-infected and 65% in HIV-uninfected) was in the same range but somewhat lower than the CDR reported for Kenya, which was 71% (59-88) for all TB cases in 2005 and 79% (66-98) in 2008. Achieving the STOP-TB partnership 2015 target CDR of 84% (38) poses substantial challenges. The differences between the CDR estimate we found and those reported for Kenya may be explained by regional differences and less successful TB control in the study region, by a higher proportion of HIV-infected in whom case detection has been reported to be lower (6, 20), and/or by different methods used to estimate CDRs and uncertainties in the assumptions. (2, 6) Data from our and other TB prevalence surveys may contribute to validation of the CDR estimation methods. National TB prevalence surveys have resulted in upward CDR adjustment in Eritrea (39) and downward adjustment in Viet Nam.(2) A national survey is therefore highly recommended in Kenya, to better assess case detection and also as a step towards direct measurement of the impact of the overall control program. (3)

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The estimated PAF of HIV on prevalent TB (48%) was lower than on notified PTB, but higher than reported in high HIV prevalence populations in Zambia (36%) (18), and Zimbabwe (33%).(36) Consequently a large burden of unrecognized PTB in HIV-infected is also contributing to community transmission,(40, 41) and to mortality in the studied population.(35) Intensified case finding among HIV-infected is WHO policy, but not implemented widely (2). Aside from barriers to effective screening, impact is limited by low knowledge of HIV status (36), which was below 20% among HIV-infected in Kenya in 2007 (23), and among persons with TB-HIV identified in the survey only 25% knew their HIV status prior to TB diagnosis. Interventions to improve uptake of HIV testing have been well received in this region. (42) Widespread knowledge of HIV status, high attendance at HIV

services, and better algorithms and diagnostic services to rapidly diagnose smear-negative TB (43), would reduce HIV-attributable TB prevalence by ICF, as well as by the effect of anti-retroviral treatment (ART) on TB prevalence. (20) In the study area availability of ART gradually increased from 2004. At the time of survey less than 10% of HIV-infected had started ART.(44)

This study also shows the importance of improving case finding of HIV-uninfected persons with TB, who were detected at a low rate and comprised half the TB prevalence, although they represented only 29% of notified cases. Improving TB case detection by enhancing the current passive case finding strategy alone would be expected to have limited success, with the reported low contact with TB care providers and known shortcomings of conventional smear microscopy.(45) Improving passive case finding by the health service, using sputum culture, CXR and additional staffing increased case detection in some high HIV prevalence urban occupational settings. (17) Health-system strengthening to this level may also enhance early care seeking by persons with TB, but is far from available in a rural African setting. In the meantime the feasibility of a mobile van to collect sputum for microscopy would be worth exploring. This approach was successful in Harare in an urban slum setting in reducing prevalence, more so than door-to-door case finding. (21) Mobile services may be appealing to mobile or migrant populations, who had high TB and TB-HIV prevalence in this study. Additional efforts may be needed to include housebound elderly. TB diagnostic services could be combined with HIV-counselling and testing. The feasibility and costs of these interventions require further study.

The disease, transmission, and movement patterns of the population classified as recent in-migrants requires further study. This predominantly young population did not (yet) meet the HDSS resident definition requiring residency in the area for at least 4 months at the HDSS enumeration round prior to the time of our survey. Although illness related migration is common in Africa (46), only 2% of the prevalent cases reported to have moved into the area because of illness (data not shown).

The maximum possible benefit from any case finding interventions would only be reached if a simple highly sensitive test for all bacteriologically active PTB were available. In our setting, this would reach approximately 1/3 of prevalent cases if applied to suspects visiting health facilities, 2/3 if applied in a community based case finding strategy in combination with the symptom algorithm used in our study and 100% if applied based on symptoms and CXR abnormalities as done in this survey, or offered to the total population. The development of such tests deserves a high priority on the global TB research and development agenda.

The design and logistical challenges of the study may have affected the reported prevalence. We observed participation bias, however a weighted prevalence estimate, adjusting for differential non-participation, was only 3-5% lower (data not shown). Laboratory cross-contamination could account for some false-positive cases. (47) HIV-infected persons may have been more likely to report symptoms suggestive of TB (48), but less likely to have CXR abnormalities. This could potentially bias the PAF estimate but a sensitivity analysis showed no significant effect (data not shown). A number of smear-negative cases may have been missed among participants who did not have or did not report symptoms suggestive of TB (18, 49), and in whom CXR abnormalities were absent (49) or misclassified, since sputum

was not cultured from all participants, and we only cultured one sputum sample. (50) Overall, we consider the reported prevalence to be minimum estimate. An additional limitation of our study is that HIV status was not obtained from all participants, only from identified cases, and was unavailable for 22 (18%) of those, in 15 (68%) because the patient had died by the time of follow up, possibly due to HIV infection.

In conclusion, we found a high burden of prevalent and predominantly undiagnosed PTB in this rural community, in HIV-infected and uninfected. There is a need to improve TB case finding. The approaches with the highest potential yield include a combination of ICF with rigorous HIV testing and improved diagnosis of smear-negative PTB, together with mobile smear microscopy services; such interventions and their evaluation should be operations research priorities.

Acknowledgements

We acknowledge the KEMRI/CDC Research and Public Health Collaboration staff , the study team, the TB and HIV laboratories, the KEMRI CRDR staff, the TB clinics, the Asembo and Gem communities, and the study participants and the CDC-Kenya Global AIDS Program. We thank Richard Chaisson for his facilitative role, and John Williamson for statistical advice. This paper is published with the approval of the Director KEMRI. The KEMRI/CDC HDSS is a member of the INDEPTH Network.

Disclaimer

The views expressed in this manuscript do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices or organizations imply endorsement by the US government.

Author contributions:

Study conception: KDC, BJM, MWB, and AHH

Study design: MWB, KDC, BJM, AHH and WAG

Study planning and conduct: AHH, WAG. HKM, JAA, LOO, BGM, KL.

Data analysis and drafting of manuscript: AHH

Revision of manuscript for important intellectual content: all authors.

