Section A

Institution: University of St Andrews

Unit of Assessment: UoA 01: Clinical Medicine

Title of case study: Tuberculosis: testing and implementing innovative treatments

Period when the underpinning research was undertaken: 2015 - 31 December 2020

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

Name(s):	Role(s) (e.g. job title):	Period(s) employed submitting HEI:
Stephen Gillespie	Professor	01 August 2010 – present
Derek Sloan	Senior Lecturer	01 January 2016 - present
Wilber Sabiiti	Senior Research Fellow	05 August 2013 - present

Period when the claimed impact occurred: 2014 - 31 December 2020

Is this case study continued from a case study submitted in 2014? No

Section B

1. Summary of the impact

Tuberculosis (TB) is a major global killer responsible for approximately 9,000,000 new cases and 1,000,000 to 2,000,000 deaths per year. It disproportionally affects low and middle-income countries. Medical research at St Andrews has developed global capacity to improve tuberculosis treatment through shorter, safer drug regimens, and improved diagnostics for monitoring treatment. Our work has resulted in:

- Development of **TB networks, treatment trial methodologies**, widely used by state, NGO and commercial concerns, that have substantially enhanced the evidence base underpinning development of novel treatments for TB, and **increased global capacity capable of delivering registration studies** in over 50 sites in 9 countries, across 4 continents.
- This work has provided evidence leading to **changes in treatment in 2018 WHO guidelines and practice** that have affected rifampicin and isoniazid novel regimens for treating drug resistant TB in Germany and the Netherlands.
- The **development and commercialization of an assay for real-time antibiotic treatment monitoring** in TB patients which is used in 6 countries with over 600 patients.

2. Underpinning research

Globally, tuberculosis (TB) is the leading cause of death from a single infectious disease agent. Our sustained research in St Andrews over the last 10 years (on the disease and the pathogen responsible) has developed global capacity to improve tuberculosis treatment and understanding of the disease and underpinned transformative change in tackling this problem in low and middle-income countries (LMICs).

Conducting and laying the groundwork in clinical trials has led to delivering new tools for tuberculosis control including evaluating new treatments and diagnostic tools. We have performed a range of clinical trials of novel and repurposed drugs. As there had been no previous regulatory trials, all of the necessary methodologies and protocols needed to be designed and tested collaboratively with partners at trial sites and regulators. This included site selection, clinical and laboratory protocols, and pharmacy manuals. The drug development process is divided into three phases: our research targets Phase II when novel drugs or regimens are first given to patients with the target disease; and phase III is when data is generated for registration by international regulatory agencies. To achieve this, we formed a series of international consortia (REMoxTB/STAND/SimpliciTB and the European-African PanACEA) with collaborators on four continents (Africa, South Asia, Europe and South America).

Registration trials

We performed the first regulatory study REMoxTB (R1), a global Phase III clinical trial conducted at nearly 50 sites in Africa and Asia designed by **Gillespie**. The St Andrews TB team's work to develop global capacity to improve tuberculosis treatment grew out of the initial REMoxTB (2008-2014) study published in 2014 and expanded in subsequent years establishing new sites in Africa Asia and South America to pursue therapeutics and diagnostics projects. In particular, St Andrews TB research has used trial data to address critical questions in tuberculosis. Examples include understanding of the toxicity of tuberculosis chemotherapy especially liver injury otherwise known as hepatotoxicity (R2), the differences in efficacies of treatment between men and women (R3) and how to interpret positive cultures after patients have completed therapy. We demonstrated the performance not only of novel regimens but established the clinical characteristics of the current standard regime, showed optimal specimen sampling methods, and set standards for sequencing relapse strains. This work has continued with two further regulatory trials: STAND (2015-2018) and SimpliciTB (2018-present) in collaboration with the Global Alliance for TB Drug Development.

Repurposing and optimising drugs

Gillespie is one of the three leads in the PanACEA consortium, which has performed a series of early phase trials including a process to determine the optimal dose of rifampicin, an antibiotic administered to prevent and treat tuberculosis, also the most important component of the current regimen, comprising four different antibiotics. This came to fruition in the establishment of the maximum tolerated dose that can be used, and in demonstrating its greater effect on killing TB bacteria (R4). Developing an innovative methodology for early phase clinical trials of novel agents, we have identified optimum dosage of an established drug and demonstrating ineffectiveness in another (R5).

Improving diagnosis and treatment monitoring

In addition to therapy, we have addressed another major barrier to controlling tuberculosis: the difficulty of diagnosis and monitoring treatment outcome. The infecting bacteria grow very slowly, and expensive facilities to ensure safety limit the availability of diagnostic services. We developed the Molecular Bacterial Load Assay (MBLA) to overcome this problem, as it detects *Mycobacterium tuberculosis* ribosomal RNA that can not only definitively diagnose the disease but can also determine whether the TB pathogen is dead or alive, allowing clinicians to monitor the response to treatment, and to adjust it accordingly (R6). We have investigated the clinical characteristics of the test in practice and its operational implementation and created models to translate MBLA results into conventional markers and *vice versa*.

