Are more dangerous strains of tuberculosis spreading in Southern Africa?

LSHTM investigators: Peter Godfrey-Faussett, Ruth McNerney, Kim Mallard, Helen Ayles.
Collaborators: ZAMBIA: ZAMBART Project; University Teaching Hospital, Lusaka; MOH Chest Diseases Laboratory. Malawi: Community Health Sciences Unit of the Ministry of Health and National TB Programme; EQUI –TB Knowledge Programme (Liverpool School of Tropical Medicine, UK and Malawi). Sudan: Molecular Tuberculosis Research Laboratory of the Ministry of Health National Health Laboratory.

Hypothesis to be tested: Beijing-type strains of *M. tuberculosis* are associated with treatment failure, disease recurrence and acquisition of drug resistance and the spread of drug resistance in Southern Africa.

Goal: To understand the epidemiology of drug resistant tuberculosis in Southern Africa

Specific Aims:

1. To identify the prevalence of the Beijing-type strain in populations in Southern Africa.
2. To establish regional capacity to type tuberculosis strains.
3. To understand the relevance of strain type to drug resistance and to outcome of treatment.

Keywords: Strain differentiation, molecular epidemiology, drug resistance.

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The relationship between tuberculosis and poverty: a pathway to explain

LSHTM investigators: Delia Boccia, Peter Godfrey-Faussett, Helen Ayles
Collaborators: ZAMBART Project, Zambia
Funding Bodies: Bill Gates Foundation via John Hopkins University

The evidence regarding poverty as a determinant of TB is inconsistent at the individual level and less conclusive than at societal level. Available studies do not describe adequately their methods of SES measurement, do not take into account the multi-dimension nature of poverty nor the role played by community level factors on the individual outcome. Finally, the pathways through which TB and poverty are related have never been tested properly.

The purpose of this study is:

1. To investigate the association between TB and poverty, using a standard quantitative method to measure poverty (the assets based index);
2. To develop and test an aetiological model of TB including individual, household and community characteristics.

Two main hypotheses have been derived:
1. Tuberculosis is associated with low socioeconomic status at individual level;
2. The association between TB and low socioeconomic status is mediated by factors acting at household and community level, linking to each other in a hierarchical pattern.

This study has important public health implications:
- It will help to better understand the dynamics of transmission and design new interventions to reduce the risk of transmission at population level, especially among the poor.
- It will allow a greater understanding of the mechanisms through which poverty acts in relation to prevalent cases of TB and self-reported cases of TB.
- Finally describing a disproportionate burden of TB among the poor hopefully will push governments to act on their specific mandate to address health inequalities, as they are unfair, unjust and avoidable.

Keywords: prevalence, poverty, socioeconomic risk factors, health inequalities, health seeking behaviours

LSHTM contact: Delia.Boccia@lshtm.ac.uk

Consortium to Respond Effectively to AIDS/TB Epidemic (CREATE): New Paradigms for Reducing HIV-Related Tuberculosis in High Burden Countries: Community Trials of Novel, Epidemiologically Based Strategies to Control HIV-Related Tuberculosis

LSHTM investigators: Helen Ayles, Peter Godfrey-Faussett, Richard Hayes, Charalambos Sismanidis, Katherine Fielding, Alison Grant, Gavin Churchyard, Liz Corbett, Ab Schaap
Collaborators: Dick Chaisson, John Hopkins University; WHO; Aurum Health Research; Municipal Health Secretariat, Rio de Janeiro; Stellenbosch University; Zambian Central Board of Health; University of Zambia
Funding bodies: Bill & Melinda Gates Foundation via John Hopkins University

The Consortium to Respond Effectively to the AIDS-TB Epidemic (CREATE) was developed to organize, implement and evaluate epidemiologically based interventions to reduce TB incidence and mortality in populations and communities with high HIV prevalence. With funding from the Bill and Melinda Gates Foundation, CREATE will strive to achieve the following outcomes over the next 5 years.

Specific Outcomes Anticipated

• Creation of a consortium of investigators and public health officials to design and run a series of complementary community-level studies of innovative tuberculosis control strategies in settings of dual epidemics of HIV and tuberculosis.

• Implementation of three community level studies in high burden countries/areas, assessing the impact of novel TB control strategies on disease incidence, mortality, drug resistance and other outcomes.

• Documentation of substantial reductions in the number of tuberculosis deaths and tuberculosis cases within the communities where novel interventions are implemented.

• Comparisons of the relative impact of the alternative strategies for reducing tuberculosis case rates and death rates across a variety of community settings.

• Identification of operational, technical and behavioural obstacles to program success with development of strategies to address these problems.

• Documentation of impact of coordinated TB/HIV interventions on HIV outcomes.

• Dissemination of results through national, regional and global meetings and publications.

• Change of global tuberculosis control policies to encompass more epidemiologically appropriate approaches to reducing death and illness from tuberculosis in the era of the HIV pandemic.