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Figure legends and footnotes

Figure 2. Selection of Study Participants from the Population in the HDSS* Area

*HDSS=Health and Demographic Surveillance System

†Of the eligible population expected according to the HDSS registration at the time of sampling, 3,314 (11%) had moved, 337 (1%) had died, 418(1%) were unable to consent, and 7,760 (26%) were not available at the time of survey. 3,726 persons were eligible, but not yet registered by the HDSS.

‡Includes 1 smear negative (MGIT) culture positive case.

Figure 3. Distribution of PTB Cases by Symptoms and Chest Radiograph Abnormality

PTB=Pulmonary Tuberculosis, CXR=Chest Radiograph, Smear=Sputum smear microscopy, + = Positive, - = Negative

* The denominators for the percentages are in the box one level upward.

† 1 participant had not provided a sample, 3 samples were contaminated on MGIT and negative on LJ.

‡Participants who did not provide any sputum sample (n=157) are considered smear-negative culture-negative

Table 1. Prevalence of Bacteriologically Confirmed PTB, and Risk Factors

PTB=Pulmonary Tuberculosis CI=Confidence Interval HDSS=Health and Demographic Surveillance System

* p ≤0.05

§Missing values of explanatory variables were multiply imputed for the multivariate analysis; 88% of records had complete data for all variables listed in the table.

†Adjusted for cluster sampling

‡A hospital, health centre or dispensary where TB drugs are dispensed under supervision of the national TB program, and staff are expected to have been trained on TB. Calculated as the absolute distance based on geographic coordinates.

Table2. Gender and Age Standardized Estimates to Determine the Population Attributable Fraction (PAF) of HIV for Prevalent PTB in the Study Area and for Notified PTB in the Province.

PTB=Pulmonary Tuberculosis; PAF=Population Attributable Fraction;

*The study population and prevalent TB cases were standardized for age and gender to the population in the Health and Demographic Surveillance system (HDSS). Home based Voluntary HIV counseling and testing data from 32.000 persons aged 15 years and above were used to estimate the number of HIV-infected persons in HDSS population (KEMRI/CDC unpublished data).

Table 3: Estimates of Patient Diagnostic Rate (PDR) and Case Detection Rate (CDR) for new PTB in HIV-infected and uninfected.

PTB+=Smear-positive Pulmonary Tuberculosis. 15+ = aged 15 years and above

*Expressed as the number of cases detected per-person year among persons having PTB.

We assumed HIV results in persons with missing results to be similar to those not missing.

Of 22 missing results, 15 were due to death before follow up and 7 were not found, refused or not tested.

Tables and Figures

Figure 1: Screening Procedures to Select Participants Eligible for Sputum Culture

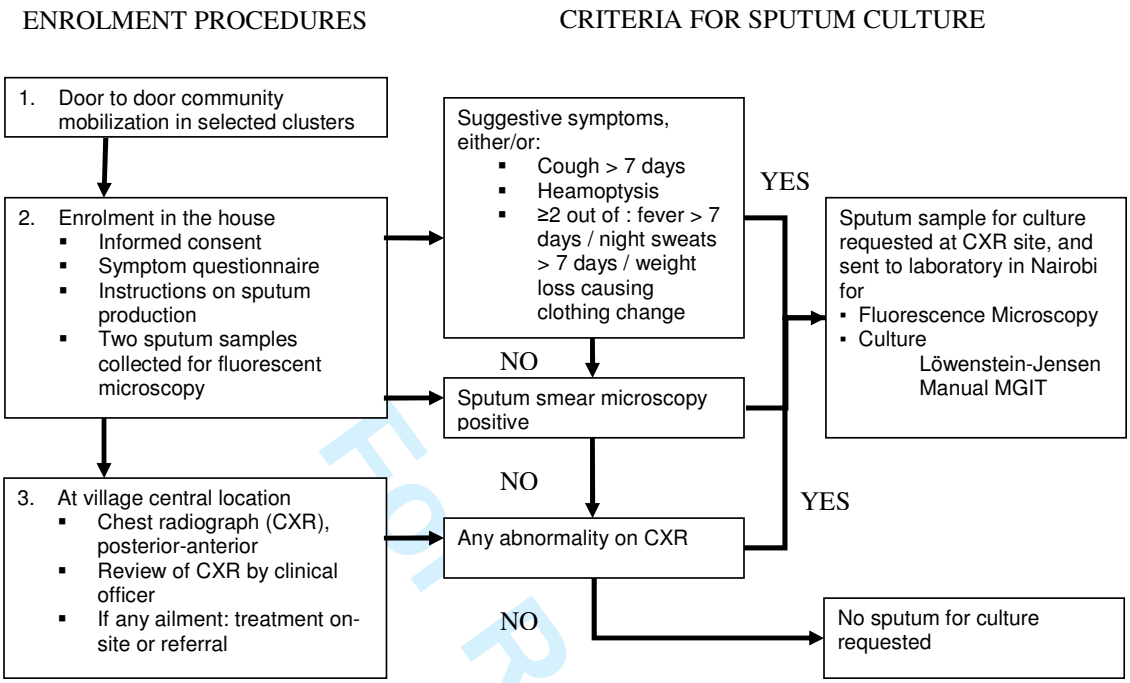
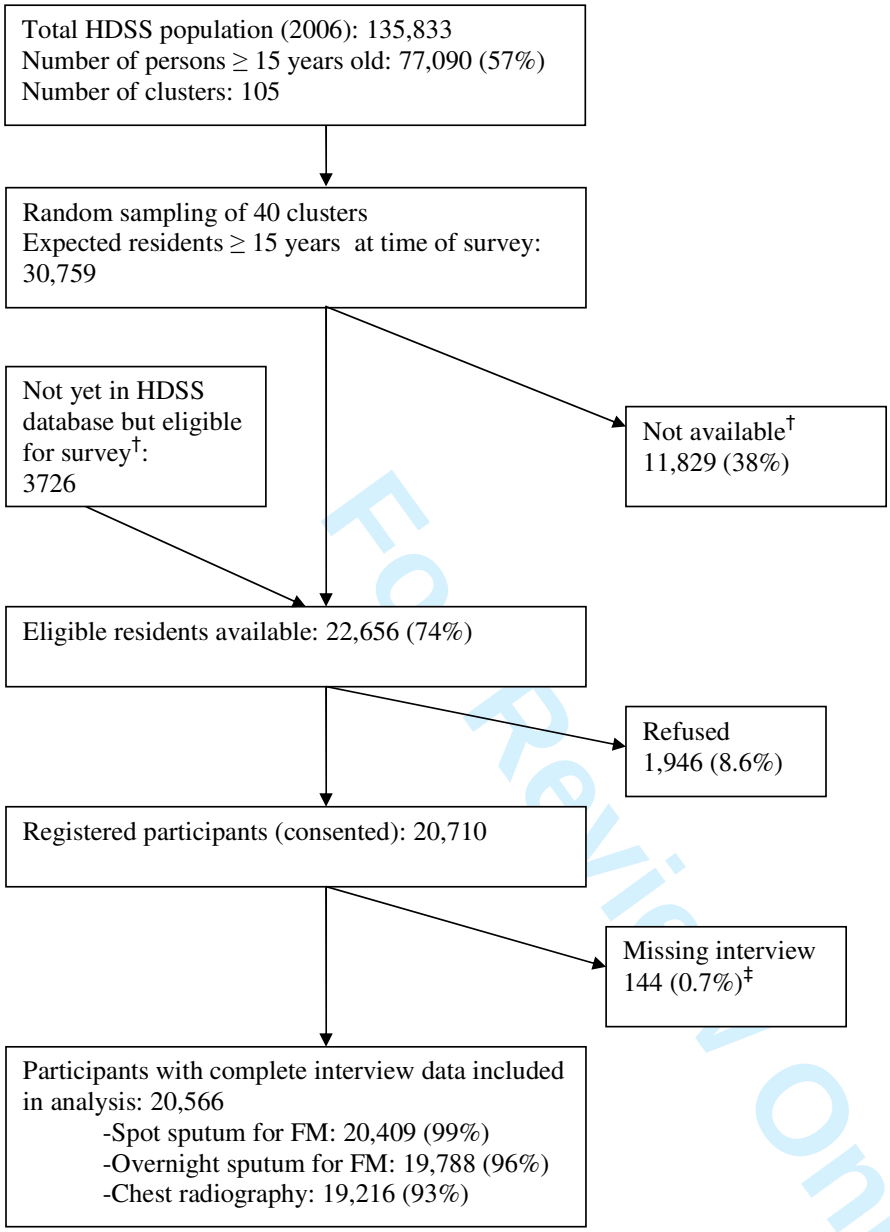


