Institution: University of Warwick and Liverpool School of Tropical Medicine

Unit of Assessment: A2 – Public Health, Health Services and Primary Care

Title of case study: Improving Access to Tuberculosis Care for the Poor in Developing Countries

1. Summary of the impact

This case study describes the impact on national and global tuberculosis (TB) control policy of research led by **Cuevas**, **Squire** and **Theobald** at the Liverpool School of Tropical Medicine (LSTM). Early research led to the publication of the World Health Organisation (WHO) Options for National TB Control Programmes 'Addressing the Poverty in TB control' in 2005**.** Further research led to WHO endorsement of same-day diagnosis of TB by smear microscopy (SM) in 2010. This strategy has been implemented in Malawi, Nigeria, Yemen, Ethiopia and Nepal. Alongside this we have developed and tested approaches to bring diagnosis and treatment for TB closer to the community. Same-day diagnosis and close-to-community approaches have led to improvements in access to TB care and treatment, and reductions in costs incurred during care-seeking by poor patients in these countries and elsewhere.

2. Underpinning research

Background

Tuberculosis (TB) is a contagious and often severe airborne disease caused by a bacterial infection. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease. Three million of the annually estimated 8.6 million cases of TB are missed by healthcare services. National surveys establish the population prevalence of TB. Data are also collected at health centres on cases diagnosed and treated. The gap of three million cases is the difference between the expected prevalence and the reported number of diagnoses (surveillance data). It is thus a combination of cases missed and cases not notified. Increasing case detection is therefore an international priority. Smear microscopy tests (the main test used for diagnosis) have a low acquisition cost and have low sensitivity. For several decades, because of the low sensitivity of SM, patients have had to provide three separate sputum samples for examination. This process requires several visits and substantial out-of-pocket expenditure. According to WHO definitions, sputum smears had to contain at least 10 bacilli (bacteria) and at least two of the three smears had to yield a positive result in order for a patient to be considered smear-positive.

Problems with diagnosis and access to service

Work in Malawi led by **Squire** (Professor of Tropical Medicine, 1995–present) assessed patient and household direct and opportunity costs of accessing TB services. To do this his team surveyed TB patients, sampled from all health facilities in Lilongwe. This demonstrated that poor patients (an income of <US$0.25/day) needed to spend 244% of their monthly income accessing TB healthcare services. In contrast, non-poor patients (an average income of US$1.23 per day**)** 'only' needed to spend 129% of their income accessing TB services.[1] The LSTM were the first to use a validated measure of poverty based on questions regarding a limited range of assets as a proxy for income.[2] Research in Ethiopia and Nigeria led by **Cuevas** (Professor of Epidemiology, 1993–present) reported similar difficulties in accessing services in Ethiopia, concluding that patient and household costs of TB diagnosis are prohibitively high even where services are free. In both settings, many patients stopped attending the services before achieving a diagnosis.

Solution 1: Improving case definitions, diagnosis and detection of TB

Studies to improve SM-based diagnosis with the goal of diagnosis in a single day were conducted by **Cuevas, Squire, Theobald** (LSTM Reader in Social Science, 1999–present), **Yassin** (LSTM Epidemiologist 2003–2010) and **Ramsay** (LSTM Fellow 2001–2008,) in Nigeria, Ethiopia, Nepal, Yemen, Brazil, Cameroon and Malawi (2006-2013). The LSTM demonstrated that most patients are diagnosed by the first two smears[3]**;** smears with low numbers (1–10) of bacilli are true-positive results**;** SM has high specificity.[4] One positive smear is sufficient for a positive SM diagnosis; and that diagnosis can be reached in one day (same-day diagnosis)**.** [4] Previous to these studies, it was perceived that smears with very few bacilli could be false positive, and thus the control programmes required that patients have at least two smears with few bacilli. By demonstrating this, control programmes could consider one smear with few bacilli as true positive. The LSTM conducted multi-country evaluations in Nepal, Nigeria, the Yemen and Ethiopia, which demonstrated that single-day diagnosis had the same level of performance as older schemes. In

total, 6,627 patients were enrolled; 6,466 had culture tests of which 1,526 were positive.[5] We also demonstrated that this approach could be used in conjunction with the new LED fluorescence microscopes.[6] We conducted a systematic review of same-day SM and presented data to the WHO to inform development of policy guidance.[7] A study in 2009 modelled that the implementation of the new WHO recommendations on smear microscopy and LED based fluorescence microscopy combined would result in substantial increases in smear positive case-detection using existing human resources.[8]

