



## Working on Tuberculosis

Tuberculosis (TB) is closely linked with poverty and it remains one of the world's foremost threats to public health. The causative bacterium (*Mycobacterium tuberculosis*) is highly adept at exploiting weaknesses in the immune system and co-infection with HIV greatly increases the risk of developing active disease. Progress is being made towards controlling TB, but in recent years fresh challenges have arisen with the emergence of multidrug-resistant forms of the disease that are extremely difficult to treat.

In recognition of the scale of the problem, and of the School's substantial research portfolio, next year will see the launch of a 'TB Centre' at the School. Already a centre of excellence, the School will benefit from the enhanced profile this will offer for our teaching and research. LSHTM is unique in the scope of studies undertaken, ranging from deciphering the genetic code of drug-resistant strains through to measuring the impact of poverty, or implementing new control strategies. The geographic reach of activities is equally extensive, with collaborating partners in all corners of the globe. This chapter gives an overview of TB research at the School with some highlights of our many achievements.

### THE BACTERIUM AND ITS HOST

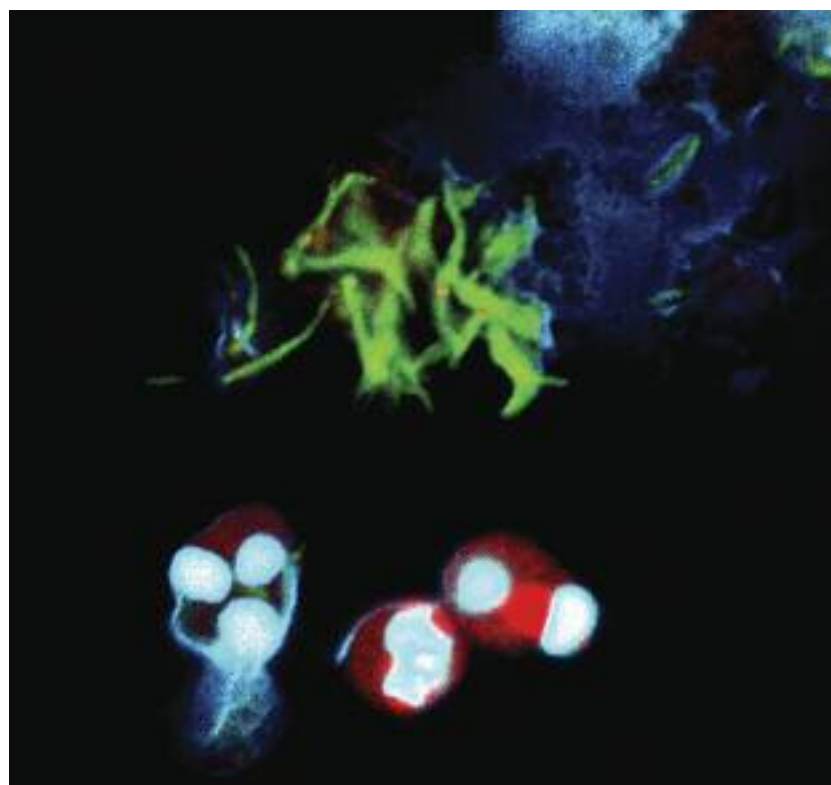
Laboratory-based investigations include an international

collaboration led by the School to sequence the individual genomes of a large collection of clinical isolates of *M. tuberculosis*. By comparing strains with different drug susceptibilities and from different regions of the world we shall be able to tease out genetic differences. A major conundrum in TB research is how the bacteria evade the immune response during infection. With colleagues in Germany, we have been investigating how human white cells that would normally trap and kill the bacteria are themselves destroyed following interaction with the *M. tuberculosis* bacilli. To help understand the kinetics of TB infection, imaging methods are being developed for monitoring bacteria in the body. Other studies have been looking for biological changes during infection that might be used to predict clinical status. In collaboration with South African scientists, microarray technology has been used to characterize both the changes in the gene expression profiles of TB patients undergoing treatment, and the differences between relapse patients and those that are fully cured. The current vaccine against TB is *M. bovis* bacillus Calmette-Guérin (BCG). Although widely used, the efficacy and duration of protection remains uncertain. A case-control study of long-term protection in the UK is being undertaken, in addition to studies of BCG-induced immune responses in infants. Variation in the strains of BCG used in

different parts of the world is being investigated by whole genome sequencing.

### EPIDEMIOLOGY

TB is an airborne disease and measuring the size of the problem and understanding its spread are fundamental to disease control. Over the last 30 years our study in the Karonga District of northern Malawi has made major contributions to our knowledge. Findings have shown that most TB infection in this rural region is due to casual contact rather than from household members and that recent infection is the predominant cause of TB in HIV-infected individuals. We have



*Mycobacterium tuberculosis* bacteria (stained green) induce necrotic destruction of human neutrophils.

