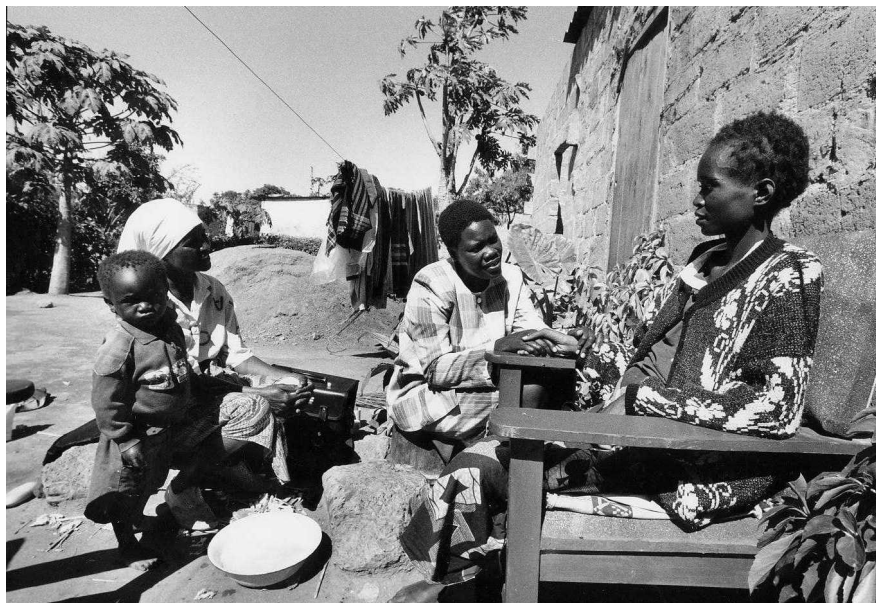


TUBERCULOSIS-RELATED RESEARCH PROJECTS 2005



London School of Hygiene
& Tropical Medicine
Keppel Street
London
WC1E 7HT
United Kingdom

<http://www.lshtm.ac.uk>

To obtain further copies of this report please contact:
alexandra.coldham@lshtm.ac.uk or telephone +44 (0) 207 927 2194

WORKING ON TUBERCULOSIS

The London School has an extraordinary breadth of research on tuberculosis (TB) within its three departments, covering a spectrum from highly technical laboratory science through to operational studies in abject townships and from detailed anthropological insights into the social context of tuberculosis through to work on macroeconomics and global health policy. The school is a major partner in the CREATE consortium funded by a grant from the Bill and Melinda Gates Foundation to John Hopkins University. The School has been awarded a DFID Knowledge Programme specifically on tuberculosis but several other Knowledge Programmes at the School include major work on the disease. Other work is funded by programme, project and fellowship grants from the Research Councils, The Wellcome Trust, industrial partners and other charities. Much of the work is linked to field sites and collaborations with national TB programmes, research partners and implementing agencies in countries where TB is more common than in the UK Major collaborations exist in Africa (South Africa, Zimbabwe, Zambia, Malawi, Uganda, Gambia, Tanzania), Asia (India, Pakistan, Nepal), Latin America (Brazil) and Europe (Russia). However, the rate of TB infection is also rising in London, and the School plays an active role in the London Infectious Disease Research Network, which has identified TB as one of its targets.

Tuberculosis lies within a rapidly changing scientific and policy environment. As the genomes of more isolates of *M. tuberculosis* and related mycobacteria, such as BCG and the leprosy bacillus are sequenced, the opportunities to develop new tools with which to prevent, diagnose and treat TB will increase. At the same time there is renewed political commitment and the development of a fully-costed 'Global Plan to Stop Tuberculosis'. The School has both the breadth of interest but also the strong connections with international and national policy makers in both rich and poor countries that can help to shape TB control in the future. Our students have a great chance to appreciate not only the technical but also the political dimensions of tuberculosis and to integrate them into the broader framework of international public health.

Peter Godfrey-Faussett

Head of DFID Tuberculosis Knowledge Programme & Reader in Infectious and Tropical Diseases

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DIAGNOSTICS

TITLE: **Evaluation of new tests for drug resistance**

LSHTM STAFF: *Ruth McNerney*

COLLABORATORS: *Muhimbili University College of Health Sciences, Tanzania.*

FUNDING: *IAEA*

SUMMARY

Current methods for screening for drug resistant tuberculosis that are used in Africa are slow, taking 4-6 weeks. More rapid detection of drug resistance might offer the opportunity for interventions to decrease transmission and thus enhance disease control.

A PCR DNA probe method (DOT BLOT) has been used to investigate a panel of 145 strains for resistance to rifampicin, isoniazid, streptomycin and ethambutol. Sensitivities for detection of resistance when compared to culture on Lowenstein Jensen (Proportion method) were 91.7, 93.5, 100 and 85.7% respectively. Specificities of 99.2, 99.1, 93.5 and 99.2% were recorded. A bacteriophage method developed at LSHTM was used to test for resistance to rifampicin and streptomycin. Sensitivity and specificity for detection of resistance to rifampicin was 92 and 99.2%, and for streptomycin 84.6 and 99.2%. The bacteriophage test was found to offer technical and cost advantages over the DOT BLOT for detection of resistance to rifampicin.

Key words: Drug resistance

TITLE: **Improved diagnosis, drug resistance detection and control of tuberculosis in Latin America**

LSHTM STAFF: *Ruth McNerney*

COLLABORATORS: *Dr Juan-Carlos Palomino, Mycobacteriology Unit, Prince Leopold Institute of Tropical Medicine, Antwerp and a consortium of Latin American laboratories*

FUNDING: *EU Concerted Action*

SUMMARY

More rapid diagnosis and detection of drug resistance might offer the opportunity for interventions to decrease transmission and thus enhance disease control. This network of laboratories will undertake multi-centre evaluation of new tools for diagnosis and drug susceptibility testing.

Keywords: drug resistance, diagnosis, Latin America

TITLE: **Investigation of strain differentiation**

LSHTM STAFF: *Hamidou Traore, Ruth McNerney, Helen Ayles*

COLLABORATORS: *ZAMBART Project; University Teaching Hospital, Lusaka; Chest Diseases Laboratory, Zambia.*

FUNDING: *DFID*

SUMMARY

Molecular typing tools such as RFLP permit us to identify strains of tuberculosis and investigate patterns of transmission. We will investigate rapid techniques that enable direct typing from clinical specimens and their relative utility to discriminate strains of tuberculosis circulating in Southern Africa.

Keywords: Strain differentiation, molecular epidemiology, transmission

TITLE: **Strategies for the management of multi-drug resistant tuberculosis in Kampala, Uganda**

LSHTM STAFF: *Peter Smith, Hamidou Traore, Maria Quigley, Alison Elliott, Ruth McNerney*

COLLABORATORS: *University of Medicine and Dentistry of New Jersey, TB Treatment Centre of the Ugandan National TB and Leprosy Control Programme (NTLP), Mulago Hospital and Makerere Medical School, Kampala, Uganda.*

FUNDING: *Burroughs Wellcome Trust Fund*

SUMMARY

This four-year study has three scientific aims:

To determine the prevalence of primary and secondary drug resistance in TB patients treated in the National TB and Leprosy Control Programme (NTLP) at Mulago Hospital.

To determine the extent of nosocomial transmission of drug resistant TB on the TB ward at Mulago Hospital and to identify host and microbial factors that predict transmission.

To evaluate new intervention applied on an individual basis to reduce nosocomial transmission of drug resistant TB:

Rapid diagnostics

Novel microbiologic and immunological approaches to monitor therapy Modified lower cost third line treatment.

The surveys undertaken during this study will systematically determine the levels of mono-resistance and multi-drug resistance among re-treatment cases of pulmonary tuberculosis and change in these rates over a four-year period. This data will be useful to the NTLP for evaluating current and establishing future programs in Uganda, plus provide valuable information leading to interventions to reduce transmission and reduce MDR-TB. The TB Treatment Center is an ideal unit to determine the scope of nosocomial transmission and to define host and bacterial factors influencing relapse. Because MDR-TB is difficult and expensive to treat, interventions shown to be cost-effective in Uganda could readily be adapted in many developing country settings. Thus, the proposed studies will allow the center at Mulago Hospital to take the lead nationally and internationally in a comprehensive approach to assess and intervene in transmission of MDR-TB in a country with a high prevalence of HIV infected people.

Key words: drug resistance

TITLE: **Are more dangerous strains of tuberculosis spreading in Southern Africa?**

LSHTM STAFF: *Hamidou Traore, Ruth McNerney, Helen Ayles, Peter Godfrey-Faussett, Kim Mallard*

COLLABORATORS: *ZAMBART Project; University Teaching Hospital, Lusaka; Chest Diseases Laboratory, Zambia. Links with collaborators in other countries of the region to be formalised.*

SUMMARY

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

Design: Prevalence surveys of Beijing-type *M. tuberculosis* will be carried out in 3 settings.

Keywords: Strain differentiation, molecular epidemiology, drug resistance

ECONOMICS

TITLE: **Role of non governmental organisations in the treatment and control of TB in Tamil Nadu, India**

LSHTM STAFF: *Stephen Jan*

COLLABORATORS: *Indian Institute of Technology (Madras)*

FUNDING: *DFID through HEFP*

SUMMARY

It is clear that the non-government sector plays an important role in providing many of the health and social services in Tamil Nadu and throughout India. (NGO in this study includes also private for-profit providers.) This study seeks to examine ways in which such service provision can be made more responsive to the requirements of funders. It takes as given the existing role played by such providers. The framework used will be principal-agent theory (with the NGO seen as acting as agent for the principal/funder). The analysis will examine the potential imperfections in this agency relationship (most notably incentive incompatibility) on the achievement of social objectives such as coverage, quality of care and access to services. This will be done by analysis of existing service agreements, interviews with relevant key stakeholders and workshops. Because the views expressed in any such dialogue are likely to be influenced by vested interest and informational asymmetries, there will be emphasis on seeking multiple perspectives and triangulation. The objective will be to come up with recommendations for better design of such agreements and ultimately promoting social objectives such as equity of access, coverage and quality of care.

Keywords: NGOs, TB

TITLE: **A feasibility study to assess the economic implications of introducing antiretroviral therapy (ART) within a mining environment in South Africa**

LSHTM STAFF: *Lilani Kumaranayake, Alison Grant, Katherine Fielding*

COLLABORATORS: *Debbie Muirhead, Charles Hongoro, Surita Roux, Salome Charalambous, Gavin Churchyard, Aurum Health Research, South Africa*

FUNDING: *Aurum Health Research, South Africa*

SUMMARY

In conjunction with a practical and therapeutic feasibility study, the aim of this study is to undertake economic analyses related to the costs and benefits of care and treatment of HIV/AIDS relating to the provision of ART in 22 companies in Southern Africa. The economic analysis will generate implications of wider-scale implementation of ART, including the development of a cost-benefit model. To-date, ART implementation has been undertaken for 18 months. Data on the first year of implementation are being analysed including costs of start-up as well as impact on labour force absenteeism. More detailed studies on the impact of ART on productivity are underway, with preliminary modelling on overall cost-benefit of ART planned as well.

Keywords: costs, cost-effectiveness, economics, ART, HIV disease, AIDS, South Africa

TITLE: **Cost-effectiveness of preventive tuberculosis therapy for HIV-infected South African mineworkers**

LSHTM STAFF: *Lilani Kumaranayake, Alison Grant, John Day, Katherine Fielding, Richard Hayes*

COLLABORATORS: *Surita Roux, Salome Charalambous, Gavin Churchyard
Aurum Health Research, South Africa*

FUNDING: *Aurum Health Research, South Africa*

SUMMARY

In parallel with a randomised trial, the aim of this study is to assess the cost and cost-effectiveness of a special clinical service ('The Prevention Clinic) established at Ernest Oppenheimer Hospital, Welkom. Interventions include the delivery of Isoniazid Preventive therapy (IPT) to employees at high risk of tuberculosis and Cotrimoxazole (CT) to those with HIV disease and a CD4 count less than 200. The study evaluates the cost and cost-effectiveness of IPT and CT in preventing tuberculosis and other opportunistic infections among South African mineworkers. The study evaluates direct costs related to health service provision and indirect costs and potential savings or benefits to the employer.