Keywords: Paradigms, HIV, epidemiology, policy, mortality, drug resistance

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ZAMSTAR: Zambia and South Africa Tuberculosis and AIDS reduction study

LSHTM investigators: Helen Ayles, Peter Godfrey-Faussett, Virginia Bond, Charalambos Sismanidis, Delia Boccia, Alexandra Coldham, Richard Hayes, Dirk Muller, Ab Schaap
Collaborators: Dick Chaisson, John Hopkins University; Nulda Beyers, University of Stellenbosch; Zambart Project, Zambia
Funding bodies: Bill & Melinda Gates Foundation via John Hopkins University

ZAMSTAR is a six year research project (2004-2010) which will be conducted by the Zambart project in Zambia and the University of Stellenbosch in South Africa. The study is a community randomized trial designed to assess the impact of enhanced case finding and household approaches to TB/HIV on TB prevalence.

The ZAMSTAR team have been conducting clinical, epidemiological, anthropological and operational research on the interactions between HIV and tuberculosis in Zambia and South Africa for more than a decade. Based on our understanding of the social context of the tuberculosis and HIV epidemics, we have developed two interventions that provide a radically different approach to diagnosis, prevention and care. The two interventions are:

- Improved Case Finding - By allowing individuals direct access to diagnostic services and empow ering communities to seek care, we will bypass the health system barriers and greatly reduce the number of people who are spreading infection.
- Integrated TB/HIV care delivered through the household - By harnessing the capacity of house holds and the community we will reduce the burden on the health system, increase the coverage and efficiency of preventive and curative tuberculosis services and break down the barriers of stig ma and denial.

This study will evaluate the interventions at the community level by means of a community randomised trial, using a factorial design. The total population involved in the study is about 1.2 million people, consisting of about 50,000 people in each of 24 communities, 8 in South Africa and 16 in Zambia. In December 2005, each community was randomly allocated to receive one or other intervention or neither or both.

The primary outcome will be the prevalence of culture positive tuberculosis among a randomly selected population of adults in each arm of the trial, measured after 3 years of the interventions. Secondary out-comes include indicators of tuberculosis and HIV programme performance and changes in HIV incidence and stigma at the household level. This study will determine the effectiveness of these interventions across two different countries and urban and rural settings, so the results should be of broad relevance to policy makers.

By March 2006, the study had carried out the following baseline studies:

- Rapid social appraisal of all sites capturing core features of social system relevant to TB and HIV. A resulting typology of diversity of urban systems was used in randomisation process.
- Intensive fieldwork in 6 sites to provide more in-depth understanding of the local experience and i mpact of TB.
- TB and HIV prevalence surveys of 5000 adults in each of two pilot areas (one peri-urban, one rural).

Interventions started in Julyl 2006 and a Secondary Outcome Cohort is being recruited.

Keywords: Paradigms, HIV, epidemiology, policy, Zambia, South Africa

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Recurrent tuberculosis: relapse or reinfection?

LSHTM investigators: Alison Grant, Katherine Fielding, John Day, Richard Hayes
Collaborators: Gavin Churchyard & Salome Charalambous, Aurum Institute, South Africa
Rob Warren & Paul van Helden, MRC Centre for Molecular and Cellular Biology, University of Stellenbosch Medical School, SA
Dick Chaisson, Johns Hopkins University, Baltimore, USA, Kevin de Cock, CDC Kenya
Funding bodies: Anglogold, South Africa

A cohort of miners with and without HIV infection are being followed after a first episode of tuberculosis. For those who experience a second episode of tuberculosis, isolates from the two episodes are being compared using RFLP techniques to determine the relative contribution of relapse and re-infection. This study started in January 1999; data collection is being completed and analysis is in progress.

Keywords: Tuberculosis, molecular epidemiology, HIV disease progression , Viral load, RFLP, South Africa

LSHTM contact: Katherine.Fielding@lshtm.ac.uk

Presentation and outcomes of TB in patients taking antiretroviral therapy (ART) and risk factor analysis for TB incidence in a cohort of patients taking ART from a workplace programme in South Africa

LSHTM investigators: Alison Grant, Katherine Fielding
Collaborators: Salome Charalambous, Gavin Churchyard, Jenny Whetham: Aurum Institute, South Africa
Funding bodies: Aurum Institute, South Africa

Objectives
To describe clinical presentation and outcomes of patients diagnosed with tuberculosis and non tuberculous mycobacterial (NTM) disease, whilst on ART. To conduct a risk factor analysis for TB incidence in the ART cohort and to compare with an historical clinic cohort of individuals fulfilling criteria to start ART before it became available.

Methods
Patients enrolled in a workplace ART programme who have been diagnosed with TB and NTM disease will be eligible for the study. Data collected from inpatient notes, outpatient TB cards and laboratory databases.