PHOTO: BOBEN CORLES

Posters to assist sample collection are being adapted for local cultures and languages.



found that HIV-infected cases play an important role in transmission, and that the provision of antiretroviral therapy for HIV infection could be increasing the amount of TB in the population. Large-scale whole genome sequencing is now being applied to the strains of *M. tuberculosis* circulating in the district and may help to explain why some strains of the bacterium spread more readily than others. Mathematical modelling of the impact of TB control interventions is a continuing strength which complements the wealth of epidemiological data generated at this and multiple other sites. A current priority is the use of mathematical models to help generalize from the results of the CREATE randomized controlled trials of strategies to reduce TB incidence in HIV prevalence areas.

## DIAGNOSIS AND CASE FINDING

### New diagnostic tools

Access to treatment is dependent on diagnosis but less than half of the estimated incident TB cases in the WHO African Region are detected each year. The School is heavily involved in evaluating new diagnostic tools and studies to examine the impact of a new molecular test (Xpert® MTB/RIF, Cepheid) are under way at several sites in Africa and Asia. The test diagnoses TB and also detects resistance to one of the major drugs (rifampicin).

In Cape Town we have demonstrated its value for early detection of TB in clients attending an HIV treatment centre where case detection rates increased by 45% when compared to smear microscopy, the only other rapid test available. Unfortunately, however, the test for drug resistance proved less reliable as false-positive results were observed. To improve access to diagnosis, simple point-of-care tests are needed and novel technologies are being investigated. We have also developed low-cost interventions to improve the quality of samples collected, and these have been adopted in Bolivia and several sites in Africa.

Implementation strategies for new tools to detect drug resistance are also being evaluated, including MODS (microscopic observation drug-susceptibility), a low-cost test based on microscopic observation of bacteria that has been developed with colleagues in Peru.

### Case finding

In addition to having reliable diagnostic tools, strategies are also needed to encourage earlier testing for TB. A trial of interventions to promote testing (active case finding) in Zimbabwe reported a dramatic (43%) reduction in the prevalence of undiagnosed infectious TB. Mobile vans were more effective than door-to-door enquiry for providing community-level diagnosis. These findings are being taken forward in Blantyre, Malawi, to investigate the hypothesis that either active TB case-finding alone, or active TB case-finding plus intensified prevention of HIV-related TB, can reduce TB incidence rates in an urban setting with a high HIV prevalence. Alternative approaches are being investigated in Zambia and South Africa, where community activities have been incorporated in a programme of enhanced case finding.

## TREATMENT

### Preventive therapy

In South African gold mines, where TB incidence is among the highest in the world, we have been investigating a novel control strategy, offering screening for active disease followed by treatment for latent infection to entire communities, rather than targeted to high-risk individuals.

### Drug-susceptible TB

Shortening the duration of treatment has been recognized by both WHO *Stop TB* and the Global Alliance for TB Drug Development as a major target for the improvement of tuberculosis control worldwide. The School is responsible for the clinical co-ordination and statistical analysis of a multi-country phase III trial of a 4-month gatifloxacin-containing regimen versus a

Mobile TB case detection,  
Harare, Zimbabwe.



standard 6-month regimen for the treatment of adult patients with pulmonary TB. This phase III trial will be the first to report on a new TB treatment regimen since the UK MRC trials conducted in the 1970s and '80s.

#### Co-infection TB/HIV

Tuberculosis is the leading cause of mortality among people with HIV infection, particularly in sub-Saharan Africa. As we and others have shown, early initiation of antiretroviral therapy can cause immune reconstitution inflammatory syndrome (IRIS) and a deterioration of TB symptoms. We are leading a multi-country randomized trial in West Africa assessing currently proposed and new strategies for the treatment of anti-retroviral-naïve HIV-infected patients with tuberculosis.

#### Drug resistance

The emergence of drug resistance threatens to

destabilize TB control. The efficacy of the WHO recommended re-treatment regimen was found to be low in Kampala, where there are patients with multidrug-resistant TB (MDRTB). Amplification of resistance was also observed during the study, which is a collaboration with partners from Uganda and the USA. Other studies in Sudan also found high levels of resistance amongst re-treatment cases, but in a national survey in Zambia and in long-term surveillance in northern Malawi, few cases were recorded. In South Africa, transmission of highly drug-resistant strains has been observed as a serious threat to public health and scientists at the School are involved in examining the genetic make-up of the bacteria by whole genome sequencing. Approaches to the management of household contacts of MDRTB index cases are under investigation in Peru where TB infection control research has already been translated into policy and practice.