Keywords: costs, cost-effectiveness, economics, TB preventive therapy, cotrimoxazole, HIV disease, South Africa

TITLE: **Impact of HIV/AIDS in the private sector – focus on mining companies with high TB/HIV prevalence**

LSHTM STAFF: *Lilani Kumaranayake,*

COLLABORATORS: *Debbie Muirhead, Gavin Churchyard, Aurum Health Research, South Africa*

FUNDING: *Aurum Health Research, South Africa*

SUMMARY

The aim of the project is to undertake both a short term and long-term study of the impacts of HIV/AIDS in a high TB/HIV prevalence setting. Estimates of impact on 8-10 private sector companies will be undertaken before the implementation of ART. Projections for future HIV/AIDS impact will also be modelled. To-date, HIV/AIDS impact has been estimated for one firm, and data collection is being undertaken in the remaining firms. Labour force characteristics which mitigate or increase impact will be identified across firms.

Keywords: costs, cost-effectiveness, economics, ART, HIV disease, AIDS, South Africa

TITLE: **Economic and epidemiological evaluation of ProTEST pilot projects in Zambia, Malawi, and South Africa**

LSHTM STAFF: *Lilani Kumaranayake, Charlotte Watts, Peter Godfrey-Faussett, Fern Terris-Prestholt, Helen Ayles*

COLLABORATORS: *Agnes Muvira, Consultant to Malawi NTP, Rhehab Chimzizi and Nicola Hargreaves, Malawi ProTEST Project.
Rokaya Ginwalla, ZAMBART, Ignatius Kayewe (Kara Counselling and Training Trust, Lusaka Zambia), Edina Sinanovic (Health Economics Unit, Cape Town), Pren Naidoo (South African Department of Health)
Harry Hausler, University of Western Cape*

FUNDING: *World Health Organisation, DFID, NORAD, South African Department of Health*

SUMMARY

The ProTEST initiative was designed, through operational research, to develop a district-based strategy for a joint TB and HIV programme, including voluntary counselling and testing and provision of isonazid preventive therapy. The study undertakes an economic and epidemiological analysis of the ProTEST pilot initiatives in Zambia, Malawi and South Africa. Cost and cost-effectiveness analysis using intermediate outcome measures and epidemiological impact (HIV infection and TB case averted) will be undertaken. In order to consider epidemiological impact, behavioural surveys related to voluntary counselling and testing, and the development of a mathematical model will be undertaken.

Keywords: costs, cost-effectiveness, economics, isonazid preventive therapy, cotrimoxazole, HIV disease, Malawi, Zambia, South Africa

TITLE: **Economic evaluation of VCT/Cotrimoxazole Provision in Thyolo, Malawi**

LSHTM STAFF: *Lilani Kumaranayake*

COLLABORATORS: *Agnes Muvira, Consultant,
Rony Zachariah, Marie-Paule Spielmann (Medecins Sans Frontieres- Luxembourg, Blantyre),
Felix Salaniponi, Tony Harries (Malawi National Tuberculosis Control Programme (NTP),
Christina Chinji (Ministry of Health and Population, Malawi),
Patrick Gomani (Malamulo Mission Hospital, Thyolo District) and Malawi NTP),
Paul Nunn (WHO)*

FUNDING: *World Health Organisation*

SUMMARY

In conjunction with an effectiveness study of a district-based initiative in Thyolo district Malawi, the study undertakes an economic evaluation of this intervention in order to estimate cost-effectiveness. The initiative introduced voluntary counselling and HIV testing within an existing TB control programme setting as well as the provision of cotrimoxazole to HIV positive patients. An analysis of this combined package is being undertaken.

Keywords: costs, cost-effectiveness, economics, cotrimoxazole, HIV disease, Malawi

TITLE: **Impact of HIV/AIDS in the private sector – focus on mining companies with high TB/HIV prevalence**

LSHTM STAFF: *Lilani Kumaranayake,*

COLLABORATORS: *Debbie Muirhead, Gavin Churchyard, Aurum Health Research, South Africa*

FUNDING: *Aurum Health Research, South Africa*

SUMMARY

The aim of the project is to undertake both a short term and long-term study of the impacts of HIV/AIDS high TB/HIV prevalence settings. Estimates of impact on 20-22 private sector companies will be undertaken before the implementation of ART. Projections for future HIV/AIDS impact will also be modelled. To-date, HIV/AIDS impact has been estimated for 10 firms, and data collection is being undertaken in the remaining firms. Labour force characteristics which mitigate or increase impact will be identified across firms.

Keywords: costs, cost-effectiveness, economics, ART, HIV disease, AIDS, South Africa

TITLE: **Public-Private Partnerships for the delivery of TB services in high TB/HIV settings**

LSHTM STAFF: *Lilani Kumaranayake,*

COLLABORATORS: *Edina Sinanovic, Health Economics Unit, University of Cape Town, South Africa*

FUNDING: *World Health Organisation, Alliance for Health Policy and Systems Research Alliance*

SUMMARY

South Africa is experiencing a TB/HIV epidemic that has serious implications for public health system resources. There is increasing interest in public-private partnerships (PPPs) for the provision of tuberculosis (TB) treatment but very little is known about the motivations for participation in partnership that are required to achieve a desirable outcome of the partnerships. Using the new institutional economics approach, this research examines the motivations for participation in existing and potential models of PPPs for the provision of TB treatment in South Africa, as well as cost-effectiveness and quality of different PPP models. Studies have been completed on the cost-effectiveness of alternative TB mechanisms.

A scaled-up response will require the involvement of both for-profit and non-profit models for tuberculosis (TB) treatment. Current research is being undertaken to estimate future resource requirements for a scaled-up response of TB care and prevention in South Africa, assessing the role of private and public sectors in alternative financing strategies in the light of the emergence of the dual HIV/TB epidemic. The research will lead to greater elaboration of options related to different financing and delivery of services structures. Both quantitative and qualitative methods will be used in order to investigate complex situations fully and to validate the findings. Some of the data will be collected at the national level while the other data at the provincial level.

Keywords: public private partnerships, TB treatment, cost-effectiveness, resource requirements.

EPIDEMIOLOGY

TITLE: **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 STAFF: *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: *EU and WHO/TDR*

SUMMARY

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

TITLE: 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 STAFF: *Helen Ayles, Peter Godfrey-Faussett, Richard Hayes, Charalambos Sismanidis, Katherine Fielding, Alison Grant, Gavin Churchyard, Liz Corbett*

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: *Bill & Melinda Gates Foundation via John Hopkins University*

SUMMARY

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

TITLE: **ZAMSTAR: Zambia and South Africa Tuberculosis and AIDS reduction study**

LSHTM STAFF: *Helen Ayles, Peter Godfrey-Faussett, Virginia Bond, Charalambos Sismanidis, Delia Boccia, Alexandra Coldham*

COLLABORATORS: *Dick Chaisson, John Hopkins University
Nulda Beyers, University of Stellenbosch
Zambart Project, Zambia*

FUNDING: *Bill & Melinda Gates Foundation via John Hopkins University*

SUMMARY

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 empowering 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 households 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 stigma 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. Each community will be 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 outcomes 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.

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

TITLE: **A cohort study to investigate the effect of tuberculosis on the progression of HIV disease in South African mineworkers**

LSHTM STAFF: *Alison Grant, John Day, Katherine Fielding, Richard Hayes*

COLLABORATORS: *Gavin Churchyard, Aurum Health Research, Welkom, South Africa
Lynn Morris & Adrian Puren, National Institute for Communicable Diseases, Johannesburg, SA
Dick Chaisson, Johns Hopkins University, Baltimore, USA
Kevin de Cock, CDC Kenya*

FUNDING: *Anglogold, South Africa*

SUMMARY

A cohort of HIV-infected miners was followed before, during and after an episode of tuberculosis to determine the effect of tuberculosis on HIV disease progression, as measured by HIV viral load. This study started in July 1999; data collection is complete. One paper has been published (J Infect Dis 2004) and a second is being written.

Keywords: HIV disease progression, HIV viral load, South Africa

TITLE: A cohort study to investigate the effect of a special clinical service on a population of HIV-infected mineworkers

LSHTM STAFF: Alison Grant, John Day, Liz Corbett, Katherine Fielding, Richard Hayes, Lilani Kumaranayake

COLLABORATORS: Gavin Churchyard & Salome Charalambous, Aurum Health Research, Welkom, South Africa
Lynn Morris and Clive Gray, National Institute for Communicable Diseases, Johannesburg, SA
Dick Chaisson, Johns Hopkins University, Baltimore, USA
Kevin de Cock, CDC Kenya

FUNDING: Anglogold, South Africa

SUMMARY

A special clinical service has been established to provide appropriate regimes of preventive therapy (isoniazid and/or cotrimoxazole) to HIV-infected mineworkers. Employees who have previously had a positive HIV test are invited to attend the clinic. This is organised such that the order of recruitment to clinic is random: this makes access to the clinic equitable, and allows the effectiveness of these preventive therapies under operational conditions to be evaluated. This study started in August 1999; data collection is complete and analysis and write up are continuing. A cost-effectiveness analysis is also being carried out.

Keywords: TB preventive therapy, cotrimoxazole, HIV disease, South Africa

TITLE: **Recurrent tuberculosis: relapse or reinfection?**

LSHTM STAFF: *Alison Grant, Katherine Fielding, John Day, Richard Hayes*

COLLABORATORS: *Gavin Churchyard & Salome Charalambous, Aurum Health Research, Welkom, 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: *Anglogold, South Africa*

SUMMARY

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

TITLE: **Randomised controlled trial to determine the effectiveness of annual vs. 6-monthly screening with mass miniature radiography (MMR) for the active case-finding of tuberculosis**

LSHTM STAFF: *Alison Grant, Katherine Fielding, Richard Hayes*

COLLABORATORS: *Gavin Churchyard & Surita Roux, Aurum Health Research, Welkom, South Africa
Dick Chaisson, Johns Hopkins University, Baltimore, USA
Kevin de Cock, CDC Kenya*

FUNDING: *SIMRAC, South Africa*

SUMMARY

The aim of this study is to determine whether 6-monthly mass miniature radiography (MMR) screening is better than annual MMR screening in the active case detection of TB among mineworkers. The workforce has been individually randomised to have MMR either annually, as is standard practice currently (the control group), or six-monthly (the intervention group) over a two-year period. The primary outcomes to be compared between the intervention and control groups are:

- 1) the proportion of TB cases detected by active detection (MMR) as compared with self-presentation;
- 2) the proportion of cases which are smear-negative, culture-positive as a proportion of all bacteriologically-proven cases and
- 3) disease severity, as measured by the extent of disease on chest radiograph at the time of diagnosis.

Data collection is complete, and analysis and write-up are in progress.

Keywords: case detection, randomised controlled trial, South Africa

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

LSHTM STAFF: *Alison Grant, Liz Corbett, Katherine Fielding, Peter Godfrey-Faussett, Richard Hayes*

COLLABORATORS: *Gavin Churchyard, Aurum Health Research, Welkom, South Africa
Dick Chaisson, Johns Hopkins University, Baltimore, USA
Kevin de Cock, CDC Kenya
Brian Williams, WHO Communicable Diseases
Nono Simelela, Dept of Health, South Africa*

FUNDING: *Bill and Melinda Gates Foundation, through the CREATE consortium*

SUMMARY

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.

Funding has been awarded by the Bill and Melinda Gates Foundation. The study is currently in preparation phase.

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

TITLE: **Evaluation of new entrants screening for the control and prevention of tuberculosis**

LSHTM STAFF: *Richard Coker*

COLLABORATORS: *Richard Pitman, John Watson, HPA; Andrew Hayward, UCL*

FUNDING: *DOH*

SUMMARY

Immigration has played an important part in the rise in tuberculosis cases seen in this country. This has led to increasing demands for new entrant screening to be strengthened. However, a number of fundamental questions need to be answered before investing heavily in new entrant screening. The most fundamental of these questions is whether or not new entrant screening can be effective and cost-effective. This study, which is concluding, has been informing government thinking on the most effective approaches to supporting control efforts. Published research from this project highlights the varied nature of policies and practices across Europe. Research has been submitted for publication on the associations between TB in new entrants and the incidence of disease in countries from which they originate, and a report produced for DoH on numbers of cases of TB likely to be averted given different screening policies. This work is receiving considerable media attention given the politically charged atmosphere that immigration engenders in the UK.