Main outcomes
Clinical Presentation
- Description of clinical presentations of patients developing TB whilst on ART
- Distribution of site of disease (pulmonary vs. extrapulmonary vs. both) and CXR features: typical v atypical
- TB smear and TB culture status of sputum/ other specimens, abd dusceptibility
- Inflammatory v non inflammatory features (evidence of immune reconstitution)

TB Outcome
- Treatment outcome (cure, completion, failure, death)
- % sputum conversion at 2 months
- CXR features at end of treatment (scarring, cavitation etc)

Risk factor analysis of TB incidence in ART cohort and a comparison of TB incidence in the ART cohort with an historical clinic cohort of individuals fulfilling criteria to start ART before it became available

Keywords: ART, HIV, South Africa, cohort,

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Thibela TB: A trial of community-wide isoniazid preventive therapy as a strategy to improve control of tuberculosis among South African gold miners

LSHTM investigators: Alison Grant, Katherine Fielding, Liz Corbett, Peter Godfrey-Faussett, Richard Hayes, James Lewis
Collaborators: Gavin Churchyard, Aurum Institute (South Africa); Dick Chaisson, Johns Hopkins University (USA); Mrs Eva Marumo, Dr Lindiwe Mvusi, Dept of Health (South Africa)
Funding bodies: Bill and Melinda Gates Foundation, through the CREATE consortium

The aim of this study is to evaluate the efficacy of community-wide TB preventive therapy (isoniazid given for 9 months to all individuals who do not have active TB) compared with standard of care in reducing TB incidence among gold miners in South Africa. A cluster-randomised controlled trial design will be used.

To compare the efficacy of isoniazid preventive therapy (IPT) given on a community-wide basis to current standard of care on TB among gold miners in South Africa.

Primary objective
To detect a 60% reduction in TB incidence in the community-wide IPT arm compared to the control arm in months 13 to 24 after enrolment, with 90% power.
Secondary objectives

- To detect at least a 40% reduction in TB case notification rates in the community-wide IPT arm compared to the control arm in months 0 to 24 after enrolment
- To describe trends in TB case notification following the intervention, the prevalence of TB at the end of the follow-up period, safety of community-wide IPT, all-cause mortality and the incidence of isoniazid-resistant TB (limited to first TB episodes)

This is an open cluster-randomised study, comparing mine shafts projected to remain operational for at least 5 years, stratified by baseline TB case notification rate. In the intervention clusters, IPT will be offered to all employees without evidence of active TB. Fifteen clusters, with shaft sizes ranging from 1000 to 10000 men, will have sufficient power to address the study objectives.

Funding has been awarded by the Bill and Melinda Gates Foundation. The study is began recruitment in July 2006 and continues to recruit cluster until December 2007. Measurement of the primary outcome of TB incidence will be competed in 2010.

Keywords: randomised controlled trial, South Africa, TB preventive therapy

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Biostatistics core of Consortium to Respond Effectively to AIDS/TB Epidemic (CREATE)

LSHTM investigators: Richard Hayes, Katherine Fielding, Charalambos Sismanidis, James Lewis, Ab Schaap
Collaborators: Larry Moulton, Johns Hopkins University (USA)
Funding bodies: Bill and Melinda Gates Foundation, through the CREATE consortium

The Consortium to Respond Effectively to the AIDS-TB Epidemic (CREATE) was developed to organize, implement and evaluate epidemiologically based interventions to reduce TB incidence and mortality in populations and communities with high HIV prevalence. With funding from the Bill and Melinda Gates Foundation, CREATE will strive to achieve the following outcomes over the next 5 years.

The main function of the Biostatistics Core is to ensure methodological rigor and statistical integrity for the studies. The Biostatistics Core provides strong support to the CREATE study teams - sometimes by developing new techniques for studying populations - and is fully involved in all stages of the studies from design to implementation to analysis.

Keywords: HIV, epidemiology, biostatistics, community-level RCTs

LSHTM contact: Richard.hayes@lshtm.ac.uk

A randomised open-label controlled trial of a 4 month gatifloxacin-containing regimen vs standard 6 month regimen for the treatment of adult patients with pulmonary tuberculosis

LSHTM investigators: Katherine Fielding, Charalambos Sismanidis, Corinne Merle
Collaborators: IRD Senegal; St Georges HMS UK; KEMRI Kenya; PNLAT Guinee; NTBCP/MRC South Africa; Hôpital Raymond Poincare France; IMT Antwerp Belgium; PNT Benin; PNT Senegal
Funding bodies: EU and WHO/TDR

Tuberculosis is currently treated with a 6-month course regimen. During this time many patients fail to adhere to treatment and default, resulting in recurrent disease which might be multi-drug resistant. A shorter duration of treatment is expected to provide improved patient compliance and at least equal or better clinical outcome.

In an attempt to reduce further the duration of treatment, several different drugs have been proposed for inclusion, including the quinolones. We will assess the efficacy and safety of a gatifloxacin-containing four month regimen in the treatment of pulmonary tuberculosis in comparison with a standard 6-month regimen in a multicentre trial in Kenya, Senegal, Benin, South Africa and Guinea.