Figure 2. Selection of Study Participants from the Population in the HDSS* Area



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†Of the eligible population expected according to the HDSS registration at the time of sampling, 3,314 (11%) had moved, 337 (1%) had died, 418(1%) were unable to consent, and 7,760 (26%) were not available at the time of survey. 3,726 persons were eligible, but not yet registered by the HDSS.

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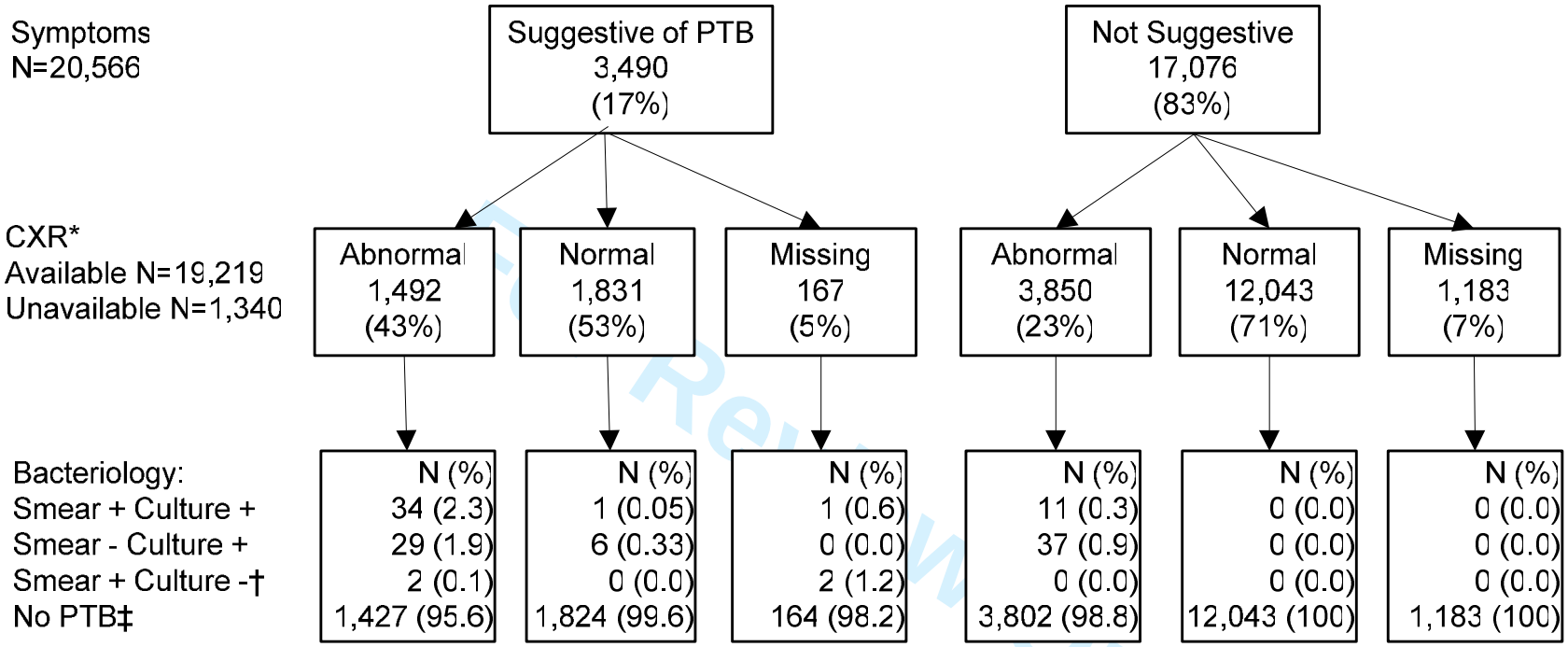
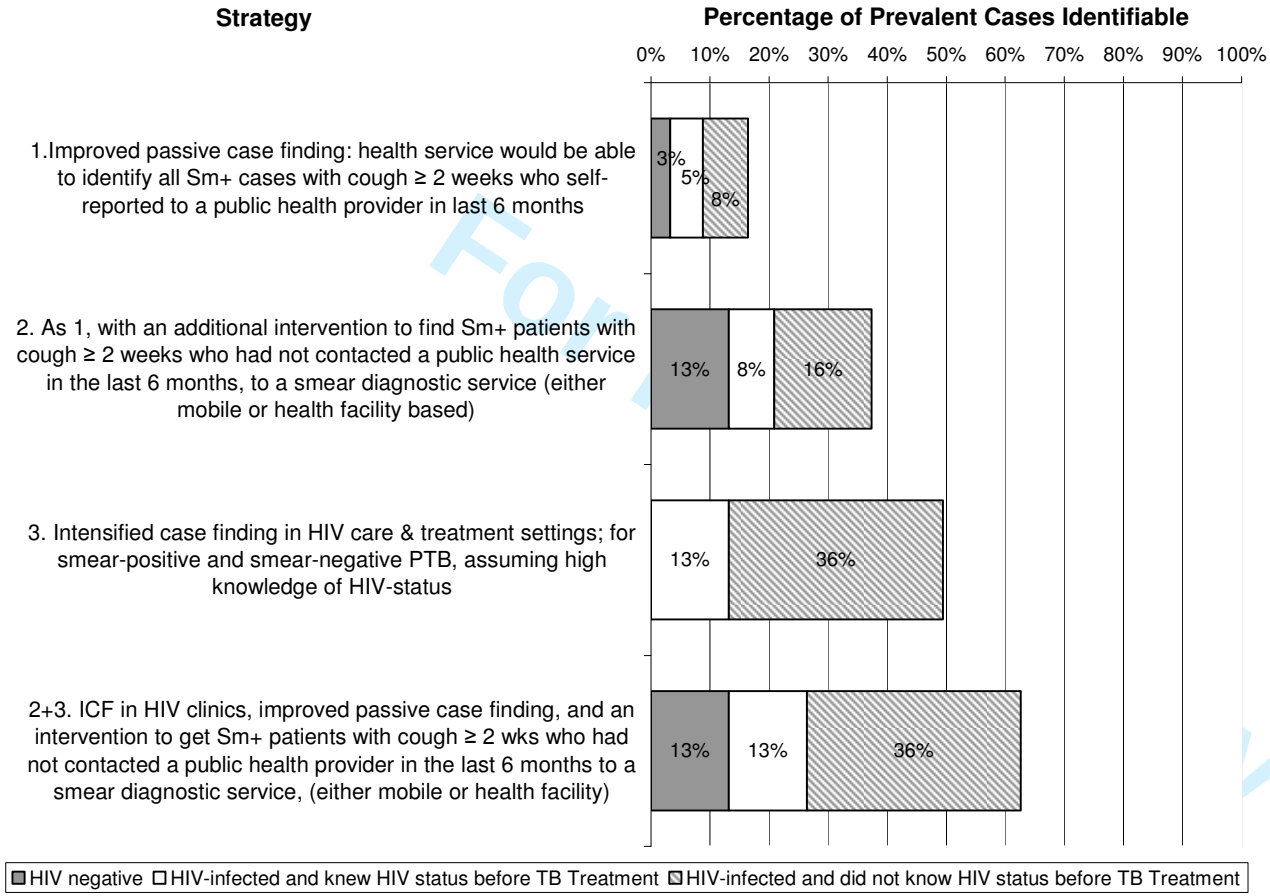


Figure 4 – Potential Yield of Applying different Case Finding Strategies on Prevalence of Pulmonary TB, and Potential Overlap with Strategies targeting HIV-infected Populations.



Tables

Table 1. Prevalence of Bacteriologically Confirmed PTB, and Risk Factors

		Cases (all PTB)	Participants	Prevalence per 1000†	Crude OR (95% CI)		Adjusted OR (95% CI)§	
Total		123	20,566	6.0				
95% CI				4.6 ; 7.4				
Design effect				1.62				
Gender and Age					p=0.05		p=0.17	
Females	15-24	14	3,752	3.7	0.53	(0.22-1.30)	0.47	(0.19-1.16)
(age in years)	25-34	17	2,426	7.0	1		1	
	35-44	12	1,932	6.2	0.89	(0.40-1.97)	1.04	(0.47-2.28)
	45-54	7	1,844	3.8	0.54	(0.20-1.45)	0.63	(0.25-1.59)
	55-64	5	1,246	4.0	0.57	(0.24-1.34)	0.64	(0.27-1.54)
	65+	10	1,771	5.7	0.80	(0.41-1.58)	0.82	(0.34-2.02)
Males	15-24	5	2,810	1.8	0.25	(0.08-0.81)	0.25	(0.08-0.78)