Keywords: Tuberculosis, screening, mathematical modelling, economics, systematic review

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

LSHTM STAFF: *Christina Rundi (DrPH student),
Supervisors: Punam Mangtani, Katherine Fielding,
Advisors: Peter Godfrey-Faussett, Laura Rodrigues*

COLLABORATORS: *Ministry of Health, Malaysia*

SUMMARY

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 affects 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 use in a cross sectional study.

Keywords: time interval, tuberculosis

TITLE: **Epidemiology of Beijing strain of tuberculosis**

LSHTM STAFF: *Judith Glynn*

COLLABORATORS: *Kristin Kremer, Dick van Soolingen, RIVM, The Netherlands*
Martien Borgdorff, KNCV, The Netherlands

FUNDING: *European Concerted Action*

SUMMARY

Objectives

To study the occurrence of the Beijing strain of tuberculosis worldwide; to assess whether it is spreading; to assess the frequency with which it is associated with drug resistance.

Methods

Collaborative study leading to a meta-analysis of available data.

Results In all, 49 studies contributed data on over 29,000 patients in 35 countries. The prevalence of Beijing/W genotype tuberculosis varied from <5% of non-immigrants in Western Europe, much of Africa, and South America and India, 7-15% in the USA, Cuba, the Middle East and Bangladesh, and 30-70% in much of South East and East Asia and the former Soviet Union. Combining information on time trends and comparisons of age groups with data on drug resistance, we found four distinct patterns to Beijing/W genotype tuberculosis: (1) endemic with no association with drug resistance (at a high level in most of East Asia and at a lower level in parts of the USA); (2) epidemic, sometimes to high levels, associated with drug resistance (in Cuba, the former Soviet Union, Vietnam, South Africa, and, at a lower level, in parts of Western Europe); (3) epidemic but drug sensitive (Malawi, Argentina); (4) very low level or absent (parts of Europe, Africa).

Conclusions

This study confirms Beijing/W genotype tuberculosis as an emerging pathogen in several areas, and as a predominant endemic strain in others. Its frequent association with drug resistance, especially multidrug resistance, highlights its importance.

Keywords: Molecular epidemiology

TITLE: **Epidemiology of mycobacterial and HIV infections in Northern Malawi**

LSHTM STAFF: *Amelia Crampin, Judith Glynn, Sian Floyd, Keith Branson, Jacky Saul, Hazel Dockrell, Paul Fine,*

COLLABORATORS: *Frank Mwaungulu, Karonga Prevention Study Malawi Francis Drobniowski, PHLS Mycobacterium Reference Laboratory, Dulwich; Sebastian Lucas, UMDS, St Thomas's Hospital*

FUNDING: *The Wellcome Trust, LEPR*

SUMMARY

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 and a series of analytical studies undertaken. In 1988-1990 a 7-fold increased risk of TB in the HIV positive individuals was found.

Results

The incidence of all confirmed TB, and 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.

Keywords : HIV, epidemiology, gender

TITLE: **Case control study of tuberculosis in northern Malawi**

LSHTM STAFF: *Amelia Crampin, Judith Glynn, Sian Floyd, Keith Branson, Jacky Saul, Hazel Dockrell, Paul Fine*

COLLABORATORS: *Frank Mwaungulu Karonga Prevention Study Malawi Francis Drobniowski, PHLS Mycobacterium Reference Laboratory, Dulwich*

FUNDING: *The Wellcome Trust*

SUMMARY

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. Household transmission studies are also ongoing. In the current study approximately 400 cases and 800 controls with their household members have been included to date. Data on HIV status, exposure to recent TB cases, helminth infection and RT23 skin test positivity are accumulating.

Key words: TB, Malawi, case control

TITLE: **Molecular epidemiology of tuberculosis in Northern Malawi**

LSHTM STAFF: *Judith Glynn, Amelia Crampin, Hamidou Traore, Sian Floyd, Keith Branson, Jacky Saul, Paul Fine*

COLLABORATORS: *Bagrey Ngwira, Frank Mwaungulu Karonga Prevention Study Malawi
Francis Drobniowski, Malcolm Yates, Caroline Murphy
PHLS Mycobacterium Reference Laboratory, Dulwich*

FUNDING: *The Wellcome Trust, LEPRO*

SUMMARY

Objectives

Study transmission and the roles of reactivation and reinfection in the epidemiology of tuberculosis.

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.

Results

RFLP results were available from 83% of culture positive patients from late 1995 to early 2003. Excluding strains with <5 bands, 72% (682/948) were clustered. Clustering rates are very high, suggesting much of the TB seen is due to recent transmission. Maximum clustering was reached using a 4-year window, with an estimated two thirds of cases due to recent transmission. The proportion clustered decreased with age and varied by area of residence. In older adults clustering was less common in men and more common in those who were HIV positive (adjusted OR 5, 2-13).

After selecting the most likely sputum smear positive source contact per case, there were 147 epidemiologically-defined source contact-case pairs. Transmission was confirmed for 44% of household and family contacts and 18% of other contacts. After adjusting for other factors, transmission was much less likely to be confirmed if the source contact was HIV positive than if they were HIV negative (odds ratio 0.32, 95%CI 0.14-0.74). Overall, identifiable social links were found for 11% of clustered cases. The estimated proportion of tuberculosis in the population attributable to transmission within the household or close family was 9-13%. Approximately half the transmission of tuberculosis in this population is from HIV positive patients.

Keywords : molecular epidemiology

TITLE: **Genetics of susceptibility to tuberculosis in Northern Malawi**

LSHTM STAFF: *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: *The Wellcome Trust, LEPR*

SUMMARY

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

TITLE: **Intensified primary health care at the workplace: Investigating the impact on HIV-associated morbidity and TB epidemiology**

LSHTM STAFF: *Liz Corbett, Anthony E Butterworth, Peter Godfrey-Faussett, Yin Bun Cheung, Richard Hayes, Lilani Kumaranayake*

COLLABORATORS: *Biomedical Research and Training Institute, Harare: Peter Mason, Steven Chandiwana. Blair Research Institute, Harare: Shungu Munyati*

FUNDING: *Wellcome Trust CDA*

SUMMARY

Time frame: Dec 00 to March 05

This project, located in the industrial area of Harare, Zimbabwe, is aiming to:-

- test whether actively promoted VCT linked to intensified primary health care at the workplace reduces HIV-associated morbidity
- determine the impact of HIV infection on TB epidemiology, including duration of infectivity before diagnosis

The study is based around a cohort of 6440 HIV-tested factory workers in 22 factory sites. The three components are:-

- 1) A site-randomised intervention to investigate the acceptability and impact of providing HIV care at the workplace. Sites have been randomised to receive access to voluntary counselling and testing (VCT) either through the industrial clinics based in each factory (on-site), or through provision of free vouchers to a centrally located VCT centre. Cotrimoxazole is offered to those in WHO stages 2 to 4, and isoniazid preventive therapy is offered to those with positive tuberculin skin tests and negative active TB disease screen. VCT uptake has been much higher at sites offering on-site services (51% versus 18% voucher uptake at off-sites).
- 2) An observational study of the impact of HIV on the epidemiology of TB. Workers at each site are being followed-up for incident TB disease and are asked to provide a sputum specimen every two months that is stored unstained, and not used immediately for diagnostic purposes. After 2 years of follow-up at each site a cross-sectional TB disease prevalence survey was carried out to determine point prevalence of active TB disease by HIV status. These data will be combined with those for TB incidence in order to estimate duration of infectivity for each HIV group (indirect method). For each smear-positive TB patient duration is also being directly assessed from the stored sputum specimens (direct method).
- 3) A linked controlled household contact study is being carried out to investigate TB transmission to household members, using TST and T-cell responses to *Mycobacterium tuberculosis* antigens (ELISPOT assays to ESAT-6 and CFP-10 peptide pools).

Data from the factory study are now being cleaned and analysed for publication. The household contact TST/ELISPOT study is ongoing.

Keywords: TB epidemiology, VCT, isoniazid preventive therapy, household contact

TITLE: What are the causes of chronic cough in Mbare, Harare, Zimbabwe ?

LSHTM STAFF: Liz Corbett, Anthony E Butterworth

COLLABORATORS: Prof. Peter Mason, Dr Themba Dhoba, Mrs Evelyn Dadirai Makanza, Mrs Shungu Munyati, Dr Stanley Mungofa, Prof. Ahmed Latif, Dr Andrew Reid, Dr Morgan Nyakabau, Dr Pasi Nziramasanga

FUNDING: Rockefeller Foundation

SUMMARY

Background:

Studies in the pre-HIV era showed that about 10% of African patients presenting to clinics with cough of 3 weeks or longer had TB. During the last two decades TB rates in sub-Saharan Africa have risen to extremely high levels, primarily as a result of the HIV epidemic. During the same time period, however, there has been an increase in the prevalence of smoking, an increasing incidence of asthma, and a marked increase in the numbers of patients with HIV-related chest disease due to opportunistic infections other than TB.

Objectives:

To investigate the spectrum of disease causing cough for 3 weeks or more, and to investigate risk factors for presenting with chronic cough, including HIV, smoking, and smoke exposure.

Methods:

- 1) A prospective case-control study based in two primary health clinic. 550 patients presenting with cough for 3 weeks or more have been recruited as cases, with controls being 550 patients with minor trauma attending the same clinics. All participants have completed a questionnaire, and provided a specimen for HIV testing.
- 2) The burden and spectrum of diseases causing chronic cough in HIV-positive and HIV-negative case patients has been investigated using a standardised diagnostic algorithm and pre-set case-definitions. Initial diagnostic specimens and investigations (from the case patients) include sputum microscopy and bacterial / TB and fungal cultures; chest radiography; full blood count; stored blood for serology, and response to antibiotics / TB treatment.

Results:

A high proportion (43%) of all patients presenting with chronic cough had TB disease. HIV prevalence overall was 83% and was 88% in TB patients. Positive sputum smears were obtained from 70% of HIV-positive TB patients and 74% of HIV-negative TB patients, using concentrated fluorescent microscopy and up to 12 sputum specimens. Culture (on LJ slopes) added relatively little (smear-negative culture-positive TB in only 8% of TB patients).

Time frame: A twelve-month study commencing in April 2003. Data collection is complete and analysis is still ongoing. One paper has been accepted for publication (Clinical Infectious Diseases), and the case-control analysis will be submitted for publication later this year.

Keywords: TB epidemiology, Opportunistic Infections, Africa, Primary Health Care

TITLE: **Risk of tuberculosis infection in nurses in Zimbabwe**

LSHTM STAFF: *Liz Corbett, Anthony E Butterworth*

COLLABORATORS: *Dr Stan Houston, Prof. Peter Mason, Dr Themba Dhoba, Prof Mary Bassett, Prof. Ahmed Latif, Dr Andrew Reid, Dr Morgan Nyakabau, Mrs Shungu Munyati*

FUNDING: *Rockefeller Foundation*

SUMMARY

Introduction and aims :

TB disease rates in sub-Saharan Africa have risen to extremely high levels, primarily as a result of the HIV epidemic. African health care workers in TB hospitals, clinics and wards have intense daily exposure to TB patients and suspects. There has been limited investigation of TB transmission to health care workers in low-income country settings. The purpose of this study is to quantify and characterize the risk of TB infection in a cohort of student nurses in Zimbabwe, a country with a reported TB incidence of over 500 per 100,000 population per year, and to investigate the correlation between serial tuberculin skin test (TST) and T-cell responses to *Mycobacterium tuberculosis* antigens (ELISPOT responses to ESAT-6 and CFP-10).

