Institution: LSTM

Unit of Assessment: UOA2

Title of case study: Advancing the clinical and public health management of multi-drug resistant tuberculosis (MDR-TB)

Period when the underpinning research was undertaken: 2010 – on-going

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
S Bertel (Bertie) Squire	Dean of Clinical Sciences and International Public Health	2010 -
Ivor Langley	Health Systems Modeller	2010 – 2019
Ewan Tomeny	Health Systems Modeller and Health Economist	2016 -
Laura Rosu	Health Economist	2017 -
Danielle Cohen	Clinical Research PhD Fellow	2012 – 2016

Period when the claimed impact occurred: 2016 – present day

Is this case study continued from a case study submitted in 2014? Y/**N NO**

1. Summary of the impact (indicative maximum 100 words)

The Liverpool School of Tropical Medicine (LSTM) has contributed to changes in World Health Organization (WHO) guidelines for the management of multi-drug resistant tuberculosis (MDR-TB) including (a) methods of diagnosis, (b) shortening of treatment duration and (c) mode of delivery. The beneficiaries are predominantly poor people with TB in low- and middle-income countries (LMIC). The shortened MDR-TB regimen has already benefitted 200,000 people, with 82 countries having adopted it. Conservatively assuming a resultant health system cost saving of USD1,545 and direct patient cost saving of USD238 per patient (as calculated for Ethiopia), an overall societal cost saving of USD357,000,000 was achieved in 2018. Some countries (including Benin, DRC, Pakistan, and Nigeria) have gone further and are rolling out primarily home-based, fully oral MDR-TB treatment using a WHO-supported operational research package to which LSTM has contributed. This approach (ShORRT – Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis) will lead to further savings for both patients and health systems.

2. Underpinning research (indicative maximum 500 words)

Problem statement: In 2018, WHO estimated that globally 10,000,000 people developed symptomatic TB disease resulting in1,500,000 deaths, including 214,000 with MDR-TB. This makes TB the world's deadliest infectious disease and the source of 1/3 of global antimicrobial resistance (AMR) deaths. Up to, and including 2011, WHO recommendations for MDR-TB treatment were:
(a) diagnosis and measurement of drug sensitivity based on bacterial culture
(b) 20-24-month's treatment including
(c) an initial period of hospital admission lasting 2-4 weeks.
This was impractical in low- and middle-income countries (LMIC) as:
(a) performing a culture test requires specialized laboratories and trained personnel, and even when evidence accumulated in favour of automated molecular diagnosis (GeneXpert®) in 2011, many countries faced challenges in deciding how – or indeed whether – to implement this costly new diagnostic
(b) the 20-24 months regimen was costly to both patients and health systems, both as a result of the overall duration of treatment requiring on-going engagement with health facilities and
(c) as a result of the high costs of the in-patient care component of the regimen.

Research Team: The collaborative research addressing these problems was led by Prof Squire as Principal Investigator (PI) on the following projects. We emphasise that a large number of non-UK-based Co-I's have been essential partners in this work, but for the purposes of this case study, only UK-based Co-I's are listed here:
(a) Health System Modelling of Molecular Diagnosis of MDR-TB (Langley, Tomeny)
(b) Economic Evaluation of the STREAM Trial (Rosu, Madan Co-I (University of Warwick) Health Economist [senior economic oversight]; Nunn & Meredith Co-I (University College London) Chief Investigators for the clinical efficacy and safety components)
(c) Malawi National TB Drug Resistance survey and trial of home-based delivery of injectable antibiotic therapy (Cohen)

Health System Modelling of Molecular Diagnosis of MDR-TB: The early detection of drug resistance in TB patients is essential to the control of the epidemic. Within all TB high burden countries, molecular techniques are becoming an important part of TB control programmes for MDR-TB. These techniques are, however, costly and provide different levels of benefit within different populations. We developed a novel approach to evaluate the complex dynamics associated with diagnosis of TB in differing contexts of epidemiology and health systems. Using health system modelling to create a virtual health system, we simulated the patient pathways to diagnosis, allowing us to understand interactions within the health system while identifying critical capacity constraints [1, 2]. This modelling included costs incurred by both the health system and patients and included workforce resources saved. The first successful implementation of the approach in Tanzania (2014) demonstrated GeneXpert®'s cost-effectiveness as a primary diagnostic but only in high-throughput health facilities. Further research conducted in collaboration with the National TB programmes in Brazil, Russia, South Africa, Ethiopia, Philippines and Kenya similarly showed considerable health system and patient benefits from GeneXpert testing, but highlighted that these benefits were site specific - dependent on many local factors; thus the model allows policy makers to prioritise their rollout to maximise benefit.