3. References to the research

The underpinning research listed here is a small representation of a much larger St Andrews body of work that stretches back to 2010, which was funded by peer-reviewed grants. All publications were published in highly ranked peer-reviewed journals, and R1, R4, R5 and R6 are part of the UoA 01 REF output submission.

R1. **Gillespie** SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, Pappas F, Phillips PP, Nunn AJ; REMoxTB Consortium. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *New England Journal Medicine,* 2014; 371:1577-87. DOI: 10.1056/NEJMoa1407426

R2. Tweed CD, Wills GH, Crook AM, Dawson R, Diacon AH, Louw CE, McHugh TD, Mendel C, Meredith S, Mohapi L, Murphy ME, Murray S, Murthy S, Nunn AJ, Phillips PPJ, Singh K, Spigelman M, **Gillespie** SH. Liver toxicity associated with tuberculosis chemotherapy in the REMoxTB study. *BMC Medicine,* 2018; 16: 46. DOI: 10.1186/s12916-018-1033-7

R3. Murphy ME, Wills GH, Murthy S, Louw C, Bateson ALC, Hunt RD, McHugh TD, Nunn AJ, Meredith SK, Mendel CM, Spigelman M, Crook AM, **Gillespie** SH; REMoxTB consortium. Gender difference in tuberculosis treatment outcomes: a post hoc analysis of the REMoxTB study. *BMC Medicine,* 2018; 16: 189. DOI: 10.1186/s12916-018-1169-5

R4. Boeree MJ, Diacon AH, Dawson R, Narunsky K, du Bois J, Venter A, Phillips PP, **Gillespie** SH, McHugh TD, Hoelscher M, Heinrich N, Rehal S, van Soolingen D, van Ingen J, Magis-

Escurra C, Burger D, Plemper van Balen G, Aarnoutse RE; PanACEA Consortium. (2015) A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *American Journal Respiratory and Critical Care Medicine*, 2015; 191:1058-65. DOI: 10.1164/rccm.201407-1264OC

R5. Boeree M, Heinrich N, Aarnoutse RE, **Gillespie** SH, Hoelscher M. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infectious Disease,* 2017; 17: 39-49. DOI: 10.1016/S1473-3099(16)30274-2

R6. **Sabiiti** W, Azam K, Farmer ECW, Kuchaka D, Mtafya B, Bowness R, Oravcova K, Honeyborne I, Evangelopoulos D, McHugh TD, Khosa C, Rachow A, Heinrich N, Kampira E, Davies G, Bhatt N, Ntinginya EN, Viegas S, Jani I, Kamdolozi M, Mdolo A, Khonga M, Boeree MJ, Phillips PPJ, **Sloan** D, Hoelscher M, Kibiki G, **Gillespie** SH. Tuberculosis bacillary load, an early marker of disease severity: the utility of tuberculosis Molecular Bacterial Load Assay. *Thorax,* 2020; **75**: 606-608, DOI: 10.1136/thoraxjnl-2019-214238

4. Details of the impact

Tuberculosis (TB) is a major global killer responsible for approximately 9,000,000 new cases and between 1,000,000 and 2,000,000 deaths per year. **Gillespie** was a speaker at the seminal meeting at which the *Cape Town Declaration* was made, that described the increasing TB burden as "a blot on the consciousness of human-kind" and called for funding and renewed emphasis on tuberculosis drug development. The St Andrews group's critical impact is a result of their research as described in section 2, and a body of work stretching back to 2010, when **Gillespie** moved to the University of St Andrews from UCL. This has encompassed the development of global TB networks, treatment methodologies and clinical capacity. The research has led to changes in treatment practice, and improved diagnostics for monitoring treatment, which led to development and commercialisation of an assay for real-time antibiotic treatment monitoring in TB patients in 2018.

Development of TB networks, treatment trial methodologies and clinical capacity

When this work first started, there were only a few sites capable of delivering TB trials data to regulatory standards. Since 2014, and through a program of clinical trials research (REMoxTB, STAND, SimpliciTB and PanACEA), the St Andrews group has helped develop capacity capable of delivering registration studies in over 50 sites in 9 countries, across 4 continents.

Multiple global collaborative consortia have been developed following **Gillespie's** creation of the Infection and Global Health Division at the University of St Andrews in 2010. The St Andrews group have worked with the Global Alliance for TB Drug Development as the clinical lead. Specifically, the group have built and developed 2 international collaborative networks with major studies REMoxTB (started in 2008, expanded from 2013, and completed in 2018), STAND (started in 2015 completed in 2018) and SimpliciTB (started 2018 and ongoing).