Methods:

A prospective cohort study at Parirenyatwa and Harare Hospitals, and Harare Polytechnic College using first year students at each institution. Students are being recruited and followed-up with an initial two-step TST at recruitment and subsequently a single TST performed 6 monthly, with simultaneous enumeration of *Mycobacterium tuberculosis* antigen specific T-cells with the ex-vivo ELISPOT technique for the nurse cohort only. Nurses will be asked to record their ward attachments between each assessment point.

Interim results:

Non-specific tuberculin sensitivity appears to be very high in Harare, resulting in a high proportion of positive 2-step tests with negative ESAT-6 / CFP-10 ELISPOTs. Non-specific boosting during follow-up is also high, with rates of Canadian TST conversions (from below to above 10mm with increase of 6mm or more) approaching 15% per PYFU in both nursing and polytechnic (control) cohorts. Rates of American TST conversions are lower (17% and 7% respectively) and significantly higher in the nursing student cohort ($p = 0.02$). Comparison with ELISPOT results and ward rotations will be made later this year.

Time frame: A three-year study starting in January 2003

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

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

LSHTM STAFF: *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*

FUNDING: *Rockefeller Foundation*

SUMMARY

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 density 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

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

LSHTM STAFF: *Laura Rodrigues*

COLLABORATORS: *Professor Mauricio Barreto, Universidade Federal da Bahia, Brazil; Dr Miguel Ayub Ajar, Director, TB Control programme, Brazil; Dr Sergio Cunha (PhD student)*

FUNDING: *DFID and Brazilian Government*

SUMMARY

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 estimate the efficacy of BCG vaccine (given to school children in a population with a high coverage of neonatal BCG) against tuberculosis and
3. To investigate how the efficacy of BCG vaccine (given to school children in a population with a high coverage of neonatal BCG) against tuberculosis and leprosy varies in areas of low and high prevalence of atypical mycobacteria
4. To describe the size of tuberculin reactions according to presence of BCG scar.
5. To estimate the validity of BCG scar as an indication of neonatal BCG vaccination.
6. To estimate frequency of adverse reactions to BCG vaccine given to school children in a population with a high coverage of neonatal BCG
7. 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 introduced a second dose.

Methods

600 schools were randomized (within 6 strata of size and socio-economic conditions of the area) into vaccination or no vaccination. 75,000 children received vaccination; another 75,000 children did not receive vaccination and were examined for a previous BCG scar and gave identifying information. Cases diagnosed through the tuberculosis and leprosy control programme are identified and their case notes reviewed; confirmed cases are linked to the database of school children in the study. Scar and vaccine card collected. Follow up continues.

Keywords : Policy, Operations Research, Immunology, Brazil

TITLE: **Protection of BCG against asthma**

LSHTM STAFF: *Laura Rodrigues; Sergio Cunha*

COLLABORATORS: *Professor Mauricio Barreto, Universidade Federal da Bahia, Brazil; Prof Álvaro A. Cruz, Universidade Federal da Bahia, Brazil*

FUNDING: *Brazilian Science Council*

SUMMARY

There is an increase in prevalence of atopic diseases in developed countries. Recent research in Africa found lower prevalence of atopy in children with a BCG scar, but this has not been duplicated in a study in a developed country.

Objectives: to estimate the efficacy of BCG against asthma.

Socio-economic and environmental information plus the ISSAC questionnaire was applied to among 1,612 children aged 12-16 years old in 36 different schools, selected on the basis of having no, one or two BCG scars. Prevalence of asthma and other atopic diseases will be estimated for children with and without a BCG scar, adjusted for potential confounding variable.

Keywords : BCG, asthma prevention, Brazil

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

LSHTM STAFF: *Laura Rodrigues*

COLLABORATORS: *Professor M Yazdanbakhsh, Leiden University*

FUNDING: *Netherlands*

SUMMARY

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 maybe 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

TITLE: **An Integrated project of investigation of the tuberculosis programme. (Projeto Integrado de Investigação em Tuberculose Programa)**

LSHTM STAFF: *Laura Rodrigues*

COLLABORATORS: *Ricardo Arraes de Alencar Ximenes (PI, Universidade Federal de Pernambuco (UFPE); Maria de Fátima Pessoa Militão de Albuquerque – (UFPE and ENSP/FIOCRUZ); Antônio Roberto Leite Campelo – Serviço de Controle da Tuberculose), Norma Cavalcanti Licínio da Silva Lucena – (Laboratório de Biologia Molecular FIOCRUZ); Wayner Vieira de Souza – Gis (NESC/FIOCRUZ) Odimariles Maria Souza Dantas – (Pediatra, UFPE)*

FUNDING: *Brazilian Government (CNPq)*

SUMMARY

A cohort consisting of 2 year intake of new cases in the city of Recife is identified, receive a 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 fingerprinting, 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.

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

LSHTM STAFF: *Laura Rodrigues*

COLLABORATORS: *Ricardo Ximenes, Brazil et al*

FUNDING: *Brazilian CNPq*

SUMMARY

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: Tuberculosis, BCG

TITLE: **An international multicentre trial for the evaluation of a four-drug fixed dose combined tablet in the initial intensive phase (2 months) of chemotherapy followed by a two-drug fixed dose combined tablet in the continuation phase (4 months) for the treatment of pulmonary tuberculosis: Study C**

LSHTM STAFF: *Dean Everett, Tobias Chirwa, Deborah Watson-Jones*

COLLABORATORS: *National Institute for Medical Research, Mwanza; Sengerema District Hospital*

FUNDING: *IUATLD*

SUMMARY

Combined preparations of antituberculosis drugs have been widely used. These have included mostly two-drug combinations of isoniazid with either PAS, thiacetazone, ethambutol or rifampicin.

The use of fixed-dose combined (FDC) drugs in the treatment of tuberculosis by National Tuberculosis Programmes (NTPs) has been recommended by both the International Union Against Tuberculosis and Lung Disease (IUATLD) and the World Health Organisation (WHO).

The advantages of FDC drugs could include preventing the emergence of drug resistance due to monotherapy, reducing the risk of incorrect dosage, simplifying procurement and prescribing practices, aiding compliance and facilitating directly observed treatment (DOT).

A major concern in the treatment of tuberculosis is to prevent the emergence of bacterial resistance to isoniazid and rifampicin. FDCs which include these two drugs, could play an important role in this aspect of tuberculosis management.

Two and three-drug FDCs, containing isoniazid and rifampicin, have been in use for a number of years. Their bioavailability levels have been evaluated as acceptable when compared to those given in separate drug formulations. The combined tablets are well tolerated and the rate of side-effects similar to that of the separate formulations.

The recommended treatments for newly diagnosed tuberculosis always contain an initial intensive phase of four drugs. The most widely used four drug regimen consists of rifampicin, isoniazid, pyrazinamide and ethambutol. It would be appropriate, therefore, if a four-drug combined tablet were available for use in the initial intensive phase.

Several pharmaceutical companies have recently manufactured such a FDC tablet containing these four drugs. However, the IUATLD recommendations originally emphasised and recently reiterated, are that only FDCs of demonstrable bioavailability should be prescribed. The four-drug FDC tablet manufactured by the pharmaceutical company Aventis, has recently undergone bioavailability studies (8) and the results were satisfactory.

In study C we are testing the effectiveness of this compound, when given in the initial intensive phase of the treatment of tuberculosis, in patients with newly diagnosed, smear positive pulmonary tuberculosis. This will be followed by four months of a two-drug FDC of rifampicin and isoniazid.

Keywords: Fixed dose combined drug

IMMUNOLOGY

TITLE: Incident tuberculosis among HIV-infected individuals receiving antiretroviral treatment in South Africa

LSHTM STAFF: *Stephen D. Lawn, Hazel Dockrell, Alison Grant, Katherine Fielding*

COLLABORATORS: *Desmond Tutu HIV Centre (Robin Wood and Linda-Gail Bekker) and Department of Microbiology (Robert Wilkinson and Lafras Steyn), Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*

FUNDING: *Wellcome Trust*

SUMMARY

This study arises from observations in Cape Town that although antiretroviral treatment (ART) greatly reduces the risk of tuberculosis (TB) in HIV-infected individuals, the risk remains higher than that among HIV-noninfected individuals. ART-induced restoration of immune responses to *Mycobacterium tuberculosis* during may be suboptimal. The major aim of this study is therefore to monitor changes in functional antimycobacterial immune responses in a prospective cohort of HIV-infected individuals commencing ART in a township in Cape Town, South Africa.

Keywords: tuberculosis, HIV/AIDS, immunology, antiretrovirals, immune reconstitution, South Africa

TITLE: **Markers of cell-mediated immunity in tuberculosis**

LSHTM STAFF: *Steven Smith, Hazel Dockrell*

COLLABORATORS: *Other partner groups of the EC TB-VAC consortium*

FUNDING: *European Commission*

SUMMARY

The European TB-VAC project aims to facilitate the development of new vaccines for TB. By co-ordinating Europe-wide efforts in areas such as TB antigen discovery, candidate vaccine development and testing and the identification of correlates of protection, promising new vaccines may move more quickly into general use.

In the UK, BCG vaccination is known to provide protection against TB in young adults. Our previous studies on immune responses to BCG, carried out in the context of the schools BCG programme, leaves us well placed to continue these studies in order to identify correlates of protection that are induced by BCG in schoolchildren.

We are currently recruiting schools to the new study in which we intend to obtain blood samples pre-vaccination, and then at time intervals post-vaccination to correspond with the peaks of effector and memory T-cell responses. These will be measured by ELISpot assay and intracellular cytokine staining followed by flow cytometry. All assays will be performed in parallel with the whole blood IFN γ ELISA assay which has proven a reliable measure of BCG-attributable IFN γ responses in the past.

As the TB-VAC project has been organised to promote collaboration, the potential to liaise with numerous groups exists. One area in which we are currently utilising these links is that of TB-related antigens. The groups of Tom Ottenhoff (Leiden University) and Camille Locht (Institut Pasteur Lille) have made a number of antigens available to us for testing in BCG vaccinees and control subjects. In addition, the Leiden group has also developed an assay to identify immunity-related expression of candidate marker genes and are willing to collaborate on the testing of samples from our UK study.

Keywords: Immunology, BCG, T-cells, TB-VAC

TITLE: **Immune responses in close contacts of TB patients**

LSHTM STAFF: *Amelia Crampin, Judith Glynn, Sian Floyd, , Keith Branson, Jacky Saul, Hazel Dockrell, Paul Fine*

COLLABORATORS: *Frank Mwaungulu Karonga Prevention Study Malawi Francis Drobniowski, PHLS Mycobacterium Reference Laboratory, Dulwich.*

FUNDING: *The Wellcome Trust, LEPR*

SUMMARY

Objectives

To follow up disease, mortality and immunological outcomes among HIV positive and negative individuals after intense exposure to tuberculosis.

Methods

Spouses of smear positive TB patients, many of whom are HIV positive, are being followed up prospectively at pre-defined intervals after exposure and being studied for their immune response to tuberculosis and risk of tuberculosis over time. CD4 counts, RT23 and candidin skin testing and whole blood assays for FN-gamma response to mycobacterial antigens are being undertaken. Isoniazid prophylaxis is being provided for those considered to be most at risk and outcomes compared to a retrospectively identified group of spouses exposed at different time intervals in the past. Approximately 300 individuals have been recruited to date.

Keywords : HIV, exposure, immunology

TITLE: **The impact of anti-TNF treatment on antibiotic efficacy in murine tuberculosis**

LSHTM STAFF: *Liz McMinn, Debbie Smith, Paul Kaye, Greg Bancroft*

FUNDING: *Centocor*

SUMMARY

The aim of this research is to examine the potential impact of *in vivo* neutralisation of TNF on antibiotic treatment efficacy of tuberculosis in a murine model. The sponsors Centocor manufacture and market therapies based on monoclonal antibody technology, which yield long-term benefits for patients with chronic diseases. Approximately 200,000 Rheumatoid Arthritis (RA) patients have been successfully treated worldwide to date with antibodies to tumour necrosis factor alpha (TNF- α). This therapy blocks the activity of TNF- α , a key inflammatory mediator. Overproduction of TNF- α leads to inflammation in RA, Crohn's disease and other immune mediated inflammatory disorders. Anti-TNF therapy reduces inflammation by specifically targeting and irreversibly binding to TNF- α on the cell membrane and in the blood. Anti-TNF therapy can also be administered in combination with the drug methotrexate, to improve physical function in patients with moderately to severely active RA who have had an inadequate response to this drug alone, and for reducing the symptoms and inhibiting progression of joint damage. There have been some concerns that in a small proportion of patients this therapy may lead to the reactivation of tuberculosis (TB) in people who have had recent or past exposure to TB. Some of these infections have been serious and further investigation is required.