Shortening of treatment for MDR-TB: Since 2010 we have been part of an international team designing, securing funding for, and implementing a multi-site, multi-arm, multi-stage randomized controlled trial (STREAM). The first phase of this trial (STREAM 1) tested a 9-11-month treatment regimen. The trial recruited patients between 2012 and 2015, follow up was complete in 2018. This was the first ever phase 3 randomized controlled trial of any treatment for MDR-TB and the first to include a within-trial health economic evaluation (led by LSTM). The final efficacy and safety results, which showed that the short regimen is non-inferior to the longer regimen, were published in 2019 [3], and the final results of the economic evaluation, reporting 2017 costs and published in 2020, showed that the short regimen decreased health system costs per case by 21% in South Africa (USD8,341 Long vs. USD6,619 Short) and 25% in Ethiopia (USD6,097 Long vs USD4,552 Short). The shorter regimen also led to financial benefits in terms of expenditure and increased earning capacity, important for the long-term financial well-being of individuals and their households. [4]. In Ethiopia, participants on the short regimen reported reductions in dietary supplementation expenditure (decrease of USD225 per case (95% CI 134-298)), and greater productivity (average increase of 5 hours worked per week, (95% CI 0.95-11.06)). Patient cost savings also arose from reduced visits to health facilities (Ethiopia decrease of USD13 per case (95% CI 11-14), South Africa decrease of USD64 ((95% CI 50-77) per case). Using income estimates for MDR-TB patients in Ethiopia, we have shown that fewer participants on the Short regimen suffered catastrophic costs, thus contributing to both Sustainable Development Goal (SDG) 3.3 and END TB targets to reduce TB-affected families facing catastrophic costs due to TB to zero by 2030 and 2035 respectively.

Shifting to out-patient management of MDR-TB: Between 2010 and 2011 we worked with the National TB Programme in Malawi to conduct the first ever national TB drug resistance survey. This demonstrated that MDR-TB was present in sporadic cases all around the country and at very low rates [5]; therefore, a centralised, in-patient model of care for MDR-TB patients would not be feasible, either for patients or health systems in a low resourced setting with low rates of MDR-TB. Consequently, between 2013 and 2015,

we explored, in a randomised trial, a model of clinical management in which patients could be cared for at home with a household member trained to deliver the injectable medications [6]. We demonstrated significant savings for both patients and health systems of home-based care: provider costs decreased from USD1100 to USD498 (2014 costs) which are substantial for health systems in countries like Malawi, where the total expenditure on health per capita is USD93. Additionally, the intervention reduced the risk of households facing catastrophic costs by 60% using a 10% threshold of annual household income and by 84% using a 20% threshold of annual household income. The study shows how home- based delivery of complex therapy can reduce catastrophic costs and help to reach the Sustainable Development Goals (SDG) and END TB targets mentioned above. It also demonstrated the importance of moving towards all-oral, out-patient delivery of treatment for MDR-TB.