	25-34	13	1,240	10.5	1.50	(0.68-3.33)	1.09	(0.46-2.59)
	35-44	12	881	13.6	1.96	(0.95-4.05)	1.49	(0.70-3.18)
	45-54	11	820	13.4	1.93	(0.91-4.07)	1.57	(0.73-3.40)
	55-64	7	801	8.7	1.25	(0.52-2.99)	1.25	(0.51-3.05)
	65+	10	1,043	9.6	1.37	(0.57-3.28)	1.42	(0.61-3.33)
Reported history of TB treatment					p<0.001		p=0.002	
None reported		114	20,115	5.7	1		1	
Previously treated		9	440	20.5	3.67	(1.95-6.88)	2.70	(1.42-5.13)
Missing§		-	11					
TB contact in the house in previous 2 years					p=0.07			
Yes		18	2,013	8.9	1.58	(0.97-2.56)		
None reported		105	18,461	5.7	1			
Missing§		-	92					
Education					p=0.37			
None		18	2,709	6.7	1			
Some primary		82	13,981	5.9	0.88	(0.58-1.34)		
More than primary		15	3,112	4.8	0.72	(0.37-1.41)		
Missing§		8	764	10.5				
Smoking					p<0.001		p=0.16	
Current Smoker		27	2,129	12.7	2.66	(1.66-4.26)	1.79	(0.96-3.34)
Past smoker		21	2,846	7.4	1.54	(0.87-2.70)	1.25	(0.61-2.53)
Never smoked		75	15,583	4.8	1		1	
Missing§		-	8					
Recent in migrant					p<0.001		p<0.001	
Known to HDSS for > 6-12 months		82	16,914	4.9	1		1	
Recent In-Migrant		41	3,652	11.2	2.33	(1.67-3.26)	2.85	(1.97-4.13)
Socio Economic Asset Score					p=0.01		p=0.05	
<25%		34	4,122	8.3	1.68	(1.16-2.45)	1.45	(1.00-2.09)
≥25%		73	14,883	4.9	1		1	
Missing§		16	1,561	10.3				
Number of persons sleeping in same house					p=0.52			
1-2		60	10,057	6.0	1			
3-4		33	5,884	5.6	1.12	(0.72-1.75)		