Solution 2: Community-based approaches to improve access to diagnosis and treatment

From 2008 to 2013, **Squire** and **Theobald** led work in Malawi demonstrating that engaging informal providers (shopkeepers) in recognising disease and referring patients doubled TB case detection and reduced the time delay to diagnosis by 75%. [9] Since 2009, **Cuevas** and **Theobald** have led studies engaging village-based health extension workers (HEWs) to facilitate access to diagnosis and treatment in Ethiopia. HEWs identify individuals with symptoms of TB and collect and prepare smears and transport to the diagnostic laboratories.[10] In the Yemen, HEWs visited the homes of adults with TB to identify secondary cases that had not consulted healthcare services and, in Nigeria, HEWs visited households in slums and tested specimens. In Ethiopia these approaches have led to a greater than 100%, increase in case detection[3], and in Nigeria, to a 70% increase.

3. References to the research (LSTM authors are underlined)

1. Kemp JR, Mann G, Nhlema Simwaka B, Salaniponi FML, Squire SB. Can Malawi's poor afford free TB services? Patient and household costs associated with a TB diagnosis in Lilongwe. Bulletin of the World Health Organisation 2007 85; 580-585.
2. Nhlema-Simwaka B, Benson T, Kishindo P, Salaniponi FML, Theobald S, Squire SB, Kemp JR. Developing socio-economic measures to monitor access to tuberculosis services in urban Lilongwe, Malawi. Int J Tuberc Lung Dis. 2007 11(1):65-71.
3. Yassin MA, Cuevas LE. How many sputum smears are necessary for case finding in pulmonary tuberculosis? Tropical Medicine and International Health Volume 8, Issue 10, October 2003, Pages 927-932.
4. Lawson L, Yassin MA, Ramsay A, Olajide I, Thacher TD, Davies PDO, Squire SB, Cuevas L. Microbiological validation of smear microscopy after sputum digestion with bleach; A step closer to a one-stop diagnosis of pulmonary tuberculosis. Tuberculosis Volume 86, Issue 1, January 2006, Pages 34-40.
5. Cuevas LE, A multi-country non-inferiority cluster randomized trial of frontloaded smear microscopy for the diagnosis of pulmonary tuberculosis. PLoS Med. 8, e1000443 (2011). (**Submitted in UoA2 REF2**).
6. Cuevas LE, Al-Sonboli N, Lawson L, Yassin MA, Arbide I, Al-Aghbari N, Sherchand JB, Al-Absi A, Emenyonu EN, Merid Y, Okobi MI, Onuoha JO, Aschalew M, Aseffa A, Harper G, de Cuevas RMA, Theobald SJ, Nathanson CM, Joly J, Faragher B, Squire SB, Ramsay A. LED fluorescence microscopy for the diagnosis of pulmonary tuberculosis: A multi-country cross-sectional evaluation. PLoS Medicine. Volume 8, Issue 7, July 2011, Article number e1001057J. **(Submitted in UoA2 REF2)**.
7. Davis JL, Cattamanchi A, Cuevas LE, Hopewell PC, Steingart KR. Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis. Lancet Infect. Dis. 13, 147–154 (2013). **(Submitted in UoA2 REF2)**.
8. Ramsay A, Cuevas LE, Mundy CJF, Nathanson CM, Chirambo P, Dacombe R, Squire SB, Salaniponi FML, Munthali S. New policies, new technologies: modelling the potential for improved smear microscopy services in Malawi. PLoS ONE 4, e7760 (2009).
9. Simwaka BN, Theobald S, Willets A, Salaniponi FML, Nkhonjera P, Bello G, Squire SB. Acceptability and effectiveness of the storekeeper-based TB referral system for TB suspects in sub-districts of Lilongwe in Malawi. PLoS ONE 7, e39746 (2012).
10. Yassin MA, Datiko DG, Tulloch O, Markos P, Aschalew M, Shargie EB, Dangisso MH, Komatsu R, Sahu S, Blok L, Cuevas LE, Theobald S. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in southern Ethiopia. PLoS ONE 8, e63174 (2013).

