

Impact case study (REF3b)

<p>Institution: London School of Hygiene & Tropical Medicine (LSHTM)</p>
<p>Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care</p>
<p>Title of case study: Screening for TB in people living with HIV</p>
<p>1. Summary of the impact Research carried out by LSHTM has had a major influence on the development of international strategies to screen for tuberculosis (TB) in HIV positive patients. Data from these studies has led directly to new screening algorithms promoted by WHO and other major policy-makers as a key entry point for TB-HIV collaborative activities. Results from these studies have been incorporated into new international guidelines on systematic screening for TB and collaborative TB-HIV activities, resulting in more than 0.5m lives saved and a rapid rise in TB screening for people living with HIV. A companion case study addresses impact on use of isoniazid preventive therapy.</p> <p>2. Underpinning research TB is a curable and preventable disease. Despite this, in 2011, 8.7m people fell ill with TB and 1.4m died. WHO has estimated in 2013 that among people living with HIV, TB caused a quarter of all deaths. Research conducted by Peter Godfrey-Faussett, Professor of International Health (joined LSHTM as MRC Training Fellow in 1989, Professor since 2005), Liz Corbett (joined as Wellcome Trust Clinical Training Fellow in 2000, Professor of Tropical Epidemiology since 2012), Helen Ayles (joined as Wellcome fellow in Tropical Medicine in 1998, Senior Lecturer since 2007) and other Department of Clinical Research researchers at LSHTM has been responsible for establishing the first clinical cohorts of HIV-infected and uninfected TB patients in Africa, identifying difficulties in diagnosis, and researching and developing effective new strategies for screening and treatment.</p> <p>LSHTM researchers launched the ProTEST Initiative (1999–2004) to demonstrate the feasibility of providing collaborative TB/HIV care for people living with HIV (PLWH) in poor settings. ProTEST facilitated collaboration between service providers. Voluntary counselling and testing (VCT) acted as the entry point for services including TB screening and preventative therapy, clinical treatment for HIV-related disease, and home-based and hospice care, in Zambia, Malawi and South Africa. Findings demonstrated that coordinating an integrated and comprehensive package of services for PLWH was relatively inexpensive.</p> <p>Previous research by Godfrey-Faussett among Kenyan sex workers and South African gold miners (1995–1999) used molecular and conventional epidemiology to demonstrate that most of the HIV-related TB in these communities was due to ongoing transmission rather than reactivation. Further findings were that for PLWH, recurrent TB was more likely to be the result of reinfection; recurrent TB for HIV-uninfected patients was the result of relapse.^{3.1} These conclusions were reinforced by similar findings from work by other LSHTM researchers working in other South African goldmines and in Malawi.</p> <p>Population-based HIV and TB disease surveys conducted by Ayles and Godfrey-Faussett (in Zambia and South Africa, 2006), and occupational health surveys in mines and factories by Corbett (in South Africa 2001–2003 and Zimbabwe, 2004–2006), found significant numbers of undiagnosed TB cases, demonstrating that DOTS (the global control strategy aimed at controlling TB transmission through prompt diagnosis of symptomatic smear-positive disease developed in the 1990s) had failed to prevent rising TB incidence rates in Africa brought about by the HIV epidemic. The researchers concluded that new approaches were needed in order to reach international targets for reducing TB, and that epidemiological studies could inform screening algorithms for both detection and prevention of active TB.^{3.2–3.4}</p> <p>For case-finding strategies, LSHTM researchers administered two large-scale community randomised trials: DetecTB (in Harare, 2006–2009) and ZAMSTAR (in Zambia and the Western Cape Province, 2006–2010). DetecTB demonstrated that wide implementation of active case-finding, particularly with a mobile van approach, could have rapid effects on TB transmission and</p>

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disease.^{3.5} In ZAMSTAR, two interventions (community-level enhanced TB case-finding and household level TB-HIV care) were implemented. Researchers found plausible evidence of a reduction in TB among communities receiving the household intervention.^{3.6}

3. References to the research

3.1 Godfrey-Faussett, P, Sonnenberg, P, Shearer, SC, Bruce, MC, Mee, C, Morris, L and Murray, J (2000) Tuberculosis control and molecular epidemiology in a South African gold-mining community', *Lancet*, 356(9235): 1066–1071, doi: 10.1016/S0140-6736(00)02730-6. Citation count: 92

3.2 Corbett, EL, Charalambous, S, Moloi, VM, Fielding, K, Grant, AD, Dye, C, De Cock, KM, Hayes, RJ, Williams, BG and Churchyard, GJ (2004) Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners, *American Journal of Respiratory and Critical Care Medicine*, 170(6): 673–679, doi: 10.1164/rccm.200405-590OC. Citation count: 89