5+	16	3,701	4.3	0.82	(0.48-1.39)		
Missing[§]	14	924	15.2				
Distance to a TB treatment facility‡					p=0.02		p=0.005
< 1 km	10	3,043	3.3	0.41	(0.22-0.75)	0.37	(0.20-0.66)
1- < 2 km	30	5,251	5.7	0.71	(0.48-1.05)	0.71	(0.48-1.05)
2- < 3 km	50	6,229	8.0	1		1	
3- < 4 km	27	4,662	5.8	0.72	(0.48-1.08)	0.69	(0.46-1.03)
4+ km	6	1,381	4.4	0.54	(0.28-1.03)	0.55	(0.29-1.05)

PTB=Pulmonary Tuberculosis CI=Confidence Interval HDSS=Health and Demographic Surveillance System[§]Missing values of explanatory variables were multiply imputed for the multivariate analysis; 88% of records had complete data for all variables listed in the table.
[†]Adjusted for cluster sampling
‡A hospital, health centre or dispensary where TB drugs are dispensed under supervision of the national TB program, and staff are expected to have been trained on TB. Calculated as the absolute distance based on geographic coordinates.

Table 2. Gender and Age Standardized Estimates to Determine the Population Attributable Fraction (PAF) of HIV for Prevalent PTB in the Study Area and for Notified PTB in the Province.

	Prevalent PTB from Survey					Notified PTB in Nyanza Province (32)				
Population	Cases*	Population Size*	Prevalence per 1000	PAF (c-b)/c	Prevalence Rate Ratio (a/b)	Cases	Population Size	Notification per 1000	PAF (c-b)/c	Notification Rate Ratio (a/b)
	Culture and/or Smear-positive					All New PTB (Smear-positive, negative and smear not done)				
HIV+ (a)	250.3	11,799	21.22	48%	7.0	11589.7	418,235	27.71	65%	14.7
HIV- (b)	199.1	65,291	3.05			5081.3	2,689,114	1.89		
All (c)	449.4	77,090	5.83			16671.0	3,107,349	5.37		
	Smear-positive					Smear-positive				
HIV+ (a)	102.5	11,799	8.69	48%	7.1	110.8	9,748	11.37	58%	11.9
HIV- (b)	80.2	65,291	1.23			64.2	67,342	0.95		
All (c)	182.7	77,090	2.37			175.1	77,090	2.27		

PTB=Pulmonary Tuberculosis; PAF=Population Attributable Fraction;
*The study population and prevalent TB cases were standardized for age and gender to the population in the Health and Demographic Surveillance system (HDSS). Home based Voluntary HIV counseling and testing data from 32.000 persons aged 15 years and above were used to estimate the number of HIV-infected persons in HDSS population (KEMRI/CDC unpublished data).

Deleted: 34)

Table 3: Estimates of Patient Diagnostic Rate (PDR) and Case Detection Rate (CDR) for new PTB (Smear-positive and Smear-negative combined) in HIV-infected and uninfected.

Population		(a) Notification rate of new PTB per 1000 population 15+	(b) Prevalence of new PTB per 1000 population 15+	(a)/(b) Patient Diagnostic Rate*	(d) Duration of disease (years) (2)	Case Detection Rate
	HIV+	27.71	20.60	1.34	0.93	56%
	HIV-	1.89	3.12	0.61	3	65%
	Total	5.37	5.79	0.93		

PTB=Smear-positive Pulmonary Tuberculosis. 15+ = aged 15 years and above

*Expressed as the number of cases detected per-person year among persons having PTB.

We assumed HIV results in persons with missing results to be similar to those not missing. Of 22 missing results, 15 were due to death before follow up and 7 were not found, refused or not tested.

Online Data Supplement

High Prevalence of Pulmonary Tuberculosis and Inadequate Case Finding in Rural Western Kenya

Anna H van't Hoog (1,2), Kayla F Laserson (1,3), Willie A Githui (4), Helen K Meme (4), Janet A Agaya (1), Lazarus O Odeny (1), Benson G Muchiri (1), Barbara J Marston (3), Kevin M DeCock (3,5), Martien W Borgdorff (2).

DETAILED METHODS

Sampling and Study Population

We randomly selected 40 of 105 clusters of 1-4 villages to obtain a sample of 20.000 participants[2], to measure a point prevalence between 0.5%-1% with a standard error ≤0.1%. Data collection took place from August 2006 through December 2007.

We grouped 217 villages in the study area in 105 clusters of 1-4 villages, with an average population size of 1279 (range 752-1959), expected to yield on average 500 study participants per cluster. We selected 40 clusters through simple random sampling. All persons aged 15 years and above who resided in these clusters for at least one month and were able to provide informed consent were eligible to participate in the study.