We have established using aerosol infection with *M. tuberculosis* models of latency and reactivation using Rifampicin-Isoniazid (RIF-INH) antibiotic therapy to achieve latency in order to mimic reactivation of human tuberculosis. The impacts of anti-TNF monoclonal antibody on *M.tb* reactivation rates from these latency models are currently being assessed. Future work will involve the impact of methotrexate and methotrexate in combination with anti-TNF monoclonal antibody on *M.tb* reactivation rates from these latency models. Standard experimental results include assessment of bacterial burdens and histology. A Category 3 cryostat facility is currently being established in order to carry out specific immunohistochemistry to investigate detailed tissue pathology and immunology. In the long term the project will focus on improvement of therapy for those patients who do reactivate *M.tb*, this will include whether antibiotic therapy can be improved, treatment time decreased, and whether it can be given in combination with anti-TNF therapy.

Keywords: *Mycobacterium tuberculosis*, anti-TNF therapy, immunology

TITLE **The impact of helminths on the response to immunisation and on susceptibility to infectious diseases in childhood in Uganda**

LSHTM STAFF: *Alison Elliott, Tamara Hurst, Hazel Dockrell, David Mabey, Richard Hayes, Linda Morison, Jimmy Whitworth*

COLLABORATORS: *P Kaleebu, B Biryahwaho. Uganda Virus Research Institute.
M Muwanga, Entebbe Hospitals, Uganda.
F Adatu, Tuberculosis Control Programme, Uganda.
N Kabatereine, Vector Control Programme, Uganda
David Dunne, Sarah Joseph, Department of Pathology, University of Cambridge.
Frances Gotch, Imperial College, London.*

FUNDING: *The Wellcome Trust*

SUMMARY

The project is being conducted in Uganda at the Uganda Virus Research Institute, and the Entebbe Hospitals.

A cohort of 2500 mothers and their babies is being set up, based at the Entebbe Hospitals. This study will examine the impact of helminth infections in pregnancy and in early childhood on childhood immunisations and on the incidence of infectious diseases in childhood. A pilot study of about 100 mothers has been conducted. In the main study mothers are randomised to albendazole or placebo and to praziquantel or placebo during pregnancy. All mothers receive both antihelminthics after delivery. Children are randomised to three monthly albendazole or placebo after the age of one year, and receive annual selective treatment for helminths based on analysis of stool samples. The main outcomes are the immunological response to childhood immunisations (particularly BCG) and the incidence of major infectious diseases in childhood (including tuberculosis).

Keywords: Immunology, cytokines, Uganda

TITLE: **T cell immune responses in tuberculosis patients**

LSHTM STAFF: *Dolly Jackson Sillah, Hazel Dockrell, Carolynne Stanley, Sian Floyd*

COLLABORATORS: *Dr Graham Bothamley, Homerton University Hospital, Department of Chest Diseases, Homerton Row, London.*

FUNDING: *Commonwealth Scholarship Secretariat*

SUMMARY

Treatment of TB is known to improve the suppressed immune responses associated with the disease. It is not clear whether improved immunity constitutes a protective response or not. This study is a comprehensive assessment of the immunological functions of T cells in pulmonary and lymph node TB patients before and after the start of chemotherapy. T cells will be obtained from peripheral blood (pre and post treatment) and from lymph node tissue (pre-treatment). The production of cytokines such as IFN- γ , IL-2 and IL-4 will be measured using ELISA and / or ELISPOT techniques. The expression of FoxP3, TGF- β and IL-10 will be analysed with real-time RT-PCR. Cellular proliferation and cell surface staining for CD4 and CD8 antigens in combination with staining for activation markers and intracellular cytokines, will be carried out using flow cytometry. Peripheral blood INF- γ responses at 2 months of treatment will be compared with that of *Mycobacterium tuberculosis* infected but healthy TB contacts in the Gambia at the end of the study (collaborative links are yet to be established).

This study may generate important and novel data on the differences in immune response at the site of infection and in the peripheral blood and may help uncover protective responses that could be useful end points in future TB vaccine trials.

Keywords: Tuberculosis, T cells, cytokines

TITLE: **The immunological mechanism of *M. tuberculosis* hypervirulence**

LSHTM STAFF: *Annemieke ten Bokum, Heidi Alderton, Debbie Smith, Greg Bancroft*

COLLABORATORS: *Royal Veterinary College: Prof. Neil Stoker*

FUNDING: *Wellcome Trust*

SUMMARY

Single gene knockout mutants of *M. tuberculosis* that are hypervirulent, i.e. cause accelerated disease and death in immunodeficient mice, have been identified in previous projects in collaboration with researchers at Queen Mary College and at GlaxoSmithKline. A number of these mutants showed accelerated growth in immunocompetent mice and in activated macrophages, without showing increased growth *in vitro*. These results indicate that *M. tuberculosis* has the intrinsic capacity to grow more aggressively *in vivo* than it usually does, and that there is a group of genes that actively suppresses bacterial growth. Clinical isolates with apparently increased virulence have also been reported, but it is unknown what impact this might have on the natural history of the disease.

This study aims to:

- Identify additional genes responsible for hypervirulence
- Identify which mutants are hypervirulent in a mouse aerosol infection model
- Determine the effects on the virulence phenotype of combining mutations and expressing genes constitutively
- Determine the impact of these mutations on the development of the innate and adaptive immune responses to infection and on the pathology of the disease in the mouse model

Keywords: hypervirulence, mycobacterial genetics, host-pathogen interactions, immunology

TITLE: **Determinants, magnitude and persistence of immune responses to BCG vaccination**

LSHTM STAFF: *Anne Ben-Smith, Rosemary Weir, Patricia Gorak-Stolinska, Maeve Lalor, Amelia Crampin, Nuala McGrath, Paul Fine, Hazel Dockrell (ITD)*

COLLABORATORS: *Dr P Anderson, Dr A Bennett, Prof P Beverley, Prof J Blackwell, Dr S Corlett, Dr M Doherty, Dr D Dunne, Dr M Newport, Prof D Young*

FUNDING: *Wellcome Trust*

SUMMARY

This is an immuno-epidemiological study within the Wellcome Trust funded programme grant “Epidemiology of Mycobacterial and HIV infection in Northern Malawi”. We are investigating immune responses following BCG vaccination in cohorts of infants and young adults in two sites: Malawi (Karonga District) and UK (WLL, CWW and Redbridge Primary Care Trusts), comparing two populations in which BCG has been shown to have differing abilities to protect against pulmonary TB. We are comparing responses of adolescents to BCG vaccination, as in our previous study (Black et al, 2002) and also of infants and children to neonatal BCG vaccination (the standard procedure in most countries).

By comparing the numbers, types and persistence of T cells in peripheral blood we aim to establish if BCG vaccination of adolescents activates memory T cells or induces a primary immune response and investigate how differences between the T cell populations present at the time of BCG vaccination influence the protective immune response against *M. tuberculosis*. Using four-colour flow cytometric techniques to evaluate T cell phenotype, we have shown that young adult Malawians have a lower percentage of naïve T cells, and a higher percentage of antigen-experienced T cells than subjects of similar age in the UK. Persistence of mycobacterial antigen specific responder cells in the CD45RO⁺ memory population is being assessed using an IFN- γ ELISPOT. Using heteroduplex analysis to investigate the clonal T cell repertoire, we have shown, in collaboration with Dr A Bennett and Prof P Beverley, EJIVR, Compton, that BCG vaccination induces fewer Mtb PPD specific clones 12 months after vaccination in Malawians than in UK subjects.

We are continuing to use a diluted whole blood assay to analyse antigen specific cytokine production prior to and following both adult vaccination (for continuity with our previous study) and neonatal vaccination. In our infant study groups, both in Malawi and the UK, we find that cord blood T cells are immunologically naïve to PPD. BCG vaccination induced marked IFN- γ secretion, with greater responses in the UK than in Malawi at 3 months post-vaccination. We aim to assess the induction of the neonatal BCG induced IFN- γ response to *M. tuberculosis* antigens and how this is influenced by genetic factors (with Dr M Newport, University of Sussex, Brighton). Additional aims for the Malawian cohort include determination of maternal influence on the immune response, in particular the influence of maternal infection with HIV and helminth parasites and helminth specific responses in newborns (with Dr D Dunne, Cambridge).

Keywords: Vaccines, BCG, T cells, cytokines, Malawi, UK

TITLE: Identification of surrogate markers of protective immunity for use in vaccine trials

LSHTM STAFF: Jackie Cliff, Hazel Dockrell

COLLABORATORS: Pauline Lukey, Ken Duncan, Rohit Mistry, GlaxoSmithKline R & D, Stevenage, UK
Nulda Beyers, Paul van Helden, University of Stellenbosch, S. Africa

FUNDING: GlaxoSmithKline Action TB Programme

SUMMARY

The primary objective of this project is to develop a robust whole blood test, which would allow the assessment of anti-mycobacterial immunity in large-scale field trials of new prophylactic and immunotherapeutic TB vaccines. It is based on the hypothesis that the ability to make and respond to IFN- γ is critical for protection against mycobacterial disease, and that CD8⁺ as well as CD4⁺ T cells play a role in such immunity.

Initially, Differential Gene Expression (DGE) technology has been used to identify novel genes which are expressed in human CD8⁺ T cells in response to *M. tuberculosis*. This was achieved by comparison of RNA from CD8⁺ and CD4⁺ T cells isolated from peripheral blood from healthy donors, following incubation with live *M. tuberculosis* [1]. Differentially expressed genes are currently being analysed by real-time RT-PCR in PBMC from healthy BCG-vaccinated and non-vaccinated donors, to determine which genes correlate with protection against tuberculosis. Their expression pattern in mouse models of protection and disease will also be analysed, in collaboration with Debbie Smith (LSHTM). We are also developing ELISA-based tests for known molecules secreted from activated CD8⁺ T cells, such as granzyme A, granzyme B, soluble CD8 and perforin.

Diagnostic markers of TB treatment efficacy and protective immunity have recently been discovered in peripheral blood samples by our collaborators at GlaxoSmithKline and at the University of Stellenbosch, using DGE technology. We are currently investigating the expression patterns of these genes in mouse models of TB infection and treatment, both in the lung and in peripheral blood, in collaboration with Debbie Smith and Heidi Alderton (LSHTM).

Keywords: CD8⁺ T cells, Differential Gene Expression, surrogate markers, CTL Assay

TITLE: **Evaluation of cellular responses against *Mycobacterium tuberculosis* in children in Korea**

LSHTM STAFF: *Hazel M. Dockrell, Hyejon Lee*

COLLABORATORS: *Cheol H. Yun, Sang-nae Cho, Jeon-Soo Shin, Ji-Eun Choi*

FUNDING: *International Vaccine Institute, Seoul Korea; British Council*

SUMMARY

There are two BCG vaccines available and currently used in Korea; one is BCG-Pasteur, given by intradermal injection, and the other is BCG-Tokyo, given by multipuncture (>17 needles) device. This pilot study will be a feasibility study to assess the immune response to *M. tuberculosis* antigens in young children who have previously received BCG vaccination by different BCG strains and methods of administration. In the study, a whole blood assay will be optimized to detect immediate effector T cells as well as central memory T cells in children. In this 10-month study (April 05-Jan 06), fifty healthy volunteers aged between 4-6 years will be recruited in the Seoul National University Boramae Hospital.

Based on preliminary results, the study will be extended to compare the different BCG strains and methods of administration in larger groups. We also hope to define the best assays to be employed in clinical trials aimed to assess vaccine effectiveness in future studies.

