Mathematical Modelling of the Clinical and Economic Impact of Proposed TB Interventions

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Mathematical modelling plays a vital role in driving both cost-effective and therapeutically-effective innovations, but is often understated and overlooked. It bridges the gap between small-scale studies showing therapeutic effectiveness, and large-scale roll-outs of new medical innovations, pharmaceutical or otherwise. During my seven-week elective placement at the London School of Hygiene and Tropical Medicine (LSHTM), I dove into the world of mathematical models as a summer researcher with the TB Modelling and Analysis Consortium, or 'MAC'. I hoped that during my time there I would be able to 'brush up' on the mathematics I hadn't touched since A-Levels, as well as contribute meaningfully to work on TB innovations across the developing world.

Any fears I had about a potentially boring placement, or one far removed from ever having clinical relevance, were quickly assuaged on my first day. Walking through the door to join my new team I saw written over the frame in large letters the words: '*WE WILL END TB*'. This set the tone for the team, and indeed my time there, whether it was in weekly group meetings, in which different members summarised their activities and aims for that academic period, or in conference calls with researchers 'in the field'. The message was clear: this was a group of professionals with the sole aim of reducing global TB burden, and who had been given the academic mandate to pursue this. If fighting TB was their 'war', then mathematics was their 'weapon'.

After being quickly introduced to the team, I joined one of the assistant professors on the **A**dherence **S**upport **C**oalition to **En**d **T**B (ASCENT) project. This project formed an international partnership, and its major stakeholders included Koninklijke Nederlandse Centrale Vereniging tot bestrijding der Tuberculose (KNCV), the Programme for Appropriate Technology in Health (PATH), the Aurum Institute, and of course, LSHTM. At the heart of the project was the question: 'How can we use modern technology to make TB treatment simpler, and more affordable, for both patients and providers?'. The cost to patients has received more public health emphasis recently, in light of the World Health Organisation (WHO) designating 'catastrophic costs' as an important outcome marker of TB treatment success. 'Catastrophic cost' refers to where the sum of direct and indirect costs associated with TB treatment exceed 20% of pre-TB annual income. In most cases this would lead to an irreversible spiral into debt and social deprivation.

The technology in question in the ASCENT project is the use of mobile phones to encourage adherence with TB medication. Large proportions of the population in many under-developed countries now have access to cheap mobile phones, representing a major paradigm shift in how citizens communicate with each other. In the past, TB drug regimens have primarily been delivered in the form of Directly Observed Treatments (DOTs) in which health care workers observe the ingestion of medication to ensure patient adherence. This programme has been largely successful in reducing TB disease burden, but has also been very cost-intensive. However, working in collaboration with the company Everwell Health Solutions, this project considered the use of new Digital Adherence Technologies (DATs), in light of the increased population proportion with access to a mobile phone, as an alternative to the traditional DOTs.

Whilst there is some variation on the exact mechanism of DATs, they mainly revolve around either recording oneself ingesting the medication at home, or texting a number found on the inside of the pill packet, to acknowledge the intake of medication. When I joined the team they had already performed a small scale roll-out of this intervention, as an alternative to DOTs, in South Africa, and had gone on to extrapolate their findings in a mathematical model to slightly different healthcare situations in countries including Ethiopia and Ukraine. The job of the mathematical modellers (and my job for the summer!) was to ask the question: what would happen if the results of the South African case study were repeated on a larger scale in another country? Specific outcomes we were interested in included money saved to patient and provider, as well as improved clinical outcomes as a result of greater adherence levels with medication.

This wasn't just an esoteric research project. The results of our modelling were to be used to apply for significant grant funding from charities dedicated to tackling TB. Given the sums of money involved it wasn't enough to simply say, 'It looks like this will work' -- stakeholders expect and demand figures and calculations to back up any claims. This is where the mathematics and the mathematical modellers come in, providing a glimpse of what the benefits of proposed interventions might include.

During my time there I looked at the mathematical model in detail, producing numerous Tornado Plots to consider which factors were most important in determining overall cost to patient and provider. Interestingly, patients were most affected by the cost of individual clinic appointments, whilst the highest cost to providers was often provided by the multi-drug resistant TB patients, who required large and expensive cocktails of antimicrobials to fight the infection. I also considered new methods for determining the extent to which TB patients will face 'catastrophic costs' in mathematical models. Previous efforts to quantify the prevalence of 'catastrophic cost' revolved around performing time-consuming and cost-intensive economic surveys, which were themselves vulnerable to reporting bias. I attempted to define a new method for estimating the extent of catastrophic cost, using widely available population characteristics such as Per Capita Income and the Gini Coefficient, to provide a cheap and rough way of estimating the prevalence of catastrophic costs. Whilst these ideas are in the early stages, a breakthrough in this area could make further mathematical models much simpler and easier to design, requiring significantly less data.

We might not have ended TB yet, but my time with the TB MAC group in LSHTM was thoroughly profitable, both for improving my knowledge in this overlooked part of public health, and also for giving me insight into the role a future clinician could play in this area. The doctor sees the patient in front of them and thinks about ways they could improve their individual quality of life. The mathematical modeller in infectious diseases considers the population as a whole, and whilst at times lacking the clinical exposure and understanding of the disease which the doctor possesses, they are able to develop and implement systematic and often subtle changes which improve the overall health of a population on a national level.

A clinician working in this area would have the unique opportunity to bring together both their understanding of the patient as an individual, whilst also considering the health of the public on a national level. I aim to foster such clinical practice in my future career.