Research Funding

- World Health Organization (Switzerland) – Tuberculosis Poverty Secretariat, **PI: Squire**.

£218,827. [2006-2010].
- World Health Organization (Switzerland) – A Multi-centric Trial of Front-Loaded Smear Microscopy in the Diagnosis of Tuberculosis. **PI: Cuevas**. £169,462. [2007-2008].
- Department for International Development (DFID)/Economic and Social Research Council (ESRC). Identifying Barriers to TB Diagnosis and Amp. Treatment Under a new Rapid Diagnostic Scheme. **PI: Theobald**. £237,584. [2008-2012].
- US Agency for International Development (USAID). TREAT TB: Technology, Research, Education and Technical Assistance for TB Project. **PI: Squire**. £1,068,390. [2009-2014].
- World Health Organization – Innovative Community-based Approaches for Enhanced Tuberculosis Case Finding & Amp; Outcome in Southern Ethiopia – Part 1. **PI: Theobald**. £446,291. [2010-2012].
- STOP TB Partnership. Innovative Community-based Approaches for Enhanced Tuberculosis Case Finding & Treatment Outcome in Southern Ethiopia - Part 2. **PI: Theobald**. £388,917. [2012-2013].
- The European and Developing Countries Clinical Trials Partnership (EDCTP) - Innovative approaches to diagnose and monitor patients with TB to facilitate conducting clinical trials for the community-based treatment of MDR-TB. **PI: Cuevas**. £686,353. [2012-14].
- TB Reach – Scaling up innovative community-based approaches to improve TB diagnosis and treatment among vulnerable and high-risk populations in Ethiopia. **PI: Cuevas.** £576,796. [2013-14].

4. Details of the impact

The LSTM's work on strategies to improve access to TB diagnosis and treatment was driven by our pro-poor and equity perspectives and our understanding of the barriers that prevent disenfranchised populations accessing healthcare services. These research programmes have directly influenced policy and local TB control programmes practice.

Policy: Achieving policy change in TB healthcare at the international level requires primary research evidence, time and extensive engagement with researchers, policymakers and funding agencies. **Squire** and **Cuevas** were invited to the WHO's annual Strategic and Technical Advisory Group (STAG-TB) meetings to discuss new evidence and give perspectives on TB, SM, poverty and access to services in 2009, 2010, 2011 2012 and 2013. **Cuevas** served as the Chair of the Stop TB Partnership New Diagnostics Working Group on SM (2007-2011). These contributions yielded numerous contributions to policy and practice. Including the STOP TB Departments adoption of a new milestone within its End of TB strategy, 'No families should face catastrophic health costs as a result of TB'. As documented in the slides of the 65th World Health Assembly in May 2012, when Member States including Brazil, UK, Italy, Swaziland, Saudi Arabia and others, called upon the WHO to develop a new post-2015 TB strategy.[a]

As a member of the WHO Advisory Committee for TB and Poverty **Squire** co-wrote the WHO Options for National TB Control Programmes 'Addressing the Poverty in TB control' not previously documented within WHO guidelines.[b] This document addresses the integration of pro-poor measures in TB control programmes and offers guidance for national TB control programmes on the practical issues involved such as engagement of close-to-community providers. The LSTM also facilitated, through the work of the TB & Poverty Subgroup of the Stop TB Partnership the further development and publication of the patient costing tool, [c] used to estimate patients' costs to assess the impact of TB on the welfare of households and individuals. **Squire** was the Secretary from 2007 to 2009.

The LSTM were commissioned as members of the core writing team of the 2011 normative guide 'Priorities in operational research to improve TB care and control', jointly sponsored by the WHO, Stop TB, and the Global Fund for AIDS, TB & Malaria. The opening statement on the WHO website refers to evidence from operational research projects paving the way for ensuring many more people have access to vital TB health services. The LSTM research findings are referenced within the documented linking the LSTM operational research to recommended practice.[d]