Study Procedures

Data collection took place between 31 July 2006 and 20 December 2007. After door to door community mobilization, a study worker visited all compounds in the sampled clusters,

accompanied by a village informant. Persons not at home were reminded and 2 revisit attempts were made. Individual written informed consent was obtained at the homes, followed by a questionnaire with questions on the presence and duration of symptoms suggestive of TB (cough, hemoptysis, weight loss, fever, night sweats, see Figure 1), history of TB treatment, household contact with TB patients, and smoking. The unique Health and Demographic Surveillance System (HDSS) identifiers of participants were confirmed or updated to allow data linkage.

We requested all participants to provide two sputum samples for microscopic examination. The study workers gave instructions on sputum collection aided by simple breathing techniques {E1} and observed the production of one spot sample. An unobserved early morning sample was collected the next day.

We requested all participants to undergo chest radiography at a mobile unit located at a nearby location. We provided transport if walking was not feasible. One chest radiograph (CXR), posterior-anterior view, 35 by 43 cm, was made using a 40 KW radiography machine, and developed in an automatic high speed film processor. CXRs were reviewed –independent of participant information- the same day onsite by a trained clinical officer, and classified as either ‘normal’ or ‘abnormal’, in case of any abnormality. At a later time, a radiologist reviewed all CXRs using a chest radiograph recording and reporting system described elsewhere. {E2} At the CXR location, we requested an additional sputum sample for culture if a participant had either symptoms defined as suggestive of TB (cough for more than 1 week and/or hemoptysis and/or two or more of the following: weight loss that led to a change in fit of clothes, fever for the last 2 weeks or more, night sweats for the last 2 weeks or more), or any abnormality on CXR or a positive sputum smear microscopy. Figure 1). Abnormalities

were not restricted to the lungs or being suggestive for PTB. Participants with any illness were treated or referred as appropriate.

Laboratory methods

Sputum samples were collected in 50 ml plastic centrifuge tubes, and kept cool before and during (daily) transportation to the KEMRI/CDC laboratory in Kisumu (±50-100 km away from the study area), where the samples for microscopy were processed. Sputum samples were liquefied and decontaminated with 4% NaOH-NALC, concentrated, stained with Auramine O and examined by fluorescence microscopy (FM). Each smear was scored by one reader in accordance with standard methods. {E3} If one or more acid fast bacilli (AFB) per equivalent of 100 immersion fields were observed (adjusted for the magnification), a second reader reviewed the slide. If the second review was also positive, the result was confirmed. A blinded independent reader also examined a random 10% sample of negative smears (mixed with positives).

Sputum samples collected for culture were transported by road to the laboratory at the KEMRI Centre for Respiratory Disease Research laboratory (CRDR) in Nairobi, at ±400 km distance within 1-4 days after collection. Sputum was processed as described above. After decontamination we incoculated each sample on two Löwenstein-Jensen (LJ) slants {E4,E5} and one 8ml Mycobacteria Growth Indicator Tube (MGIT^{TM} Manual Mycobacterial Growth System, Becton Dickinson, Franklin Lakes, USA) {E6}, using separate sterile Pasteur pipettes and pipette tips, respectively, for each sample. A slide for FM was made from the concentrate prior to culture. LJ slants and MGIT tubes were incubated at 37^{o}C and read weekly for 8 and 6 weeks respectively. Löwenstein-Jensen slants were considered positive for *M.tuberculosis* complex by conventional phenotypic identification tests {E4,E5}or

Capilia test, an immunochromatographic assay (FIND and Tauns Co. Ltd). {E6} Mycobacterial growth in the MGIT tubes was determined by a 365 nm UV transilluminator manual reader, followed by Ziehl-Neelsen microscopy and species identification was confirmed by Capilia. {E7} To monitor laboratory cross-contamination, simulated specimens {E8} were included in every batch of media as negative and positive (H37Rv strain) controls. All negative and positive controls were negative and positive on microscopy and culture, respectively. Negative controls following positive samples were negative.

Case definitions

Smear-positive prevalent PTB was defined as two or more smears positive for AFB, unless positive on culture for nontuberculous mycobacteria and not for *M.tuberculosis* complex), or one positive smear and a positive culture. Culture-positive, smear-negative prevalent PTB was defined as a culture positive for *M.tuberculosis* complex without a positive smear. A positive culture was defined as (i) growth of ≥ 5 colonies on LJ medium with AFB confirmation by ZN smear, a positive Capilia test or a standard identification profile {E4, E8}, or (ii) a MGIT culture with growth, showing AFBs on ZN microscopy and a positive Capilia test.

Data collection among TB cases

Participants with PTB were interviewed about presence and duration of symptoms and contact with health providers and referred for TB treatment. HIV testing and CD4 cell count (FacsCalibur® Becton Dickinson, San Jose, CA) were performed.were done, after consenting and counseling. HIV infection was defined as presence of antibodies against HIV on standard ELISA tests in parallel (Enzygnost anti HIV-1/HIV-2 Plus®; Dade Behring Diagnostics, Marburg, Germany, and Vironostika HIV Uni-Form II Ag/Ab® Biomerieux, Boxtel, The

Netherlands) and a third ELISA test (BioRad HIV-1/2 Plus O EIA®, Bio-Rad Laboratories, Redmond, WA) if discordant.

HIV-infected TB patients were offered HIV care and treatment in line with national guidelines.

Data processing and statistical analyses

Every participant was assigned a unique study number that was bar-coded to link the study forms, samples and radiographs. Questionnaire data were collected on handheld computers (PDA). Data on household registration, radiography reporting and culture results were entered on scannable forms (Cardiff Teleforms®, Autonomy Cardiff, San Diego, California, USA). Responses to questionnaires addressing care seeking behaviors and the results of AFB smear testing were entered manually, the latter double, and discrepancies resolved from the original forms. Different data sources were cross-checked for validity.