The sterilising activities of the regimens will also be compared in the intensive phase using methods which correlate with ultimate relapse rates.

Keywords: treatment, RCT, multicentre, gatifloxacin, short-course

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Identifying and Evaluating Prognostic and Surrogate Markers for Response to Treatment for Tuberculosis

LSHTM investigators: Patrick Phillips (PhD student), Supervisors: Katherine Fielding, Abdel Babiker Advisors: Andrew Nunn, Mike Kenward
Collaborators: MRC-Clinical Trials Unit

Tuberculosis (TB) kills 2 million people worldwide every year and global incidence is still growing at 1% per year. Existing drugs are forty years old and new treatments are needed to effectively combat TB in HIV-infected individuals, tackle drug resistance and shorten treatment duration (currently six months). Several new treatment regimens have reached Phase III clinical trials. Many more are expected to follow over the next few years. Phase III clinical trials for TB use long-term response as the primary endpoint leading to trials that are expensive and time-consuming, taking in excess of five years to complete. A well validated surrogate marker will shorten and simplify clinical trials, ultimately speeding the drug development process.

Recent advances in the statistical evaluation of surrogate endpoints will be reviewed. Data from twelve randomised controlled TB trials conducted by the Medical Research Council in the 1970s and 1980s (11,000 participants and 61 different treatment regimens) will be used to identify prognostic markers for long-term response to TB treatment and evaluate these markers as surrogates for response to TB treatment

Keywords: surrogate marker, treatment

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Epidemiology of mycobacterial and HIV infections in Northern Malawi

LSHTM investigators: Amelia Crampin, Judith Glynn, Sian Floyd, Nuala McGrath, Keith Branson, Jacky Saul, Hazel Dockrell, Paul Fine
Collaborators: Karonga Prevention Study, Malawi, Francis Drobniewski, HPA National Mycobacterium Reference Unit, London
Funding bodies: The Wellcome Trust, LEPRA

Objectives
Studies of the relationship between HIV and mycobacterial disease.

Methods
The Karonga Prevention Study in Northern Malawi has been studying tuberculosis and HIV since the 1980's, initially in the context of a large BCG vaccine trial. Detailed descriptive epidemiological data have been collected, a series of analytical studies undertaken, and two treatment trials have been conducted.
A new series of studies will focus on the effects of anti-retroviral roll-out on tuberculosis in the population

Results
Theses studies have shown that the incidence of new smear positive TB in adults rose to a peak of 2.0/1000 in the late 1990s but appears to have decreased by 2001 to 1.5/1000. Two thirds of cases are now HIV positive. The rise in incidence was greatest in 30-44 year olds and was particularly marked for women, leading to a decrease in the male:female ratio for TB incidence from 1.3 to 0.8. The proportion of new smear positive TB cases attributable to HIV rose from 17% in 1988-90 to 57% in 2000-01, but the estimated rate of smear positive TB in the absence of HIV fell from 0.78/1000 to 0.45/1000.

Conclusions:
Without HIV the incidence of smear positive TB would have fallen in this population. Instead it has risen and is predominantly affecting young adults and women. There is some evidence that the HIV-associated TB epidemic may have passed its peak.

Antiretrovirals were introduced into the district in 2005.

Keywords: HIV, epidemiology, gender

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Case control study of tuberculosis in northern Malawi

LSHTM investigators: Amelia Crampin, Judith Glynn, Sian Floyd, Keith Branson, Jacky Saul, Hazel Dockrell, Paul Fine, Neil French
Collaborators: Karonga Prevention Study Malawi; Francis Drobniewski, HPA Mycobacterium Reference Laboratory; Adrian Hill, Oxford University
Funding bodies: The Wellcome Trust

Objectives
To analyse the relationship between HIV (and other risk factors including helminth infection and contact with other TB cases) and mycobacterial infection and disease.

Methods
The Karonga Prevention Study in Northern Malawi is currently undertaking its third generation case-control study of risk factors for tuberculosis including HIV and genetic factors. Household transmission studies have also been conducted.

Results
Analyses to date have demonstrated the increased risk associated with household and other contacts with TB and have quantified the increasing relative risk for the association with HIV as the epidemic matures

Keywords: Malawi, case control

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Genetics of susceptibility to tuberculosis in Northern Malawi

LSHTM investigators: Paul Fine, Amelia Crampin, Sian Floyd, Keith Branson, Jacky Saul
Collaborators: Adrian Hill, Fredrik Vanberg, Graham Cooke: Wellcome Trust Centre for Human Genetics, Oxford
Funding bodies: The Wellcome Trust, LEPRA

Objectives
Studies of the genetics of susceptibility to tuberculosis

Methods
The Karonga Prevention Study in Northern Malawi includes a case-control study of risk factors for tuberculosis. Study of genetic risk factors started in 1996. To date over 30 polymorphisms have been assessed for their association with tuberculosis, separately for HIV-positive and HIV-negative TB. Genes investigated include NRAMP, Vitamin D receptor, HLA-DR2, mannose binding lectin, IL-10, TNF-alpha, interferon-gamma, and toll receptors. A family-based study using sib pairs is being used for a genome scan of susceptibility loci.