Keywords: Tuberculosis, BCG vaccination, Korea

OPERATIONS RESEARCH

TITLE: **DFID Tuberculosis Knowledge Programme**

LSHTM STAFF: *Peter Godfrey-Faussett, Ruth McNerney, Alexandra Coldham, John Porter, Judith Glynn, Ginny Bond, Karina Kielmann, Hamidou Traore, Lilani Kumaranayake, Liz Corbett, Alison Grant, James Hargreaves*

COLLABORATORS: *John Walley, James Newell, Sarah Escott, Kamran Siddiqi, Zafar Ullah, Nuffield Institute for Health, Leeds, Amir Kahn, Association for Social Development, Pakistan, Mukund Uplekar, WHO, Sheela Rangan, Centre for Health Research and Development, India Moses Sinkala, Mpundu Makassa, Seraphim Kaminsa, Lusaka Urban Health Management Team, Zambia*

FUNDING: *DFID*

SUMMARY

The Tuberculosis Programme links the London School of Hygiene & Tropical Medicine with the Nuffield Institute for Health, Leeds. It is a multidisciplinary programme covering the next five year period. The objectives are to:

- A. Facilitate closer collaboration between researchers, policy-makers and implementing agencies in the different countries
- B. Better understanding of the social, economic and cultural influences on access to services for TB and adherence to treatment in Southern and West Africa and the Indian sub-continent
- C. Develop and test affordable approaches to improving the speed and accuracy of diagnosis
- D. Test new strategies to improve coverage and treatment outcome in TB control programmes in Southern Africa, India, Pakistan and Nepal
- E. Evaluate innovative ways to promote synergy between services for TB and HIV in countries most affected by the dual epidemic
- F. Explore approaches to reduce the threat of multi-drug resistant TB
- G. Understand the impact on disease control programmes, of different approaches to Health Sector Reform between Malawi and Zambia
- H. Explore the factors that facilitate and constrain the policy transfer of DOTS from international to national contexts in South Africa and Mozambique
- I. Develop effective communication strategies to reach international, national and local health and TB policy makers and practitioners

Details of individual studies supported by the programme are provided under separate headings within this booklet. Further information on this programme can also be found at:

<http://www.lshtm.ac.uk/dfid/tb/>

TITLE: **The Intervention with Microfinance for AIDS and Gender Equity – IMAGE Study**

LSHTM STAFF: *James Hargreaves, John Porter, Paul Pronyk, Julia Kim, Charlotte Watts, Linda Morison, Stephen Jan*

COLLABORATORS: *Joanna Busza, Chris Bonell, Vicki Strange, Institute of Education
Rural AIDS & Development Action Research (RADAR) Programme, WITS University School of Public Health, SA
National Department of Health and Welfare, South Africa
Small Enterprise Foundation (SEF)*

FUNDING: *Ford Foundation, Swedish International Development Agency, HIVOS Netherlands, AngloPlatinum*

SUMMARY

The Intervention with Microfinance for AIDS & Gender Equity (IMAGE) is a structural intervention for HIV/AIDS that brings together two main components:

- A poverty -focused microfinance programme
- A curriculum of gender and HIV education with the aim of facilitating community mobilization activities

The Pilot Phase of this work (2001-2004) was developed to test the efficacy of the IMAGE intervention. Employing a cluster randomized design, the research brought together intensive qualitative and quantitative evaluation to examine the impact of the intervention on social, economic and behavioural vulnerability to HIV. The two endpoints for the work were the incidence of HIV infection and gender-based violence. As the first structural intervention for HIV or gender violence to take place in a developing country, the protocol was reviewed and registered at the Lancet (www.thelancet.com)

The Expansion phase of the IMAGE work (2005-2007) builds on the Pilot phase and has the following key components:

- Conduct a full quantitative and qualitative analysis of data from the Pilot Phase of the project
- Scaling up the intervention over a 2000 km² area along a high-transmission area slated to become the largest platinum mining shelf in the southern hemisphere
- Conduct a full economic evaluation of the work, including cost-effectiveness and cost-benefit analyses
- Conduct a process evaluation - a form of evaluation forming an important adjunct to randomized controlled trials that allows for a detailed exploration of acceptability of an intervention, potential mechanisms of action, and the generalizability / replicability of the strategy to other countries and contexts.

Keywords HIV/AIDS, Poverty Alleviation, Microfinance, Evaluation, South Africa

TITLE: **Understanding the true burden of tuberculosis in a rural South African population**

LSHTM STAFF: *Paul Pronyk, James Hargreaves*

COLLABORATORS: *Kathleen Kahn – School of Public Health, University of the Witwatersrand, Harry Hausler, South African Department of Health*

FUNDING: *DFID*

SUMMARY

This research will describe the incidence and prevalence of tuberculosis in a rural sub-district. The setting is a Demographic and Health Surveillance Site comprised of 20 villages and c. 60 000 people in South Africa's northeast. Methods employed include a survey of hospital record data on passive case finding, a single-pass active case finding survey of chronic coughers in 10 000 households, and a record of TB related deaths generated through the use of a verbal autopsy process. Data is being collected that will accurately describe the incidence of TB in a well-described population with a known denominator, the prevalence of sputum positive TB among undiagnosed active cases, and the incidence and prevalence of registered and unregistered TB deaths in the community – painting an accurate picture of the epidemiology of the disease in a high HIV prevalence setting.

Keywords: Tuberculosis, epidemiology, active case finding, verbal autopsy, South Africa

TITLE: **Providing HIV/AIDS Care in under-resourced settings**

LSHTM STAFF: *Paul Pronyk*

COLLABORATORS: *Rural AIDS & Development Action Research Programme,
School of Public Health, University of Witwatersrand
Perinatal HIV Research Unit, Johannesburg, South Africa
(PHRU)*

FUNDING: *USAID/PEPFAR*

SUMMARY

LSHTM is currently at the forefront of providing and evaluating comprehensive HIV/AIDS Care in resource poor settings through its work in Limpopo Province - a remote rural area of the country. The site builds on previous experience as a WHO ProTEST Site for TB/HIV collaboration. In partnership with South African colleagues at PHRU parallel patient cohorts (capturing more than 3000 patients) have been established at this site and at an urban site in Soweto - reflecting the vast contextual differences between urban township and rural areas that characterizes much of the southern African region.

A broad portfolio of research activities is emerging around the provision of comprehensive HIV/AIDS care, which includes the recent introduction of anti-retroviral therapy. These sites provide the opportunity to interrogate a number of clinical, social and health systems questions that arise within a rapidly evolving policy environment, where major gaps in capacity and programme implementation exist. Best practice models arising from the work have the potential to inform the scaling up of HIV services in much of the region.

Keywords: HIV/AIDS, South Africa, under resourced-settings

TITLE: **Developing sustainable tuberculosis services in Kemerovo and Samara Oblasts**

LSHTM STAFF: *Richard Coker, Martin Mckee, Dina Balabanova*

COLLABORATORS: *Francis Drobniowski, King's College, London, Rifat Atun, Imperial College Management School, Imperial College of Science Technology and Medicine, London*

FUNDING: *DFID*

SUMMARY

Over the past decade, driven in large part by Russia's economic and political travails, its unwieldy and inefficient health care system, and massive rates of incarceration, tuberculosis has flourished. Notification rates almost tripled between 1991 and 1997. It has been suggested that the 'epidemiological pump' is the prison system (it has been estimated that approximately one in ten of Russia's one million detainees have active tuberculosis), and the fractures in service provision between this system and the civil population. Rising rates of tuberculosis are made far worse by the potentially devastating impact of multi-drug resistant tuberculosis.

The social and economic changes Russia has witnessed over the past decade have dealt severe blows to the country's large medical and public health systems; the capacity to respond to the country's emerging health crisis is insufficient. The aim of this project is to support the development of an approach to tuberculosis control that is cost-effective, sustainable, and in-line with internationally accepted practice. The project, now concluded, dovetails with ongoing DFID-supported projects in microbiological and epidemiological support, and other internationally supported initiatives in the region. At present 20 research publications have arisen from the project, with approximately a further 20 either submitted or in preparation.

Keywords: Russia, prison, MDR-TB, cost-effective, sustainability

TITLE: **The Prevention of Mother to Child HIV Transmission and ProTEST: A combined approach**

LSHTM STAFF: *Helen Ayles, Peter Godfrey-Faussett, Virginia Bond, Lilani Kumaranayake*

COLLABORATORS: *National AIDS/TB/STD/Leprosy co-ordinator CboH, Zambia, MTCT Working Group, Lusaka, Kara Counselling and Training Trust, Lusaka, Zambia, Lusaka Urban District Health Management Board*

FUNDING: *WHO*

SUMMARY

In countries with a high prevalence of HIV infection, the best available control strategies, promoted by the world's aid agencies and WHO, are failing to prevent the rising incidence of tuberculosis. Tuberculosis affects predominantly young, economically active, adults, on whom the development of the poorest countries depends.

Recent initiatives aimed at preventing mother to child transmission of HIV are detecting women who are HIV positive, but are not addressing their healthcare needs in terms of prevention of opportunistic infections, TB detection, STI management etc.

A complete package of measures is needed to encompass both of these initiatives and to harness the community capacity that has arisen in most cities with a high prevalence of HIV. Such a package would reduce transmission of *M.tuberculosis* by improving case-finding and treatment; reduce reactivation of *M.tuberculosis* by establishing preventive therapy services and reduce transmission of HIV by enhancing voluntary HIV counselling and testing (VCT) services and reduce mother to child transmission.

The proposed innovation will:

Encourage VCT and MTCT counselling and testing services as an entry point to integrated management and prevention of HIV-related TB, and STIs

Enhance collaboration between government health services and community organisations

Introduce TB-related issues into HIV-related social mobilisation and activism

Its success will be measured by the impact on the community's burden of TB and other HIV related illness. Economic and social science evaluations will determine the potential cost-effectiveness and sustainability of the package. Success will also be measured by process indicators of demand for and acceptability of the package, equity of access to the services provided and cohort analysis of those treated for tuberculosis or with preventive therapy

Keywords: MTCT, VCT, HIV, STIs, preventive therapy, sustainability

TITLE: **Action Research Unit in an urban area with a high prevalence of both HIV and Mycobacterium tuberculosis**

LSHTM STAFF: *Helen Ayles, Peter Godfrey-Faussett*

COLLABORATORS: *District Health Management Team – Dr M Makasa, Mr G Samungole, ZAMBART Project –Dr J Banda University of Zambia Medical School; University Teaching Hospital, Lusaka*

FUNDING: *DFID*

SUMMARY

The Action Research Unit of Lusaka District management Team is established within the district headquarters and aims to bridge the gap between research and practice.

The key problem as identified by the Lusaka District Management Team is the high rate of sputum smear negative patients notified in the district. The first study undertaken by the ARU followed TB suspects at urban health centres in order to evaluate whether they were asked for sputum to be submitted and if so who gave them instructions and how they were followed.

Preliminary results demonstrate that a major barrier is a lack of sputum containers and further studies are underway to establish the reason for this, attitudes of staff towards sputum and its collection and also monitoring of the quality of received sputum samples.

Keywords: Action research, diagnostic process, adherence, Zambia

TITLE: **Timing and its significance in the diagnosis and treatment of tuberculosis: A multinational study**

LSHTM STAFF: *Helen Ayles*

COLLABORATORS: *ZAMBART Project Amos Nota; Tropical Disease Research Unit of WHO, Dr Jane Cunningham, Universidad Peruana Cayetano Heredia, Peru Dr E Gotuzzo; Tuberculosis Research Centre, Chennai, India-Dr R rajeswari; department of Community Medicine, Chiang Mai University, Chiang Mai, Thailand- Dr Ratana Panpanich*

FUNDING: *WHO*

SUMMARY

Purpose: To gain a quantitative and qualitative understanding of the TB diagnostic process and examine the impact of delay across disease categories and geographic settings.