In collaboration with the Global Alliance for TB Drug Development, since 2014/15, we have added 5 African sites, and trial capacity has grown to over 50 sites in 9 countries, across 4 continents and is capable of delivering registration studies rapidly, and has recruited over 2,670 people (participants) across these studies (S1). Specifically, since 2014, we have developed the PanACEA consortium (Pan African Consortium for the Evaluation of Antituberculosis agents; **Gillespie** is one of three principal investigators), one of the largest collaborations of European and African partners with a wide range of skills (PanACEA I, 2008-2015, and PanACEA II, refunded in 2017), which has grown from 11 institutions in 6 countries to 16 institutions, recruiting patients into commercial and other studies (S2). Through the PANBIOME, STAND, SimpliciTB and PanACEA consortia led by Gillespie since 1 August 2014, the following results have been accomplished. PANBIOME in 2015 resulted in 4 additional sites implementing the MBLA as part of the Biomarkers expansion programme in PanACEA. STAND in 2018 successfully increased trial capacity from 16 sites to 26 sites in 8 countries spanning over 4 continents, Europe, Africa, South America and Asia. SimpliciTB has added over 26 sites, in 8 countries also covering 4 continents. This combined success has resulted (between 2017 and 2020) in an increase, from approximately 10 to over 50, in the number of sites able to perform trials to regulatory standard from 2016/2017.

The building of site capability has been a continuous process starting with REMoxTB and

continuing after 2014, with 5 new sites being engaged in Africa since 2015. The Executive Director of European and Developing Countries Clinical Trial Partnership (EDCTP) stated "*As part of the REMoxTB trial running from 2008 to 2014 and as part of the groups continued research, sites in high TB Burden countries were identified, personnel were trained and the facilities were outfitted to conduct the phase 3 TB drug trial. Since 2014, this has had a lasting impact. South African sites, for example, that were part of this early effort now represent the epicentre of cutting-edge TB research, with the capacity to play a central role in the funding of new TB cures"* (S2). Further, the Executive Director of EDCTP commented on the benefit of the consortium and development of trial capabilities in sub-Saharan Africa: "*the research and professional development support of St Andrews TB research group and the consortium has formed key players, and the consortium transformed the ability of African scientists to conduct research by increasing trial site capacity and expanded TB expertise*" (S2). The PanACEA sites have "*contributed to the development of critical diagnostic, treatment and research infrastructure in low- and middle-income countries from 2014-2020. This research has resulted in the number of sites increasing in Tanzania from 3 to 5.*", as evidenced and corroborated by the Director General of NIMR-Mbeya (S3).

Through their research, St Andrews and the Global Alliance consortium have supported and mentored female scientists and made significant progress in addressing the gender imbalance in Global Health clinical scientists in East Africa. Before the St Andrews research collaboration with Tanzania, there were no female African science leaders in the area of TB; as of 2020, there were 5 and this number is rising (S4). Providing evidence of this change, one of those leaders says: "*through mentorship of Professor Stephen Gillespie and Dr Derek Sloan and resources support, and as part of collaborating on (STAND, SimpliciTB and PanBIOME from 2014 to 2020) I mastered a steep learning curve and achieved leadership in the TB field. Currently, I have established a functional clinical trial unit at my institute capable of conducting phase 2 and 3 studies. Also, I have developed a TB research group in my country and systematised research in two sub-categories: health system and clinical research. The group has 5 PhDs, including 2 female and the group continues to benefit mentorship and collaborations with St Andrews experts*" (S4).

The work of the St Andrews research group has delivered new tuberculosis clinical trials: PanACEA Multi-Arm Multi-Stage-TB Trial and STAND/SimpliciTB have played a central role in finding new and improved cures for TB (R1, R4 and R5). For these trials, it was necessary to develop all the methodologies needed to deliver a regulatory standard study. After the completion of the REMoxTB trial (2014), we used the extensive dataset to establish many of the tools and protocols that underpin subsequent clinical trials, e.g. STAND and SimpliciTB, which Gillespie led (R2 and R3). "*The methodologies developed and the network have contributed greatly to the registration of our novel drug pretomanid in 2019 by the US Food and Drugs Administration (FDA) and in 2020 by the European Medicines Agency (EMA)*" according to the Global Alliance (S1). This included many of the methods for the day-to-day management of tuberculosis clinical trials that have become the standard for how TB clinical trials should be managed. Gillespie, and colleagues from his collaborations, provided these details to the European Medicines Agency when revising TB regulatory guidelines in 2018, and members of our consortium presented evidence that formed the basis of the revisions of the advice that has now been published (S5). The TB Alliance, sponsors of the clinical trials, have acknowledged that: "*St Andrews and the consortium have made ground-breaking contributions to develop methodologies that have resulted in the generation of evidence for new drugs for tuberculosis*" (S1).