Keywords: genetic epidemiology, Malawi, HIV

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Molecular epidemiology of tuberculosis in Northern Malawi

LSHTM investigators: Judith Glynn, Amelia Crampin, Hamidou Traore, Sian Floyd, Keith Branson, Jacky Saul, Paul Fine
Collaborators: Karonga Prevention Study Malawi; Francis Drobniewski, Malcolm Yates, HPA National Mycobacterium Reference Unit, London
Funding bodies: The Wellcome Trust, LEPRA

Objectives
The Karonga Prevention Study is the only long term population-based molecular epidemiological study of tuberculosis in an area with a high prevalence of HIV. It thus gives a unique opportunity to examine transmission patterns and the relationship between HIV and tuberculosis in detail, in particular the relative importance of recent and past infection, and how HIV affects this.

Methods
The Karonga Prevention Study in Northern Malawi includes a case-control study of risk factors for tuberculosis. All tuberculosis cases (and controls) are interviewed about their contacts with tuberculosis. All positive cultures are fingerprinted. Recent infection is inferred from “clustering” of identical strains.

Results
To date we have analysed data on clustering over 7 years, and have estimated that two thirds of tuberculosis cases had arisen from recent transmission, and found higher rates of clustering among HIV positive than among HIV negative individuals.
In molecular studies of contacts and individuals over time we have shown: that less than half of the tuberculosis cases in people with a previous smear positive case in their household or close family have acquired tuberculosis from these source contacts, and that transmission of M tuberculosis from smear positive HIV-infected cases was half that from HIV negative cases; have used novel methods to estimate the proportion of tuberculosis cases in the population arising from transmission of M tuberculosis from HIV-infected cases; and have estimated rates of change of DNA fingerprint patterns, and found re-infection disease in HIV positive but not HIV negative patients.

Further analyses are assessing relapse and reinfection rates and determinants of cluster size

Keywords: molecular epidemiology

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The effects of HIV on TB; a mathematical model

LSHTM investigators: Rein Houben, Judith Glynn, Paul Fine
Collaborators: Karonga Prevention Study (Malawi); Emilia Vynnycky (HPA)
Funding bodies: Wellcome Trust (for Karonga Prevention Study)

Objectives
To explore how HIV affects TB.

Methods
We will build a mathematical model for the interaction between HIV and TB. This will be fitted to long term trends in HIV and TB as measured by the Karonga Prevention Study in Malawi. The availability of detailed molecular data, since 1996, will allow us to assess the possibly different effects of HIV on TB due to recent or past M tuberculosis infection.

The final model will allow us to explain and predict the course of the TB epidemic in an area where HIV is endemic and help us explore which interventions are most effective in reducing the spread of TB in a HIV affected area.

Keywords: TB transmission, HIV, mathematical modelling

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An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis (Rifaquin)

LSHTM investigators: Liz Corbett
Collaborators: Dr Amina Jindani (Chief Investigator), Tom Harrison, Professor Denny Mitchison, David Coleman, Professor Andrew Nunn, Heather Clouting, Dr. Mark Hatherill, Dr. Gavin Churchyard, Dr. Zulmira Almeida da Silva, Dr. Stanley Mungofa, Simunkai Zizhou, Dr. Janneke van Dijk
Funding bodies: European Developing Country Clinical Trials Partnership

Introduction and aims
In this 4 country trial, we are assessing whether rifapentine (a rifamycin) and moxifloxacin (a quinolone), when given together, can achieve these objectives. In previous trials, when rifapentine was given at the standard dose of 600mg once weekly, relapse rates were unacceptable and some HIV positive patients who relapsed, had bacilli resistant to rifamycins. We are testing whether doubling the dose of rifapentine can reduce the overall relapse rates and eliminate rifamycin resistance in those HIV positive patients who may relapse.
Laboratory experiments suggest that replacing isoniazid with moxifloxacin could strengthen the treatment. We are also assessing whether, by substituting moxifloxacin for isoniazid, it is possible to simplify, and even reduce the duration of, the continuation phase of treatment.
The possibility of increased side effects from a high dose of rifapentine and of moxifloxacin will be monitored closely.

Methods
An open-label 3-arm trial to compare a standard control regimen with two alternative treatment regimens for the treatment of tuberculosis (TB).
Disease/patients studied
Patients diagnosed with TB by having 2 sputum smear specimens positive for tubercle bacilli on direct smear microscopy.

Trial interventions – research and control
Two regimens will be compared with a standard control regimen.
Control Regimen : 2 months of daily ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR).
Study Regimen 1: 2 months of daily ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 2 months of twice weekly moxifloxacin and rifapentine (2EMRZ/2P2M2).
Study Regimen 2: 2 months of daily ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 4 months of once weekly moxifloxacin and rifapentine (2EMRZ/4P1M1).