Survey data were linked to the HDSS, to determine: (i) education level; (ii) recent in-migration, defined as a person who did not meet HDSS residency criteria at the time of collection of the HDSS data available to the survey (approximately 6-12 months previous), either due to recent in-migration or extreme mobility. For the HDSS, a minimum residency period of 4 months is required; (iii) to compute the absolute distance to health facilities, based on geographic coordinates; (iv) the number of persons registered as sleeping in a house; and (v) socio-economic status, which was based on an asset ranking score. Principal component analysis (PCA) method was used to generate weights for the following broad household characteristics: occupation of participant and spouse, source and quality of water, source of fuel for cooking, livestock and asset ownership. {E9} The scores were used to rank the study participants in socio-economic status quartiles.

Statistical analyses were done using SAS 9.1 survey procedures (SAS Institute Inc., Cary, North Carolina, USA) for crude, stratified and multivariable analyses, which takes correlation within the cluster into account using the Taylor series (linearization) method to estimate the covariance of the regression coefficients.

The reported risk factors for prevalent PTB were examined in a univariate logistic regression model, then stratified for gender and added (forward selection) to a logistic regression model based on known (biological) plausibility, statistical significance in univariate analysis ($p<0.20$) and contribution to the model. Missing values of explanatory variables were multiply imputed. {E10}

Differences in proportions were tested with chi-square test, or Fisher's exact test if the sample was small. All reported prevalence estimates, odds ratios and 95% confidence intervals were adjusted for cluster sampling.

Population attributable fraction and case finding

In order to assess the population impact of HIV, we estimated the population attributable fraction (PAF) of prevalent PTB due to HIV in the population aged 15 years and older, and on notified PTB for comparison. For the former, since HIV status was only available for PTB cases, we extrapolated age- and gender-specific HIV prevalence rates from home based HIV testing and counselling of 32,000 persons aged 15 years and older in the HDSS area (KEMRI/CDC, unpublished data) to estimate the number of HIV-infected study participants. To estimate the PAF of HIV on notified PTB, we obtained age- and gender-specific HIV prevalence in the provincial population from a national HIV survey {E11}, and used the Nyanza Province (2007) reports of TB notifications and HIV prevalence among notified PTB patients: in adult TB patients (≥15 years), 62% of new notified smear-positive, and 70% of all new notified PTB patients (new smear-positive and negative combined) were HIV-

infected.{E12} For smear-positive PTB we standardized age- and gender-specific PTB prevalence, PTB notification (both stratified by HIV status), and HIV prevalence rates to the 2006 HDSS population structure. For smear-positive and smear-negative notified PTB combined the same standardization was not applied, since smear-negative PTB notifications and HIV prevalence in smear-negative PTB patients are not routinely reported by age group. We used the same data on provincial TB notifications, HIV prevalence, and standardization approach to estimate HIV-specific patient diagnostic rates (PDR) and case detection rates (CDR) for new PTB cases. The PDR is the rate at which prevalent cases are detected by control programs and can be measured as the number of reported cases per 100,000 persons per year divided by the prevalence per 100,000 {E13}. The case detection rate was calculated as proposed by Dye et al {E14}, and expresses the proportion of new PTB cases detected during the reported year, derived from the PDR and the rates (obtained from other reports {E15} at which patients die or self-cure:

$$CDR = \frac{PDR\ pyr^{-1}}{\left(PDR + \frac{1}{d}\right) pyr^{-1}} \qquad \{E15\}$$

The duration of disease (d) was assumed to be about 3 years in HIV-uninfected and the disease duration ratio of 0.31 in HIV-positive people as compared with HIV-negative people.{E15} For the estimation of the PDR and CDR re-treatment cases (i.e. treated within previous 2 years) were excluded from the prevalent cases, to be consistent with notifications of new PTB.

We also calculated the number of persons with prevalent PTB who would have been detected by approaches to improve TB case finding that are currently not in place: improved case detection at health facilities, an intervention providing smear microscopy on a regularly basis to everyone in the community with cough ≥ 2 weeks, and intensified case finding in HIV-

infected (ICF). This analysis was restricted to 91 of 117 (78%) participants with prevalent PTB who were not on TB treatment at the time of survey, and had complete data on HIV status and contact with care providers.

The study protocol was approved by the scientific and ethical steering committees of the Kenya Medical Research Institute (protocol number 943) and the institutional review board of the US Centers for Disease Control and Prevention (protocol number 4712).

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ADDITIONAL TABLES

Table E1: Distribution of gender and age of the number of eligible persons expected according to the HDSS* database, the number of eligible persons found and the number who agreed to participate.

	Registered in HDSS	Eligible persons found	% of Registered†	Participants	% of Found‡
Female	17,030	14,123	83%	13,055	92%
Age group (yrs) 15-24	6,012	4,146	69%	3,776	91%

	25-34	3,022	2,666	88%	2,451	92%
	35-44	2,303	2,094	91%	1,939	93%
	45-54	2,142	1,974	92%	1,854	94%
	55-64	1,441	1,345	93%	1,252	93%
	65+	2,110	1,898	90%	1,783	94%
Male		13,729	8,532	62%	7,655	90%
Age group (yrs)	15-24	6,087	3,135	52%	2,832	90%
	25-34	2,453	1,456	59%	1,256	86%
	35-44	1,532	1,001	65%	889	89%
	45-54	1,247	915	73%	827	90%
	55-64	1,060	877	83%	804	92%
	65+	1,350	1,148	85%	1,047	91%
Total		30,759	22,655	74%	20,710	91%

*HDSS = Health and Demographic Surveillance System.
†p<0.001 for the trend by age group in males and in females, and for the difference by gender.
‡p=0.04 for the trend by age group in males, and <0.001 in females.