3. References to the research (indicative maximum of six references)

1. **Langley I**, Lin HH, Egwaga S, Doulla B, Ku CC, Murray M, Cohen T, **Squire SB**. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. Lancet Glob Health. 2014. DOI: 10.1016/S2214-109X(14)70291-8
2. **Langley I**, **Squire SB**, Dacombe R, Madan J, Lapa e Silva JR, Barreira D, Galliez R, Oliveira MM, Fujiwara PI, Kritski A. Developments in Impact Assessment of New Diagnostic Algorithms for Tuberculosis Control. Clin Infect Dis. 2015. DOI: 10.1093/cid/civ580
3. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, van Deun A, Dat PT, Lan N, Master I, Mebrahtu T, Meressa D, Moodliar R, Ngubane N, Sanders K, **Squire SB**, Torrea G, Tsogt B, Rusen ID; STREAM Study Collaborators. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med. 2019. DOI: 10.1056/NEJMoa1811867
4. Madan JJ, **Rosu L**, Tefera MG, van Rensburg C, Evans D, **Langley I**, **Tomeny EM**, Nunn A, Phillips PP, Rusen ID, **Squire SB**; STREAM study health economic evaluation collaborators. Economic evaluation of short treatment for multidrug-resistant tuberculosis, Ethiopia and South Africa: the STREAM trial. Bull World Health Organ. 2020. DOI: 10.2471/BLT.19.243584
5. Abouyannis M, Dacombe R, Dambe I, Mpunga J, Faragher B, Gausi F, Ndhlovu H, Kachiza C, Suarez P, Mundy C, Banda HT, Nyasulu I, **Squire SB.** Drug resistance of Mycobacterium tuberculosis in Malawi: a cross-sectional survey. Bull World Health Organ. 2014. DOI: 10.2471/BLT.13.126532
6. **Cohen DB**, Mbendera K, Maheswaran H, Mukaka M, Mangochi H, Phiri L, Madan J, Davies G, Corbett E, **Squire B.** Delivery of long-term-injectable agents for TB by lay carers: pragmatic randomised trial. Thorax. 2020. DOI: 10.1136/thoraxjnl-2018-212675

4. Details of the impact (indicative maximum 750 words)

Our research has helped the WHO in the formulation of guidelines and national TB programmes and Ministries of Health, predominantly in LMIC, but also in the UK in formulation of national policies. These programmes have consequently incurred considerable savings in the costs associated with TB treatment. The impact of these policies and guidelines are global and the beneficiaries are predominantly poor people with TB in LMIC's with high TB burdens.

Molecular Diagnosis of MDR-TB

Our modelling demonstrated the need for a clear understanding of how health systems and patients would be affected, prior to the full roll-out of new diagnostic methods. The result has been that since 2018, molecular testing is being deployed in a manner that is tailored to specific epidemiological and health system contexts to efficiently and effectively guide choices between first-line and MDR-TB regimens and to maximise TB case finding [1]. For example:

a) in Tanzania our modelling work prioritised initial GeneXpert rollout to high throughput health facilities;

b) in the Philippines rollout of GeneXpert is well underway, and continued use of our modelling is helping to guide decision makers towards the provinces and sites to be prioritised;

c) in Kenya, health system modelling is being used to decide on relative positioning of chest X ray screening and GeneXpert in TB case-finding algorithms.

Shortening of Treatment for MDR-TB

Prior to the STREAM 1 trial, WHO recommended the 9-11-month short regimen based on 'very low quality' evidence, so the shorter treatment had to be tested in a randomised trial setting. The health economic component led by LSTM showed that the short-regimen leads to economic benefits for health systems and patients. These benefits are substantial, even when taking into account additional costs of safety monitoring (as high-dose moxifloxacin and clofazimine administered in the short regimen were known to increase the risk of prolongation of the QT interval- a measurement made on an electrocardiogram used to assess some of the electrical properties of the heart, and thus increase the possibility of adverse events).

Squire, Langley, and Rosu participated in dissemination and discussion of the preliminary results of both the clinical and economic elements of the trial, including to the WHO Guideline Group in 2018 [2]. These and the final published clinical results, demonstrating non-inferiority of the 9-11-month regimen (compared to 20 month), contributed to the formulation of two updates to the WHO guidance on management of MDR-TB [3,4] and the WHO 2019 consolidated guidance endorsing shortened regimens with economic benefits for both patients and health systems [5]. Since October 2018, 82 countries, mostly in Africa and Asia, reported having adopted shortened MDR-TB regimens. The methodology developed in the STREAM trial is currently being used in further work, namely:

- Phase 2 of the STREAM trial [6]
- The "Cost and cost-effectiveness analysis" section of the ShORRT operational research package developed by WHO/TDR to support rollout of all-oral shortened MDR-TB regimens.[7]

These all-oral regimens will permit wide-scale shift to out-patient management of MDR-TB resulting in further savings for patients and health systems.