Primary outcome measure
1. Combined rate of failure at the end of treatment and relapse by 18 months
2. Presence of rifamycin monoresistance (RMR) in relapse cultures of HIV infected patients
3. Occurrence of serious adverse events at any time during chemotherapy

Secondary outcome measure
- Sputum culture results at two months after the initiation of chemotherapy
- Rate of completion of chemotherapy according to the protocol
- Number of observed doses of chemotherapy ingested
- Any adverse events

Duration: Patients will be followed up for 18 months from the commencement of chemotherapy. Follow-up visits will occur monthly until 12 months then at 15 and 18 months
Time frame: A four year study starting in December 2006

Keywords: TB epidemiology, TB infection, Cohort study, Africa

LSHTM contact: Liz.Corbett@lshtm.ac.uk

Health worker access to HIV/TB prevention, treatment and care services in Africa: situational analysis and mapping of routine and best practice

LSHTM investigators: Liz Corbett (overall PI), John Porter, Natasha Palmer, Yin Bun Cheung
Collaborators: Zimbabwe: Peter Mason, Ethel Dauya, Matilida Zvinavashe, Tariro Makadzange Ethiopia: Professor Yemane Berhane, Kenya : Caroline Nyamai-Kisia and Dennis P Ochieng Malawi: Rhehab Chimzizi Mozambique: Santos Alfredo Nassivila South Africa: Salome Charalambous World Health Organisation: Badara Samb, Vincent Habiyambere, Francesca Celletti, Rose Pray, Carla Obermeyer
Funding bodies: World Health Organization

Introduction and aims
This study has been commissioned in order to inform the "Treat" element of the "Treat, Train and Retain" strategy being developed by WHO in response to the critical shortage of health workers in Africa. The main focus of this 6 country study is to identify gaps, barriers and potential solutions in five key areas: -

1. Policy, legislation and provision of services concerned with the occupational safety and welfare of health workers
2. Prevention of HIV within and outside the workplace
3. Access to HIV counseling and testing services for health workers
4. Infection control for TB within the workplace
5. Access to care and support for health workers who know themselves to be HIV positive or who have TB disease, and their families, within and outside the workplace. The focus here is on anti retroviral therapy (ART), isoniazid preventive therapy, and management of TB suspects for further evaluation and anti-TB treatment if indicated

Methods
Responsible Officers at the Ministry of Health (or country equivalent) will be interviewed to ascertain Policy relevant to the study. The success of policy implementation and dissemination will be assessed through comparison of National policy with observed and reported facility policy and practice.
Routine practice
Within each country 6 health facilities are being randomly selected using a 3 stage cluster sampling:

- Selection of 2 provinces per country
- Selection of 3 districts within each selected province
- Selection of one health facility in each selected district.

Weighed-sampling by size has been used for each step (respectively, population size for steps 1 and 2, and facility staff complement for step 3).
At each selected health facility staff will be called for interview in random order, with recruitment continuing until 10 health workers in focal cadres (registered nurses, certified nurses, midwives, clinical officers, and doctors) have been interviewed, along with up to 10 staff belonging to other cadres.

Facilities will be asked to publicize the visit and ask for volunteer Key Informants with experience of attempting to access ART for self or immediate family, or a recent needlestick injury. Facilities will also be inspected and assessed for policy and practice at the institutional level. Gaps in knowledge and inconsistencies will be assessed by comparing responses of individual health workers with observed and reported practice at the facility level.

A simple search strategy has been developed, whereby a broad range of stakeholders are asked for Best Practice nominations. Facilities can be nominated for more than one of the 4 main categories (HIV prevention, HIV testing, TB infection control, HIV care including ART). Facilities offering unusually good general health care are also being considered, as this may include access to ART through the private sector.

Time frame: A 6 month study starting in Jan 2007

Keywords: TB epidemiology, TB infection, Cohort study, Africa

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A cluster randomised trial of two intensified TB case-finding strategies in an urban community severely affected by HIV

LSHTM investigators: Liz Corbett, Anthony E Butterworth, Peter Godfrey-Faussett, Richard Hayes, Yin Bun Cheung
Collaborators: Prof. Peter Mason, Dr Abbas Zezai, Dr Stanley Mungofa, Dr Lovemore Mbengeranwa, Mrs Shungu Munyati, Dr Owen Mugurundi, Prof Simba Rusikaniko, Dr Chris Dye, Prof Brian Williams, Prof Gavin Churchyard
Funding bodies: Wellcome Trust

Introduction and aims
TB disease rates in sub-Saharan Africa have risen to extremely high levels since the onset of the HIV epidemic. Increased case-finding at community level has potential to improve TB control

Methods
This is a cluster-randomised comparison of two case-finding interventions to 120,000 adults: periodic door-to-door enquiry for TB symptoms and periodic visits by mobile TB clinics. Each intervention will be delivered twice per year for 6 rounds to 42 neighbourhoods in high densitiy suburbs of Harare. TB suspects identified during the intervention will be investigated with sputum microscopy. Before and after the intervention a TB disease and HIV infection survey will be carried out in 1 in 10 randomly selected households from each neighbourhood. The pre-intervention survey will also include TST testing. A poverty ranking and GPS coordinates will be obtained from each of the households in the intervention area.