Changed treatment practice and guidelines

We have challenged conventional wisdom about the dosage of the most important drug (rifampicin) in tuberculosis regimens performing a series of studies indicating that higher doses of this antibiotic are more effective (PanACEA - RUNMC, conducted 2010 to 2018, described in R4) (PanACEA MAMS-TB trial, and HighRif studies conducted 2013 to 2020, described in R5). PanACEA has identified the rifampicin dose in World Health Organisation (WHO) guidelines was underdosed and have completed a series of studies to show that the optimal dose was 4 times higher than that in the WHO guidelines (was 10 mg/kg but was increased to 40mg/kg). This development has entered clinical practice in the national treatment centres in Germany and the Netherlands for the treatment of pulmonary and meningeal tuberculosis (S6). In addition, our

research (R1) has been used to inform 2018 WHO clinical guidelines for treatment of patients infected with isoniazid resistant strains (S7, p. 31).

Development and commercialization of a real-time antibiotic treatment monitoring assay

Improvements in therapeutic treatment regimens are only one side of the coin when it comes to translating this impact into improved patient outcomes. The other is the ability to monitor the effect of treatments to inform patient management. Classically, it has been difficult to monitor the response to tuberculosis treatment due to the slow growth of the organism in culture. Our research addressed this problem and produced a molecular assay which has been commercialised and is now being used for real-time antibiotic treatment monitoring TB patients in 6 countries.

Since 2011, we have developed a unique molecular tool, the tuberculosis Molecular Bacterial Load Assay (TB-MBLA), which overcomes this problem by detecting the number of live organisms in four hours compared to current methods that take up to 42 days. Working with patients from the PanACEA MAMS-TB trial (conducted between 2013 and 2018), our research provided evidence that the use of TB-MBLA could inform clinical decision making in real-time, and that its use could expedite drug TB clinical trials (R6).

The assay has been commercialised between University of St Andrews spinout enterprise, SOI Ltd in 2018, under the trademark of "VitalBacteria". As of 1st December 2020, the assay has been bought and distributed in 6 countries (UK, Germany, Ghana, Zambia, Tanzania and Singapore), has been used to monitor treatment in over 600 people (patients) and had sales of GBP56,957 (S8). The assay is the world's only rapid and effective custom-designed molecular test for TB treatment monitoring. An independent medical research charity, LifeArc, are developing this further for implementation into clinical practice.

Through a TB Stakeholder conference held in 2018, which brought together health professionals and policy makers from 16 countries across the globe, and a 2-day training of 17 experts in TB-MBLA technology transfer, St Andrews created an international TB-MBLA users' group consisting of 30 groups in 18 countries for TB diagnostics and treatment management. Through this engagement activity and global reach, the impact that TB-MBLA has for real-time antibiotic treatment monitoring has been recognised by the Treatment Action Group, stating, "*In as little as three days, 16S ribosomal RNA that is detected by MBLA is able to indicate the bactericidal effect of TB drugs and to provide a long-term assessment of treatment response for slow responders*" (S9, p. 15). Moreover, the World Health Organisation, included it as an important new diagnostic for TB in their Global Tuberculosis Report 2018, stating "*St Andrews University, Scotland has developed a novel approach for real-time monitoring of a patient's response to TB treatment. The Molecular Bacterial Load Assay (MBLA) is a real-time reverse transcriptase quantitative PCR (RT-qPCR) that uses 16S-ribosomal RNA (rRNA) targets to quantify the* M. tuberculosis *bacillary load over the course of treatment*" (S10, p. 155).

5. Sources to corroborate the impact

S1. Supporting letter from TB Alliance corroborating the pivotal role of REMoxTB and subsequent trials in the setting of the protocol and trial site development process
S2. Supporting letter from Executive Director of EDCTP
S3. Supporting Letter from Tanzanian Minister of Health
S4. Supporting letter from Director-Research Training & Innovation, Kibong'oto Infectious Diseases Hospital, Tanzania – corroborating gender balance in Africa
S5. Agenda of meeting with EMA for regulatory guidelines, corroborating the role REMoxTB methodology had in shaping the guidelines
S6. Supporting letter from the Coordinator of the PanACEA Consortium corroborating the countries who have adopted the increased rifampicin dose in their nation guidelines
S7. WHO treatment guidelines for isoniazid resistant tuberculosis https://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf
S8. SOI Ltd document to support the economic impact of VitalBacteria
S9. Report from Treatment Action Group into Tuberculosis Diagnostics pipeline https://www.treatmentactiongroup.org/wp-content/uploads/2020/10/pipeline_TB_Diagnostics_2020_final.pdf
S10. WHO Document corroborating the novel development of MBLA TB treatment monitoring https://www.who.int/tb/publications/global_report/gtbr2018_main_text_28Feb2019.pdf