Shifting to out-patient management of MDR-TB

Financial well-being of MDR-TB patients and their households is a function of duration of treatment, but also driven by the extent to which treatment is delivered through in-patient care. Modelling of the data in STREAM 1 established that an out-patient model would lead to significant health system cost savings compared to an in-patient model. These findings fed into the global discussions (STAG-TB) on the need to shift to all-oral regimens in general to facilitate out-patient care. WHO issued a rapid communication in December 2019 [8] recommending this shift but only recommending rollout of the 9 month all-oral regimen under operational research conditions and for certain patients; those without extensive disease and without resistance to fluoroquinolines. LSTM supported implementation of this recommendation through contribution to the ShORRT package which is now being used to rollout all-oral, home-based MDR-TB treatment in several countries, including Nigeria, Pakistan, Benin and DRC [9].

Since March 2020 Malawi has moved to primarily home-based, fully oral MDR-TB treatment lasting 18-24 months. While injectables are no longer needed for MDR-TB in Malawi, it should be noted that our home-based care trial in Malawi [10] demonstrated that training patient-nominated lay people to deliver injectables offers a sustainable opportunity for home-based management of patients with forms of drug-resistant tuberculosis, such as extensively resistant TB (XDR-TB), where injectables are still required [11].

Advocacy and method development

As a member of the Board of The International Union Against Tuberculosis and Lung Disease (2003-2016) including 3 years as President (2008-2011), and a member of the Strategic and Technical Advisory Group for TB (STAG-TB) of the WHO (2016-2018), Squire has played a leading advocacy role for equity-focussed approaches to TB management. He has played a pivotal role in ensuring that the impact on patient costs is incorporated into economic analysis of TB interventions and models of care, contributing to the inclusion of the target to end catastrophic costs for TB patients in the WHO End TB Strategy, launched in 2015. As a member of the WHO Task Force on patient costs, he worked with Tomeny and international

colleagues to develop a robust methodology for assessing TB patient costs [12]. This methodology has become the gold standard for assessing patient costs, and Squire and team incorporated this into within-trial economic evaluations with the latest development being the inclusion of quality of life assessments [6].

As a member of the UK NICE Guideline Development Group for TB (2013-2015), Squire has successfully advocated for the inclusion of molecular testing for drug resistance in NICE TB Guidelines [13], which has led to more rapid identification and treatment of MDR-TB in UK clinical practice.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Testimonial from the previous TB Programme Manager, Tanzania **and** TB Programme Manager, Philippines.
2. WHO: Position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results, page 7. (https://www.who.int/tb/publications/2018/Position_statement_shorter_MDR_TB_regimen/en/)
3. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis. 2018 (WHO/CDS/TB/2018.15) https://www.who.int/tb/areas-of-work/drug-resistant-tb/guideline-update2018/en/
4. WHO rapid communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis. 2018 (WHO/CDS/TB/2018.18) https://www.who.int/tb/publications/2018/rapid_communications_MDR/en/
5. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019. (WHO/CDS/TB/2019.7), page 40. https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/
6. Rosu L, Madan J, Worrall E, Tomeny E, Squire B; STREAM Study Health Economic Evaluation Collaborators. Economic evaluation protocol of a short, all-oral bedaquiline-containing regimen for the treatment of rifampicin-resistant tuberculosis from the STREAM trial. BMJ Open. 2020. DOI: 10.1136/bmjopen-2020-042390
7. ShORRT Research Package, page 52. (https://www.who.int/tdr/research/tb_hiv/shorrt/en/)
8. WHO rapid communication: Key changes to the treatment of drug-resistant tuberculosis (WHO/CDS/TB/2019.26) https://www.who.int/tb/publications/2019/rapid_communications_MDR/en/
9. Testimonial from Scientist, WHO special programme for research on disease of poverty (TDR), Geneva
10. Cohen DB, Mbendera K, Maheswaran H, Mukaka M, Mangochi H, Phiri L, Madan J, Davies G, Corbett E, Squire B. Delivery of long-term-injectable agents for TB by lay carers: pragmatic randomised trial. Thorax. 2020. DOI: 10.1136/thoraxjnl-2018-212675
11. Testimonial from Program Director at National Tuberculosis Control Program, Malawi.
12. Tuberculosis patient cost surveys: a handbook 2017. WHO (https://www.who.int/tb/publications/patient_cost_surveys/en/)
13. NICE guidelines: (https://www.nice.org.uk/guidance/ng33)