The primary outcome measure will be comparison of the cumulative number of cases identified under each method over 6 rounds.

Secondary outcomes include before: after intervention comparison of point prevalence of TB in the whole study area.

Baseline data will be used to investigate the distribution of TB infection and HIV infection in Harare, and whether there is any clustering of the two infections at the household level, or by poverty ranking.

Time frame: A four and a half year study starting in March 2005

Keywords: TB epidemiology, TB infection, Cohort study, Africa

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A randomized controlled trial of a second dose of BCG vaccination against tuberculosis

LSHTM investigators: Laura Rodrigues
Collaborators: Professor Mauricio Barreto, Universidade Federal da Bahia, Brazil; Dr Miguel Ayub Ajjar, Director, TB Control programme, Brazil; Dr Sergio Cunha (PhD student)
Funding bodies: DFID and Brazilian Government

The overall aims of the existing suite of projects are:

1. To estimate the efficacy of BCG vaccine (given to school children in a population with a high coverage of neonatal BCG) against tuberculosis and
2. To investigate how the efficacy of BCG vaccine (given to school children in a pop ulation with a high coverage of neonatal BCG) against tuberculosis and leprosy varies in areas of low and high prevalence of atypical mycobacteria, with time since vaccination and by form of disease
3. To describe the size of tuberculin reactions according to presence of BCG scar.
4. To estimate the validity of BCG scar as an indication of neonatal BCG vaccination.
5. To estimate frequency of adverse reactions to BCG vaccine given to school chil dren in a population with a high coverage of neonatal BCG
6. To estimate the costs of preventing a case of tuberculosis and of leprosy with BCG vaccination and with treatment.

Neonatal BCG vaccination is recommended by WHO in countries with a high incidence of tuberculosis, and is believed to be the most widespread vaccine in the third world. There is evidence that BCG protection wanes with time in most settings.

WHO has pronounced recently against giving a second dose of BCG vaccine, arguing that there is no evidence that a second dose would add protection, and that scarce resources should be used for case-finding and treatment. This recommendation is controversial: many countries offer a second dose of BCG vaccination, usually at school, and do not appear to plan to stop in spite of WHO recommendation. Brazil has recently suspended the recommendation of a second dose based on the first follow up period. Follow up continues.

Keywords: Policy, Operations Research, Immunology, Brazil

LSHTM contact: Laura.Rodrigues@lshtm.ac.uk

Case control studies of the efficacy of BCG against tuberculosis: duration of efficacy and effect of a second dose

LSHTM investigators: Laura Rodrigues
Collaborators: Ricardo Ximenes, Brazil et al
Funding bodies: Brazilian CNPq

A number of case control studies in Brazil to explore aspects of the efficacy, including effect of second dose, effect of age at vaccination and duration of neo natal protection.

Keywords: BCG

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The effect of helminth infection in mothers on the immunological reactions to BCG vaccination and development of atopy

LSHTM investigators: Laura Rodrigues
Collaborators: Professor M Yazdanbakhsh, Leiden University
Funding bodies: Nederlands

Helminthic infections are prevalent in developing countries. It has been suggested, as an alternative explanation to the hygiene hypothesis, that the down regulation of immune-responses caused by helminths may be behind the lower prevalence of atopy in developing countries. It is also been suggested that immunoresponses to BCG in the newborn may be modulated by helminthic infection in the mother.

Objectives: To study cytokine production in neonates before and after vaccination with BCG and other vaccines in mother with and without helminth infections during pregnancy; to follow up these neonates and study onset of atopy and their immunological profile after acquisition of helminthic infections.

Keywords: BCG, atopy, helminths, cytokine production

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An integrated project of investigation of the tuberculosis programme. (Projeto Integrado de Investigação em Tubeculose Programa)

LSHTM investigators: Laura Rodrigues
Collaborators: Ricardo Arraes de Alencar Ximenes (PI , Universidade Federal de Pernanbuco (UFPE); Maria de Fátima Pessoa Militão de Albuquerque – (UFPE and ENSP/FIOCRUZ); Antônio Roberto Leite Campelo –Servico de Controle da Tuberculose), Norma Cavalcanti Licínio da Silva Lucena – (Laboratorio de Biologia Molecular FIOCRUZ); Wayner Vieira de Souza – Gis (NESC/FIOCRUZ); Odimariles Maria Souza Dantas – (Pediatra,UFPE)
Funding bodies: Brazilian Government (CNPq)

A cohort consisting of 2 year intake of new cases in the city of Recife is identified, receive an entry questionnaire, culture and fingerprinting, and outcomes are evaluated, with the following objectives:

- To identify risk factors (RF) for treatment outcomes.
- To determine the frequency and RF for primary and secondary drug resistance.
- Identify RF for absence of clinical cure.
- Establish with patients are infected with MTB of the same lineage trough finger printing, estimate frequency of reactivation, reinfection.
- Establish the patterns of spatial distribution of cases.
- Estimate the efficacy of a second dose of BCG

Keywords: programme evaluation, MDR, fingerprinting, geographical distribution, efficacy of a second BCG dose.