3.3 Ayles, H, Schaap, A, Nota, A, Sismanidis, C, Tembwe, R, De Haas, P, Muyoyeta, M, Beyers, N and Godfrey-Faussett, P for the ZAMSTAR Study Team (2009) Prevalence of tuberculosis, HIV and respiratory symptoms in two Zambian communities: implications for tuberculosis control in the era of HI', *PLoS One*, 4(5): e5602, doi: 10.1371/journal.pone.0005602. Citation count: 40

3.4 Corbett, EL, Bandason, T, Cheung, YB, Munyati, S, Godfrey-Faussett, P, Hayes, R, Churchyard, G, Butterworth, A and Mason, P (2007) Epidemiology of tuberculosis in a high HIV prevalence population provided with enhanced diagnosis of symptomatic disease, *PLoS Medicine*, 4(1): e22, doi: 10.1371/journal.pmed.0040022. Citation count: 70

3.5 Corbett, EL, Bandason, T, Duong, T, Dauya, E, Makamure, B, Churchyard, GJ, Williams, BG, Munyati, SS, Butterworth, AE, Mason, PR, Mungofa, S and Hayes, RJ (2010) Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial, *Lancet*, 376(9748):1244–1253, doi: 10.1016/S0140-6736(10)61425-0. Citation count: 45

3.6 Ayles, H, Muyoyeta, M, Du Toit, E, Schaap, A, Floyd, S, Simwinga, M, Shanaube, K, Chishinga, N, Bond, V, Dunbar, R, De Haas, P, James, A, Gey van Pittius, NC, Claassens, M, Fielding, K, Fenty, J, Sismanidis, C, Hayes, RJ, Beyers, N and Godfrey-Faussett P, the ZAMSTAR Team (2013) Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial, *Lancet*, 382(9899): 1183–1194, doi: 10.1016/S0140-6736(13)61131-9. Citation count: 0

Key grants

Godfrey-Faussett, TB Knowledge Programmes, DFID, 1995-2001, £1.4m; 2001–2006, £2.9m.

Godfrey-Faussett, Zamstar: Zambia & South Africa TB and AIDS Reduction Study, Bill & Melinda Gates Foundation, 2004–2014, £17m.

Corbett, Senior Clinical Research Fellowship (supplemented by an extension), Wellcome Trust, 3/2005–11/2010, £2m.

Porter, TARGETS Consortium, DFID, 2006-10, £5.1m.

Other funding from EU, WHO, Beit, Colt Foundation.

4. Details of the impact

Data and new algorithms developed by LSHTM researchers are fundamental to ongoing global strategies to combat TB. As a direct result of their research and case findings, and their wide experience in the field and in terms of TB service provision at community level, LSHTM has been called upon to advise policy-makers at the highest level.

The impact of LSHTM research is clearly evidenced by current WHO guidance promoting the integration of HIV and TB services. This guidance is based on LSHTM's ProTEST research where the case-finding approach was first formally articulated and recommended in 2004^{5.1} but has had ongoing impact. WHO guidelines re-issued in 2012 stated: "The [2004] policy, which provided

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guidance for Member States and other partners on how to address the HIV-related TB burden, **has been one of the most widely accepted policies issued by both departments** ... more than 170 countries had reported implementing its components by the end of 2010.^{5.2}

In 2010–2011, Ayles, Corbett and Grant undertook meta-analyses of data from LSHTM's African population surveys in collaboration with WHO and Centres for Disease Control and Prevention (CDC) and developed a simplified symptom-based screening algorithm that relies on the absence of all four clinical symptoms (current cough, night sweats, fever and weight loss) to identify PWLH who have less likelihood of active TB and hence are eligible for isoniazid preventive therapy to prevent latent TB infection. Use of this algorithm is included in WHO's 2010 revision of TB guidelines. Wide dissemination through WHO and aimed at health care workers, policy-makers and health programme managers working in the field of HIV/AIDS and TB means the algorithms now form a standard part of global diagnostic practice.^{5.3}

The impact of LSHTM population surveys is demonstrated through WHO's promotion, since 2011, of prevalence surveys modelled after those developed by LSHTM as a key measure to understand the progress of TB control throughout the world. This guidance is included in the new WHO handbook published in 2011 designed for TB experts, survey investigators, researchers and advisors at national and international level. WHO says it has ensured the standardisation of methods across multiple surveys in more than 20 countries in African, Eastern Mediterranean, South-East Asian and Western Pacific regions. Ayles was lead author of Chapter 6 which covers, among other things, the purpose of interviews in a TB prevalence survey and guidance on how to design questionnaires. Findings and methods used in the ZAMSTAR project are also heavily cited in the workbook where it is featured as a full case study. LSHTM approaches to design, sampling, microbiology, data collection and analysis are offered as a template for new studies.^{5.4}

In 2012, Godfrey-Faussett chaired the WHO review of evidence that saw LSHTM equivocal results for the impacts of case-finding at a community level incorporated into new guidelines on systematic screening for TB. Based on LSHTM research, the resulting document sets out basic principles for prioritising risk groups and choosing a screening approach at community level.^{5.5} Ayles and Corbett were also members of the Guideline Development Group.