Table E2. Participation, suggestive symptoms, chest radiograph abnormalities and bacteriologically confirmed cases by cluster

Cluster Number	Eligible persons found	Participants in Analysis	Suggestive Symptoms	CXR available	CXR Abnormality	Smear+ cases	Smear- culture+ cases
		n	n	n	n	n	n
39	694	615	231	587	264	1	7
44	705	579	104	521	174	2	1
43	554	490	67	459	100	2	0
35	708	670	126	648	143	2	0
21	313	242	23	214	34	0	0
31	559	487	59	458	81	0	1
19	577	536	82	519	94	4	4
10	514	445	70	426	101	2	0
5	527	481	109	471	199	4	0
36	366	332	78	325	105	0	1
24	601	547	134	514	93	1	5
23	380	322	73	285	37	0	1
26	614	564	126	523	80	0	2
27	446	426	69	408	27	1	0
29	650	620	92	596	41	1	2
33	615	574	84	551	63	2	0
13	530	454	55	407	51	2	4
1	753	645	102	581	53	1	0
8	741	674	97	599	131	1	5
97	600	560	85	541	91	0	4
60	458	399	79	362	68	1	1
55	677	617	76	596	96	1	2
73	365	333	30	319	66	2	1
56	592	552	92	516	140	2	1
57	730	683	125	649	166	1	4
61	696	647	124	598	209	1	4
64	608	578	99	542	174	0	1
65	482	453	69	424	120	0	1
102	415	364	76	335	165	2	2
69	529	478	96	433	131	7	3
76	412	365	56	334	108	2	0
82	666	628	100	601	243	0	3
104	406	367	57	344	207	0	1
88	548	505	79	486	174	0	4
84	545	509	80	482	220	3	2
85	760	694	97	621	244	0	0
79	449	403	50	373	154	1	1
93	624	599	76	550	229	1	2
96	625	547	57	489	244	1	1
95	622	582	106	529	222	0	1
Total	22,656	20,566	3,490	19,216	5,342	51	72

CXR=Chest Radiograph +=positive

Table E3. Prevalence of Smear-Positive Pulmonary TB, by possibly associated factors

		No. of Participants in the Survey	Smear-Positive PTB cases	Prevalence per 1000[†]
Total		20,566	51	2.5
95% CL				1.6 ; 3.4
Design effect				1.66
Gender and Age group (years)				*
Females	15-24	3,752	7	1.9
	25-34	2,426	8	3.3
	35-44	1,932	4	2.1
	45-54	1,844	5	2.7
	55-64	1,246	1	0.8
	65+	1,771	3	1.7
Males	15-24	2,810	1	0.4
	25-34	1,240	6	4.8
	35-44	881	6	6.8
	45-54	820	3	3.7
	55-64	801	5	6.2
	65+	1,043	2	1.9
Reported history of TB treatment				*
None reported		20,115	45	2.2
Previously treated		440	6	13.6
Missing		11	-	
TB contact in the house				
Yes		2,013	8	4.0
None reported		18,461	43	2.3
Missing		92	-	
Education				
None		2,709	5	1.9
Primary		13,981	38	2.7
Secondary/post secondary		3,112	4	1.3
Missing		764	4	5.2
Socio Economic Score				
<25%		4,122	12	2.9
≥25%		14,883	34	2.3
Missing		1,561	5	1.2
Smoking				*
Current Smoker		2,129	14	6.6
Past smoker		2,846	8	2.8
Never smoked		15,583	29	1.9
Missing		8	-	
Recent in migrant				*
Known to HDSS for > 6-12 months		16,914	33	2.0
Recent In-Migrant		3,652	18	4.9
Number of persons sleeping in same house				
1-2		10,057	20	2.0
3-4		5,884	18	3.1

5+	3,701	9	2.4
missing	924	4	4.3
Distance to a TB treatment‡ facility			
< 1 km	3,043	5	1.6
1- < 2 km	5,251	14	2.7
2- < 3 km	6,229	19	3.1
3- < 4 km	4,662	12	2.6
≥ 4 km	1,381	1	0.7

†Adjusted for cluster sampling
*Rao-Scott Chi-Square Test p ≤0.05.
‡A hospital, health centre or dispensary, where TB drugs are dispensed under supervision of the national TB program, and staff are expected to have been trained on TB treatment and diagnosis. Calculated as the absolute distance based on geographic coordinates.

E4. Characteristics and prevalence of bacteriologically confirmed PTB in study participants known to the HDSS for longer versus recent in-migrants.

	Known to HDSS for > 6-12 months					Recent In-Migrant					
	Cases (all PTB)		Participants		Prevalence per 1000	Cases (all PTB)		Participants		Prevalence per 1000	p-value*
	n	%	n	%		n	%	n	%		
Total	82		16,832		4.9	41		3,611		11.4	
Gender											0.57
Female	45	54.9%	10,596	63.0%	4.2	20	48.8%	2,310	64.0%	8.7	
Male	37	45.1%	6,236	37.0%	5.9	21	51.2%	1,301	36.0%	16.1	
Age											0.0002
15-24	11	13.4%	4,601	27.3%	2.4	8	19.5%	1,935	53.6%	4.1	
25-34	13	15.9%	2,790	16.6%	4.7	17	41.5%	846	23.4%	20.1	
35-44	13	15.9%	2,424	14.4%	5.4	11	26.8%	365	10.1%	30.1	
45-54	16	19.5%	2,399	14.3%	6.7	2	4.9%	247	6.8%	8.1	
55-64	10	12.2%	1,910	11.3%	5.2	2	4.9%	125	3.5%	16.0	
65+	19	23.2%	2,701	16.0%	7.0	1	2.4%	93	2.6%	10.8	
Type of PTB by Sputum smear			n.a.					n.a.			0.70
negative	49	59.8%				23	56.1%				
positive	33	40.2%				18	43.9%				
HIV status			n.a .					n.a .			<0.0001
Pos	24	29.3%				27	65.9%				
Neg	44	53.7%				5	12.2%				
Unknown	13	15.9%				9	22.0%				
Suggestive symptoms by survey definition											0.33
Yes	47	57.3%	2,842	16.9%	16.5	28	68.3%	573	15.9%	48.9	
No	35	42.7%	13,990	83.1%	2.5	13	31.7%	3,038	84.1%	4.3	
Chest radiograph abnormal											0.74
Abnormal	74	90.2%	4,637	27.5%	16.0	39	95.1%	592	16.4%	65.9	
Normal	6	7.3%	11,199	66.5%	0.5	1	2.4%	2,668	73.9%	0.4	
missing	2	2.4%	996	5.9%	2.0	1	2.4%	351	9.7%	2.8	

HDSS= Health and Demographic Surveillance System PTB=Pulmonary Tuberculosis n.a.= not available.
*Fisher's exact test

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