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Factors prolonging time interval from onset of symptoms to treatment among pulmonary tuberculosis patients in Sabah, East Malaysia

LSHTM investigators: Christina Rundi (DrPH student)
Supervisors: Punam Mangtani, Katherine Fielding,
Advisors: Peter Godfrey-Faussett, Laura Rodrigues
Collaborators: Ministry of Health, Malaysia

Sabah has a 2 fold higher incidence of tuberculosis in comparison to other states in Malaysia which exceeds 100 per 100 000 population. The importance of shortening time interval in the management of TB is to decrease suffering and risk of death as well as to reduce the risk of spread to contacts and the community. Time interval is associated, among other factors, to health seeking behaviour and perception of TB by patients and the community. The purpose of this research is to better understand the perception and health seeking behaviour and patterns in relation to tuberculosis and to describe how these factors affect time interval in the management of the disease. It involves in-depth interviews and focus group discussions to inform on a questionnaire that will be used in a cross sectional study.

Keywords: time interval

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The effect of neonatal BCG vaccination on HIV progression and vaccine-induced immunity in infants: a randomized clinical trial in Western Cape, South Africa

LSHTM investigators: Anneke Hesseling, Peter Godfrey-Faussett, Kim Mulholland, Paul Fine
Collaborators: Nulda Beyers, Mark Cotton, Desmond Tutu TB Centre and Kid Cru Paediatric HIV Unit, Stellenbosch University, South Africa; Willem Hanekom, Gregory Husssey, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa

Study hypothesis and specific aims

The impact of the human immunodeficiency virus-1 (HIV) on child health in developing countries is significant. The UNAIDS estimates that 570 000 -740 000 children annually are newly infected with HIV, the majority by mother-to-child transmission. More than 90% of these infections occur in sub-Saharan Africa. Although children account for approximately 4% of total HIV infections, they contribute to approximately 20% of AIDS deaths, reflecting the rapid progression to disease in the paediatric population seen in developing countries. The mechanisms behind the high observed rate of paediatric HIV progression in developing countries are poorly understood. Potential contributing factors include frequent infectious diseases and antigenic exposure, the quality of the immune response, malnutrition, breastfeeding, maternal factors, viral and host genetic factors.

There are limited data specifically characterizing the neonatal and early post-natal period in HIV- infected infants, a time where children may be particularly vulnerable to factors predisposing to HIV progression, and when routine childhood vaccinations are administered according to the World Health Organization (WHO) Expanded Programme on Vaccination (EPI) schedule of vaccination at birth, 6, 10 and 14 weeks. Bacille Calmette-Guerin (BCG), a live attenuated *Mycobacterium bovis* vaccine, is currently routinely given to HIV-exposed infants at birth in developing countries. HIV-infected infants are at risk both local and disseminated BCG disease. Further, in HIV-infected neonates who have been acutely infected with HIV, the role of routine vaccinations as antigenic stimulus and its relation to immune activation and HIV disease progression have not been investigated. We postulate that BCG, a live attenuated *Mycobacterium bovis* vaccine, a potent stimulus for both specific and non-specific immune responses in infants, may pathologically interact with HIV in vertically infected infants, leading to HIV progression.

This study will assess the effect of BCG vaccination on HIV disease progression, CD4+ T cell count and viral load in count in HIV-infected infants. Further study aims include investigating the effect of the timing of BCG vaccination on BCG-specific and *M. tuberculosis*-specific immune responses and responses to other childhood vaccines.

Keywords: BCG, HIV, viral load, infants

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Cohort study of risk of tuberculosis by time since HIV infection in South African goldminers

LSHTM investigators: Judith Glynn
Collaborators: Pam Sonnenberg, HPA, London; Jill Murray, National Institute for Occupational Health, Johannesburg; Gill Nelson, Wits Health Consortium, Johannesburg; Stuart Shearer, Andre Bester, Gold Fields Limited, Johannesburg.
Funding bodies: The Colt Foundation

Objectives
To assess the risk of tuberculosis by time since infection with HIV, changes in tuberculosis incidence over time, and the effect of HIV on outcome of tuberculosis

Methods
We are assessing the risk of tuberculosis using routinely collected data in a retrospective cohort study in four goldmines. In a cohort of nearly 2000 men with known dates of sero-conversion and a comparison group of HIV negative miners we have already shown that the risk of tuberculosis starts to rise soon after HIV infection. We are extending the study to assess longer term risk and associations with time off work and mortality.

Keywords: South Africa, cohort, HIV

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Immunology