Objectives:

Study 1

1. To quantify time to diagnosis and treatment at patient, health provider and laboratory stages in newly diagnosed pulmonary and extrapulmonary tuberculosis patients in 4 geographically diverse disease endemic countries.
2. To determine the factors associated with TB diagnostic delay
3. To determine the economic impact of the diagnostic process on newly-diagnosed TB patients and their caregivers.
4. To examine the impact of prolonged diagnostic delay on smear bacillary load, morbidity and smear conversion at 2 months
5. In pulmonary TB patients, to examine the relationship between time to diagnosis, smear conversion at 2 months and treatment failure.
6. To assess patient perceptions of impediments in the diagnostic process

Study 2

1. To determine the frequency and timing of diagnostic drop-out among a cohort of TB suspects
2. To determine the factors associated with drop-out
3. To assess drop-outs perceptions of the diagnostic process
4. To ascertain the outcome of drop outs 1 month following request for investigations

Study 3

To assess district nurse/health assistant and laboratory technicians perceptions of impediments to the diagnostic process

This study is now complete and analysis is ongoing.

Keywords: Delay, Diagnostic pathways, Zambia

TITLE: **ProTEST Expansion in Zambia**

LSHTM STAFF: *Helen Ayles, Peter Godfrey-Faussett*

COLLABORATORS: *Zambia CBoH- Dr L Kafwabulula, LDHMT- Dr M Makasa;
ZAMBART- Dr J Banda, Dr K Shanaube*

FUNDING: *GFATM, WHO*

SUMMARY

The ProTEST initiative was piloted in Zambia, Malawi and South Africa. The successful pilots have stimulated the formation of international TB/HIV policy by WHO and the adoption of the initiative for roll-out in the countries involved (as well as several others)

As part of Zambia's successful bid to the GFATM, ProTEST expansion has been planned for all districts in Zambia. LSHTM, through ZAMBART project has been mandated to develop training materials for this expansion and to train districts in its implementation. Zambart project will monitor and evaluate the implementation of ProTEST in districts.

Keywords: TB/HIV, Programme roll-out

TITLE: **Zambia National TB/HIV Survey**

LSHTM STAFF: *Helen Ayles, Peter Godfrey-Faussett*

COLLABORATORS: *Zambia Central Board of Health- Dr L Kafwabulula;
Zambart project- Phales Mitimangi, Andy Mwale*

FUNDING: *Gates Foundation: Create start up grant*

SUMMARY

A nationwide survey of all 72 health districts in Zambia will determine the degree to which each district is prepared for combined TB/HIV services. The survey will visit every district and within each district visit all TB diagnostic centres, VCT centres and HIV support groups. Standard questionnaires will be completed at each health facility compiling statistics on TB and HIV, laboratory capacity and supplies, drug stocks and the linkages with other service providers. All HIV support groups in the country will be visited and documented.

The report will be used by the Central Board of Health and Zambart Project for planning of expansion of TB/HIV services.

Keywords: TB/HIV, survey

TITLE: **Understanding The Demand For Health Services In Cape Town, South Africa: Implications For Health Equity and Effective TB Care**

LSHTM STAFF: *Anne Mills, Kara Hanson, Lucy Gilson, Jolene Skordis (Research Degree Student)*

COLLABORATORS: *Andrew Boulle, School of Public Health at the University of Cape Town. Kermyt Anderson, University of Oklahoma. Lucy Gilson, University of the Witwatersrand*

FUNDING: *This investigation received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Jolene Skordis is supported by a scholarship from the Commonwealth Trust.*

SUMMARY

1) Primary Aim

To explore health seeking behaviour in the Western Cape of South Africa, and understand its determinants, in order to discern whether the current level and composition of supply is equitable; and thus to inform National health policy and the global debate around scaling up access to health care for the poorest groups.

2) Introduction

Global interest in inequalities and meeting the needs of the poorest has yet to be translated into adequate local policy knowledge. Research on inequity in South Africa has thus far focused on health outcomes or service utilisation in rural populations, with findings dominated by insufficient health service supply. Models of health seeking behaviour and economic demand are traditionally constructed at the individual level, making little allowance for seeking as a social phenomenon, influenced by cultural norms and established familial or community habits. Barriers to access are usually presented as a list of mutually exclusive factors rather than an interdependent whole, where the relative importance of each barrier varies between individuals, communities and illness-experiences.

3) TB as a case study

TB/HIV co-infection is a global concern, and failure to effectively treat TB in poorer countries highlights global inequities in health. South Africa experiences some of the highest prevalence rates of both diseases. In the Western Cape, TB prevalence is rising faster than the rest of the country while cure rates are falling despite widespread and free provision of DOTS for TB. Literature from other settings ascribes poor cure rates to delays in seeking treatment, delays in diagnosis and failure to adhere to the treatment regime i.e. poor health seeking behaviour. Selecting a curable disease such as TB, which affects only the poorest groups in the Western Cape, enables the evaluation of social context on individual decision-making while controlling for supply factors. Supply in the Western Cape is relatively high, further enabling a detailed analysis of barriers posed by gender, stigma, socio-economic factors and poor service quality, while still considering service utilization and health outcomes.

Keywords: Demand, TB, Health service use, Equity

TITLE: **The necessity of history: Contextualising the introduction of Anti-Retroviral Treatment in Zambia**

LSHTM STAFF: *Virginia Bond*

COLLABORATORS: *Lyn Schumaker, Principal Investigator, Wellcome Unit for the History of Medicine, University of Manchester*

FUNDING: *Wellcome Trust*

SUMMARY

This is a pilot study to explore from a historical and an anthropological perspective key issues involved in the acceptability of and adherence to anti-retroviral (ARV) therapy in Zambia. Building on historical research conducted by the principal investigator in Zambia on past explanatory models of disease and treatment, and anthropological work conducted by the co-investigator on TB and HIV in Zambia, the two social scientists aim to see if experiences with other diseases and Western bio-medical treatment are of relevance for HIV/AIDS and ARV treatment programmes. The focus of the pilot is specifically on understanding the meaning of common side effects related to ARV treatment and concerns about ARVs ‘spoiling’ the body, and whether these are partially understood by recourse to explanatory models about previous diseases (for example, Tuberculosis, cancer) and the Western treatment associated with these diseases. The implications of this analysis for adherence to ARVs will be also explored.

People living with HIV and AIDS, traditional healers and health staff in Lusaka, Choma and Luapula were interviewed individually and using focus group discussions from September to November 2004. The data is currently being analysed for the purpose of dissemination, a publication and a fuller Wellcome proposal. The latter aims to use a historical and anthropological approach to explore parallel experiences in TB and HIV management, including disclosure of illness status and a fuller range of issues affecting patient adherence to treatment regimes.

Keywords: History, ARVs, HIV and AIDS, adherence, Zambia

TITLE: **Investigating Private Sector Delivery of Services for the Management of Adult HIV Patients in Pune, India**

LSHTM STAFF: *Karina Kielmann, John Porter*

COLLABORATORS: *Sheela Rangan, Kabir Sheikh, Deepali Deshmukh, Vinita Datye, Sucheta Deshpande, Saju Joseph, Solomon Salve, Suchitra Desai, Centre for Health Research and Development (CHRD), Maharashtra Association of Anthropological Sciences (MAAS), Pune, India
Ram Gambhir, Department of Anthropology, University of Pune*

FUNDING: *DFID, WHO SEARO*

SUMMARY

A series of studies looked at the management of HIV within the private medical sector (private medical practitioners, private laboratories and private pharmacies) during the time period January 2002 and November 2003 in the city of Pune, and between March and November 2004 in three rural sub-district areas of Pune district located in Western Maharashtra, India. The objectives of the studies were to document current practices of private health care providers in the diagnosis and management of HIV patients, to identify factors influencing provider decision-making in the management of HIV patients and to describe the social, economic and health policy contexts within which private providers make these decisions. The studies used a range of survey and qualitative mapping and interviewing techniques. Two-hundred and fifteen private practitioners, 36 private laboratory staff and 82 private pharmacy staff were included in the urban surveys; in addition, 27 private practitioners and 12 key informants with specialised knowledge on HIV were interviewed in-depth. In the rural component, 202 private practitioners, 13 private laboratory staff and 75 private pharmacy staff were included.

Most of the private medical providers are engaged in diagnosing HIV and large volumes of HIV testing are being undertaken in the private medical sector. Marginally more rural providers are testing and diagnosing HIV. One explanation for this could be the complete lack of access to HIV testing facilities in the public sector at the sub-district level. Routine HIV testing was found to be a common practice; most private laboratories perform rapid tests and the diagnosis of HIV is most often made on the basis of a single test. The norms for pre-test and post-test counselling, as mandated by the National AIDS Control Organization, are seldom adhered to in this setting. Provider perceptions of their clients' education, understanding and financial status influence communication and management practices, which are highly individualistic and characterised by uncertainty. The use of anti-retroviral therapy by physicians is limited, although anti-retroviral drugs are available in most pharmacies in urban as well as rural areas.

Keywords: private medical sector, HIV, management practices, India

TITLE: **Understanding Quality of Care in the Revised National TB Control Programme (RNTCP) in India**

LSHTM STAFF: *Karina Kielmann, John Porter*

COLLABORATORS: *Sheela Rangan, Aarti Kelkar-Khambete, Anuprita Shukla, Sameer Pawar, Madhuri Mankar, Saju Joseph, Deepali Deshmukh, Vinita Datye, Abhay Kudale, Anagha Pradhan from Centre for Health Research and Development (CHRD), Maharashtra Association of Anthropological Sciences (MAAS), Pune, India*
 Vikas Inamdar from the City TB Control Society, Pimpri Chinchwad Municipal Corporation, Pune. Dilip Jagtap from the Pune City TB Control Society. Rajesh Singh from Garhwal Community Development and Welfare Society

FUNDING: *DfID, Target TB, Inter Aide*

SUMMARY

A series of studies are looking at understanding the quality of the RNTCP, using access as a key indicator for quality. The first of these studies was undertaken between May and December 2004 in Pimpri Chinchwad Municipal Corporation in Pune district, an urban programme, which has been showing consistently good performance in terms of the case detection and outcome targets. It is also one of the first programmes to include private practitioners known to be the preferred provider for most patients, by making them DOT providers. The study interviewed 117 new sputum positive patients between one week and one month of treatment initiation in the RNTCP.

There is not much delay on the part of patients in seeking care for early symptoms of TB. Despite the knowledge of government health services, the majority of patients still prefer to seek help from the private sector. Delays in suspicion of TB and referral to the RNTCP are significantly less for patients seeking care from private practitioners collaborating with the RNTCP. Patients, whose per capita monthly income is 22 USD, spend about 20 USD prior to entry into the RNTCP on shopping for diagnosis and treatment. Once they enter the RNTCP diagnosis and treatment initiation are done without much delays. Access to Microscopy Centres in the RNTCP is a problem in terms of time and money spent by patients in reaching the centre, but access to DOT Centre is good, indicating that DOT has been decentralised in order to make it more convenient for patients. While the study found most patients lacking in knowledge and information about important aspects of TB diagnosis and treatment, patients indicated RNTCP staff behaviour to be rude and impolite.

Studies to further explore the issue of quality using access, in particular for the poor and vulnerable groups are planned in Pune city. In Mumbai, Inter Aide, a French agency, which is implementing a GFATM-funded Urban DOTS project, has requested help in designing and conducting a series of baseline studies to document access to the RNTCP, in particular to the poor and vulnerable groups in urban slums. Another study comparing the quality of care in NGO-run TB programmes with that of the RNTCP is planned in Dehradun district in the northern state of Uttaranchal. Provider studies to understand provider perceptions regarding quality are also planned in Pimpri Chinchwad Municipal Corporation.

Keywords: quality of care, access, TB, treatment, India

TITLE: **Counselors' experiences and practices around HIV counseling and informed consent in research and VCTC settings in Pune city, India**

LSHTM STAFF: *Karina Kielmann, John Porter*

COLLABORATORS: *Anita Shankar, Johns Hopkins Bloomberg School of Public Health, Dept. of International Health
Sucheta Deshpande, Vinita Datye and Sheela Rangan of Centre for Health Research and Development (CHRD), Maharashtra Association of Anthropological Sciences (MAAS), Pune, India*

FUNDING: *DfID*

SUMMARY

The Indian National AIDS Control Organisation (NACO) adopted WHO guidelines relating to HIV-testing in 2002. However, much of HIV-testing takes place in the private medical sector where practices of informed consent are rare and pre- and post- test counselling often inadequate (Sheikh et al *in press*, Kielmann et al, *in press*, Datye et al *under review*). Even in research and clinical settings where guidelines are in place, questions arise as to what patients really understand by informed consent and to what extent they can actively engage with the counselling on offer (Sastry et al 2004). Objectives of this study are to document the process of HIV counseling and informed consent in the VCTC and research settings in Pune city and to highlight challenges faced by counselors during HIV-counselling and obtaining informed consent. In-depth interviews are being conducted with eleven to twelve counsellors from research and VCTC settings. The interviews examine counsellors' perceptions and experiences with HIV-counselling, their communication practices and their understanding of the importance and feasibility of informed consent in the Indian cultural context. In particular, we focus on how consent is obtained, and adapted according to the local situation as well as counsellors' perceptions of patients' reactions and response to informed consent procedures.