The WHO revised the SM definitions for smear-positive TB in 2007[e], recommending that the third smear examination could be dropped, based on the evidence presented. The findings of LSTM systematic reviews commissioned in 2010 by the WHO were sent to the expert group who considered available options. **Cuevas** and **Squire** were members of the expert groups convened to examine the evidence. The LSTM supported the group as most of the relevant data came from LSTM studies. **Cuevas** attended the meeting in September 2009, where the evidence was

discussed and then again at the STAG with **Squire** where the expert committee report was approved as policy.[f] The revised policy for same-day diagnosis includes the revised definitions and an accelerated method for collecting specimens as conducted in the LSTM studies. Although implementation of policies takes time, several countries (for example, Nigeria, Somalia and Tanzania) and international organisations (for example, Doctors Without Borders (Medicins Sans Frontieres)) are already implementing this approach. Although it is too early to document impact at the population level, the US Agency for International Development (USAID) has funded the LSTM (2010–present) to model the medium-to-long-term cost and/or health benefits of these approaches.

Practice: The National TB Programme in Malawi is currently engaging informal providers in recognising disease and referring patients as part of national policy. The Nigerian National TB and Leprosy Control programme is exploring whether the Global Fund could provide financial support to include *Community-based approaches* within its programme, a statement can be provided from the National Coordinator to corroborate Nigerian approaches.[g] The Ethiopian Regional and National Health services are expanding a Community-based approach from a base of three million to seven million population as a package of the regional and national Health Extension Programme. Our work engaging community health workers has been described as a 'pathfinder for TB' by the WHO. Work in Ethiopia was highlighted on the WHO website in 2013, where the, Executive Secretary of the Stop TB Partnership said: "*To stop TB*, *we must bring quality TB care to poor and marginalized communities we can capitalize on two of the world's greatest resources - people and communities - to ensure that no one gets left behind. I am particularly pleased to see that this project has served as a pathfinder, encouraging further investment and scale up from the Ethiopian government and the Global Fund*". [h]

The successes of these approaches have received international publicity, and were promoted in 2013 by the WHO Stop TB Partnership as 'leading the way'. During the United Nations General Assembly in New York in 2013 the governments of the UK and USA hosted the 'Millennium Development Goal Countdown 2013'. For Millennium Development Goal (MDG) 6, a single case study was selected; the case study was the LSTM 'TB REACH Ethiopia' project on community level health extension workers, which **Theobald** (LSTM) presented on behalf of the Global fund, [i] as case detection more than doubled in south Ethiopia in the 2 years after the project was implemented. A figure illustrating this can be corroborated in reference.[j]

5. Sources to corroborate the impact

a) WHO/Global TB Programme. Post 2015 Strategy and Targets, 23rd Stop TB Partnership Coordinating Board Meeting, 11 – 12 July 2013, Ottawa, Canada http://www.stoptb.org/assets/documents/about/cb/meetings/23/1.13-0%20Presentations/Session%2006_Post%202015%20Strategy_Raviglione.pdf

b) The WHO Options for National Control Programmes, published in 2005, implemented between 2008 and 2013. http://whqlibdoc.who.int/hq/2005/WHO_HTM_TB_2005.352.pdf

c) STOP TB, TB & Poverty Sub Group, Patient Costing Tool http://tinyurl.com/o7rhpq6

d) 2011 normative guide "Priorities in operational research to improve TB care and control", (WHO, Stop TB, and the Global Fund for AIDS, TB & Malaria.) http://www.who.int/tb/features_archive/operational_research_priorities/en/

e) The WHO 2007 policy statement on Same-day diagnosis of tuberculosis by microscopy is available at http://tinyurl.com/pjlwfmu.

f) The revised WHO policy for same-day diagnosis, which included the revised SM definitions plus an accelerated method for collecting specimens, was issued in 2011: http://tinyurl.com/oxaaxae.

g) **Person who can be contacted:** National Manager, Nigeria Tuberculosis and Leprosy Control Programme – to indicate that the programme wants to expand ACF to selected Nigerian states. (Identifier 1).

h) http://www.stoptb.org/news/stories/2013/ns13_035.asp Quote from the Executive Secretary of the Stop TB Partnership with reference to LSTM project in Ethiopia.

i) United Nations General Assembly MGD6 countdown case study, "Tackling TB in Ethiopia". (http://tinyurl.com/ml96kgq). "Ethiopian community health workers help double the number of vulnerable people provided with TB Care"

j) A figure illustrating this, based on data from the Regional TB Control programme, is at: http://tinyurl.com/omr7vwl.