Also in 2012, WHO issued a new updated policy on collaborative TB/HIV activities for national programmes and other stakeholders.^{5.2} Godfrey-Faussett was an active member of WHO's Policy Updating Group and Ayles acted as an external peer reviewer in the preparation of this new policy aimed at establishing and strengthening mechanisms for integrated delivery of TB and HIV services internationally. LSHTM findings and experience on the integration of services for TB with those for HIV through community-based organisations from the DetecTB project are referenced under the section on carrying out joint planning to integrate services.

Further impact has been made through LSHTM researcher participation in international workshops and meetings such as the Regional TB/HIV Implementation Workshop and Core Group Meeting of the Global TB/HIV Working Group held in Maputo, Mozambique, 10–12 April 2013. Ayles provided an official commentary on the latest in TB diagnostic technologies to an audience of >120 participants, comprising key international partners (e.g. The President's Emergency Plan for AIDS Relief, Global Fund) and community and civil society representatives from 14 African countries representing 70% of the TB/HIV burden worldwide.^{5.6}

WHO estimates that through the LSHTM-influenced collaborative TB-HIV activities, more than 400,000 lives have been saved since 2005, and more than 3m PLWH are now screened for TB each year.^{5.7}

5. Sources to corroborate the impact

5.1 WHO (2004) *Interim Policy on Collaborative TB/HIV Activities*, WHO/HTM/TB/2004.330, WHO/HTM/HIV/2004.1. Geneva: WHO,

http://whqlibdoc.who.int/hq/2004/who_htm_tb_2004.330.pdf (accessed 11 November 2013)

(guidelines for national programmes and other stakeholders. LSHTM/ProTEST references 7 and

8).

5.2 WHO (2012) *WHO Policy on Collaborative TB/HIV Activities: Guidelines for National Programmes and Other Stakeholders*. Geneva: WHO, http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en/index.html (accessed 11 November 2013) (DetectTB is referenced in Chapter 3:A.3.3, Involving nongovernmental and other civil society organisations and communities. p. 19).

5.3 WHO (2011) *Guidelines for Intensified Tuberculosis Case-finding and Isoniazid Preventive Therapy for People Living with HIV in Resource-constrained Settings*. Geneva: WHO, http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf (accessed 11 November 2013) (Ayles, Grant and Godfrey Faussett are among those named as WHO Guidelines Group; p. 8, algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings; Ayles and Corbett's research is further cited in GRADE profile table 1, p. 20).

5.4 WHO (2011) *Tuberculosis Prevalence Surveys: A Handbook (The Lime Book)*. Geneva: WHO, http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/resources_documents/thelimebook/en/ (accessed 11 November 2013) (p. 81, Chapter 6, Interviews, data collection tools and informed consent, lead author Helen Ayles; ZAMSTAR findings and research featured in Chapters 4, 6, 8, 15, including on p. 87; case studies for symptom screening: Case 1: Zambia - the ZAMSTAR Pilot prevalence survey).

5.5 WHO (2013) *Systematic Screening for Active Tuberculosis: Principles and Recommendations*. Geneva: WHO, <http://www.who.int/tb/tbscreening/en/index.html> (accessed 11 November 2013) (for the critical outcomes of increased case-finding and community impact, the ZAMSTAR data was the highest quality evidence available; see GRADE tables on p. 94ff in guidelines document).

5.6 WHO (2013) *Report of the 18th Core Group Meeting of the TB/HIV Working Group, Regional TB/HIV Implementation Workshop & 18th Core Group Meeting of the Global TB/HIV Working Group, 10–12 April, Maputo, Mozambique*. Geneva: WHO, http://www.who.int/tb/challenges/hiv/report_of_the_18th_tb-hiv_core_group_meeting.pdf (accessed 11 November 2013) (reference to Ayles is made on pp. 2–3 of the report; see also http://www.who.int/tb/challenges/hiv/maputo_main/en/index.html).

5.7 Personal reference: WHO Director, Stop TB Department, WHO. To corroborate health consequences of research impact on WHO guidelines, principles and recommendations.