Keywords: HIV testing, HIV counselling, ethics, informed consent, India

POLICY

TITLE: **Implementation of HIV diagnostic testing policy in India: a study of policy-practice links in the urban formal medical sector**

LSHTM STAFF: *John Porter, Kabir Sheikh*

COLLABORATORS: *Sexual Health Resource Centre, New Delhi*

FUNDING: *Aga Khan Foundation, DfID, University of London*

SUMMARY

Physician-advised HIV testing is the commonest setting for named HIV testing in India, which has the second largest population of HIV positive individuals in the world. There is evidence that doctors in India do not adhere to recommended national policy guidelines in advising HIV tests, including taking specific informed consent, pre-and post-test counselling, re-confirming test results before disclosure, maintaining confidentiality of test results, and ensuring continued care and support. This research study uses a policy analysis approach to examine these gaps in implementation of HIV testing policies. Different groups of actors involved in implementation: policy-planners, doctors, and intermediary agencies have differing interpretations of the implementation process. This study will explicate each of these perspectives in order to understand the nature of the implementation gaps, and identify ways of bridging the gaps. The study will be based in public and private hospitals and clinics, and in offices of policy-planners and implementing agencies, in Delhi, the capital city of India. A combination of qualitative methods will be used including interviews of doctors, key actors of the health system and expert key informants; and analysis of policy documents. Policy mapping including backward and forward mapping techniques will be used, and the “framework approach” for policy research will be used to analyze the data. It is expected that the findings of this study will contribute to our understanding of the implementation of HIV/AIDS policies, and of the governance of medical behaviour, in India and globally.

Keywords: India, HIV testing, VCT, policy analysis, implementation, medical regulation

TITLE: **Decentralization, Integration and Devolution of Power: A Study of the Financial Management Systems of District-level Societies in Pune, Maharashtra**

LSHTM STAFF: *John Porter*

COLLABORATORS: *Sheela Rangan, Abhay Kudale, Deepali Deshmukh, Sameer Pawar. Centre for Health Research and Development (CHRD), The Maharashtra Association of Anthropological Sciences (MAAS)
Dr. Abhay Pethe, B. Venkatesh Kumar, Nitin Wagle. Department of Economics, Department of Civics and Politics, Mumbai University*

FUNDING: *National Commission of Macroeconomics and Health (Ministry of Health and Family Welfare, Govt. of India) and Department of International Development, UK*

SUMMARY

In India, State- and District-level societies have been established for implementing various national health programmes in order to bypass cumbersome financing procedures existing in government health systems, help secure programme funds, eliminate delays, and promote flexibility in management and use of funds through empowerment of state and district level officials. This study was undertaken in order to explore the procedures adapted and followed for decentralization, devolution of powers, decision making dynamics, planning abilities, bottlenecks in procurements, expenditures, disbursement and also regarding planning for resource allocation. Financial data from all the disease control societies were collected and analysed. Interviews were conducted with programme managers and district health administrators.

The flow of funds is regular for almost all programmes and the reporting is being done as per guidelines. The spirit of decentralization is perceived and appreciated by all programme managers and district functionaries. The guidelines for budgets and expenditures are fairly rigid, but this rigidity in the guidelines provides programme managers clarity and empowerment and helps them take responsibility and become accountable, though clearly there is an expressed need for receiving training in financial management. The concept of formation of societies as a way of involving the community in programme implementation is not seen to be successful since most NGO and civil society representatives who are members, show minimal interest and participation in functioning of the societies, very often for fear of compromising their positions. It is clear that the district officials, who are used to the bureaucratic ways of functioning in the government systems, need to be sensitised about the societies and made to take more interest in its functioning.

Keywords: Decentralization, District Health Societies, Financial Management

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COLLABORATORS

Please note this list is not comprehensive. If you should require further information please contact the relevant member of LSHTM staff. Contact details for LSHTM personnel can be found on the School Website at: <http://www.lshtm.ac.uk/>

Anderson, KG. Department of Anthropology, University of Oklahoma, *E-mail: ganders@ou.edu*

Anderson, P. Statens Seruminstitut, 5 Artillerivej, DK 2300 Copenhagen S, Denmark

Atun R. Management School, Imperial College, 53 Prince's Gate, London, UK

Ayub Ajjar M. *see Barreto, M*

Barreto, M. Instituto de Saúde Coletiva, Universidade Federal da Bahia, Rua Padre Feijó, 29 4o andar - Canela / Salvador-BA BRAZIL 40110-170

Beverley, P. The Edward Jenner Institute of Vaccine Research, Compton, Newbury, Berkshire, RG20 7NN, UK

Beyers, N. Faculty of Health Sciences, PO Box 19063, Tygerberg, 7505, Cape Town, South Africa

Blackwell, J. Cambridge Institute for Medical Research, Wellcome Trust Building, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2XY, UK

Bothamley, G Department of Chest Diseases, Homerton University Hospital, Homerton Row, London

Boulle, A. Senior Researcher, Infectious Disease Epidemiology Research Unit, School of Public Health and Family Medicine, University of Cape Town. *E-mail: aboulle@cormack.uct.ac.za*

Centre for Health Policy, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, P.O. Box 1038, Johannesburg, 2000, RSA

Chaisson, R. John Hopkins University, 1830 E. Monument St, 463A Baltimore MD 21287-0003, USA

Changalucha, J. Director NIMR Mwanza: nimr@africaonline.co.tz

Cho, S-n. Medical College, Yonsei University, 134 Shinchon-dong, Seoul 120-752, Korea Tel: 82 2 361 5282 Fax: 82 2 392 9310

Choi, J-E. SNU Boramae Hospital, Boramae Hospital, Sindabang-dong, Seoul 156-707, Korea Tel: 82 2 840 2176 Fax: 82 2 831 2826

Churchyard, G. Aurum Health Research, PO Box 87, Welkom 9460, South Africa, email: gchurch@mjvn.co.za

Corlett, S. CCDC, Redbridge & Waltham Forest Health Authority, 2-14 Ilford Hill, Ilford, Essex, IG1 2QX, UK

Doherty, M. Statens Serum Institut, 5 Artillerivej, DK 2300 Copenhagen S, Denmark

Drobniewski, F. Department of Microbiology and Infection, King's College, Denmark Hill, London, UK

Dunne, D. Cambridge University, Department of Pathology, Microbiology & Parasitology, Tennis Court Road, Cambridge CB2 1QP, UK

Gambhir, R. Reader and Head of Department, Department of Anthropology, University of Pune Ganeshkhind, Pune 411 007. Maharashtra, India

Hayward, A. UCL Centre for Infectious Disease Epidemiology, Department of Primary Care and Population Sciences, Royal Free and University College Medical School, London NW3 2PF

Health Economics Unit, Unit is University of Cape Town, Barnard Fuller Building, Anzio Road, Observatory, Cape Town, RSA

Inamdar, Vikas. City TB Programme Manager and Member Secretary, City TB Control Society Talera Hospital, Chinchwad, Pimpri Chinchwad Municipal Corporation, Pune 411 033, Maharashtra, India

Indian Institute of Technology (Madras), Chennai-600 036, India.

Jagtap, D. City TB Programme Manager and Member Secretary, District TB Control Society Pune Municipal Corporation, Gadikhana Hospital, Shivaji Road, Mandai, Pune 411 002, Maharashtra, India

Kahn, A. Association for Social Development, House No. 1, Street 47, Sector F - 7/1, Islamabad, Pakistan, Email: asd@isb.paknet.com.pk

Kahn, Kathleen. School of Public Health, University of Witwatersrand, Acornhoek 1360, South Africa.

Klein, M. Department Immunohematology and Blood Transfusion, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

Kremer, K. RIVM, PO Box 1, 3720 BA Bilthoven, The Netherlands

Kumar, B. Venkatesh. Ph.D, Lecturer, Dept. of Civics and Politics, University of Mumbai Ranade Bhavan, B-Wing, Second floor, Vidyanagari, Kalina (E), Mumbai – 98

Locht, C. Institut Pasteur de Lille, 1, Rue du Professor Calmette, F-59019 Lille Cedex, France

Lukey, P. Respiratory Pathogens, GlaxoSmithKline R&D, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

Morris, L *see Puren, A.*

Mayunga, S. District TB and Leprosy Co-ordinator, Sengerema District Hospital

Munyati, S. Blair Research Institute, Box Cy 573, Causeway, Harare, Zimbabwe.

Newport, M. Cambridge Institute for Medical Research, Wellcome Trust Building, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2XY, UK

Ottenhoff, THM. Department Immunohematology and Blood Transfusion, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

Palomino, J-C. Prince Leopold Institute of Tropical Medicine (ITM), Nationalestraat 155, B-2000 Antwerp, Belgium

Pethe, A. Dean, Faculty of Arts, Professor of Urban Economics & Regional Development, Dept. of Economics, Ranade Bhavan, B-Wing, Second floor, Vidyanagari, Kalina (E), University of Mumbai, Mumbai – 98

Pitman, R. Communicable Disease Surveillance Centre, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ

Puren, A. National Institute for Virology, Sandringham 2131, South Africa

Rangan, S. CHRD-MAAS, 64/5 Anand Park, Pune 411007 India

Roux, S. *see Churchyard, Gavin*

Rural AIDS & Development Action Research Programme, University of the Witwatersrand, PO Box 2, Acornhoek 1360, South Africa pronyk@soft.co.za

Shin, J-S. Medical College, Yonsei University, 134 Shinchon-dong, Seoul 120-752, Korea Tel: 82 2 361 5282 Fax: 82 2 392 9310

Singh, R. Coordinator, Garhwal Community Development and Welfare Society, Mussoorie Road, Chamba Tehri – Garhwal, Uttaranchal, India.

Sinkala, M. Lusaka District Health Management Team, PO Box 50827, Makishi Road, Lusaka, Zambia.

Stey, L. Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Stoker, NG. Department of Pathology and Infectious Diseases, Royal Veterinary College, Royal College Street, London NW1 0TU

Tembwe, R. Chest Diseases Laboratory, Ministry of Health, PO Box 34566, Lusaka, Zambia, [email:cdl@zamnet.zm](mailto:cdl@zamnet.zm)

Temu, M. Co-ordinator NIMR Mwanza: nimr@africaonline.co.tz

Thomas P. Sexual Health Resource Centre, W-113 Greater Kailash – I, New Delhi 110048, India.

Tosiri, I. Medical Officer in Charge, Sengerema District Hospital

van Helden, P. Faculty of Health Sciences, PO Box 19063, Tygerberg, 7505, Cape Town, South Africa

van Soolingen, D. RIVM, PO Box 1, 3720 BA Bilthoven, The Netherlands.

Walzl, G. *see van Helden, Paul*

Watson, J. Communicable Disease Surveillance Centre, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ

Wilkinson, R. Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Wood, R. Desmond Tutu HIV Centre, Department of Microbiology, University of Cape Town, Private Bag, Rondebosch, 7701, South Africa.

Yazdanbakhsh, Professor. Leiden University, Rapenburg 70, PO Box 9500, NL-2300 RA Leiden, The Netherlands

Young, D. Dept of Medical Microbiology, Wright Fleming Institute, St Mary's Hospital Medical School, Imperial College, London W2 1PG, UK

Yun, CH. International Vaccine Institute SNU Research Park, PO BOX 14, Seoul 151-600, Korea Tel: 82 2 881 1188 Fax: 82 2 881 1211