Institution: University of Warwick

Unit of Assessment: B10 - Mathematical Sciences

Title of case study: Mathematical and Economic Modelling of Neglected Tropical Diseases: improving the quality of life of tens of millions of people

Period when the underpinning research was undertaken: 2015-2020

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:**
Kat Rock	Associate Professor	Feb 2015 – Present
Matt Keeling	Professor	Jan 2002 – Present
Deirdre Hollingsworth	Professor	Jan 2013 – Oct 2017
Simon Spencer	Associate Professor	Sep 2010 – Present
Louise Dyson	Associate Professor	May 2015 – Present

Period when the claimed impact occurred: 2017-2020

Is this case study continued from a case study submitted in 2014? N

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

Warwick's mathematical epidemiologists have played a leading role in the control of two neglected tropical diseases (NTDs) – *gambiense* human African trypanosomiasis (gHAT, or sleeping sickness) and lymphatic filariasis (LF, or elephantiasis). These diseases cause thousands of deaths and ruin millions more lives in some of the world's poorest countries. Funded by the Bill and Melinda Gates Foundation, Warwick research recommended and validated public health strategies for sleeping sickness in the Democratic Republic of the Congo and Chad. These interventions have resulted in significant progress towards eliminating sleeping sickness transmission for good by protecting around 740,000 people. Warwick modelling also outlined a vital assumption in the World Health Organization's 2017 guidelines for mass drug administration against elephantiasis. In 2019 the resulting triple-drug or 'IDA' therapy was administered to 45,200,000 at-risk people in 11 different countries – 0.6% of the world's total population.

2. Underpinning research (indicative maximum 500 words)

Neglected tropical diseases (NTDs) are a diverse set of around 20 illnesses that limit the life chances of over 1,000,000,000 of the world's poorest people; in response, successive World Health Organization (WHO) roadmaps have set a goal to reduce by 90% the number of people requiring treatment for NTDs by 2030. Research towards the elimination, of transmission and as a public health concern respectively, has been highlighted below with reference to two NTDs:

- Human African trypanosomiasis (HAT), or sleeping sickness, is transmitted by infected tsetse flies and is usually fatal without treatment. The *gambiense* strain (gHAT) accounts for >95% of cases. In 2009 there were around 10,000 cases worldwide, with approximately 80% found in the Democratic Republic of the Congo (DRC), and with most of the rest in Chad, Guinea, Central African Republic, Chad and Angola. Overall, over 51,000,000 people are at risk across 24 countries. In 2018 global, annual case reporting dropped below 1,000 for the first time.
- Lymphatic filariasis (LF), or elephantiasis, is transmitted by worms; extreme swelling of the limbs, breasts or genitals results in severe disability. There are estimated to be around 36,000,000 people at present with chronic ailments resulting from LF, with around 893,000,000 at risk of the disease in 49 countries.

Achieving the WHO's ambitious target would require a coordinated response from national and international actors: donors, funders, endemic countries, disease experts, big pharma, NGOs and the research community. Mathematical epidemiologists at Warwick's Zeeman Institute for

Systems Biology and Infectious Disease Epidemiology Research (Rock, Hollingsworth, Keeling, Dyson, Spencer and others) have established international reputations for the combination of mathematical, health economic and epidemiological research expertise required.

The Bill and Melinda Gates Foundation (BMGF) and the Task Force for Global Health (TFGH), recognising the need for policy-relevant mathematical modelling to support the WHO's global strategy and local NTD elimination programmes, funded the NTD Modelling Consortium in 2015 **[G1]**, an international partnership of 9 relevant institutions led by Hollingsworth (Warwick 2013-2017; Oxford from 2018 **[G2]**). The purpose of the consortium is to provide holistic modelling support for NTD elimination, including overview studies of how best to meet elimination targets **[3.1]**. Additional BMGF grants at Warwick funded disease-specific modelling projects on HAT **[G3**, **G4]** (PI: Rock) and LF **[G5]** (PI: Hollingsworth) which produced a large volume of policy-relevant modelling research.

In 2015 Rock modelled the gHAT control strategy for regions in former Bandundu province of the DRC **[3.2]**. The Warwick model variants were the first to be fitted to longitudinal surveillance data from DRC. They estimated the impact of current control policies and projected the likelihood of meeting elimination targets. The analysis suggested additional strategies such as vector control (e.g. killing flies using insecticide-impregnated targets) and/or improved screening may be required to reach elimination in specific settings. It suggested that there may be a portion of people at a high risk of acquiring infection who are not being accessed by the existing screening programme. Subsequent work by Rock **[3.3]** extended this analysis to cover 168 health zones comprising the entire DRC. This work estimates the median time to end of transmission (EOT) and the associated uncertainty for each health zone under different elimination strategies and identifies those that would most benefit from intensified public health interventions.

Rock and collaborators performed similar validation of gHAT measures in Chad where vector control and improved passive screening had already been introduced in the Mandoul region from 2014 **[3.4]**. This work quantified the effect of these interventions – concluding that approximately 63% and 9% transmission reduction came from vector control and improved passive screening respectively. Additional work in **[3.5]** provides a review of the feasibility of the WHO goal of ending gHAT transmission globally by 2030 accounting for likely discrepancies between reported cases and actual infection and uncertainties stemming from variations in passive screening levels and possible animal reservoirs.

In 2017 **[3.6]** Hollingsworth and collaborators used modelling to assess the case for a change of WHO guidelines on elimination of LF. Prior to 2017, mass drug administration (MDA) with double drug therapy of diethylcarbamazine and albendazole (DA) was recommended by the WHO as the preferred approach to LF elimination in endemic areas. The efficacy of this approach was modelled in **[3.6]** and compared to other potential MDA strategies. It was found that in both high- and low-prevalence settings, the triple drug therapy, IDA (ivermectin, diethylcarbamazine and albendazole), required fewer rounds of MDA to reach elimination compared to the DA double drug regimen, thereby offering the possibility of reaching elimination targets sooner.

3. References to the research (indicative maximum of six references) **Warwick = Bold**

All research papers excepting preprints were published in peer-reviewed journals

[3.1] Hollingsworth, T. D., Adams, E. R., Anderson, R. M., Atkins, K., Bartsch, S., Basáñez, M.-G., Behrend, M., Blok, D. J., **Chapman, L. A. C.**, Coffeng, L., **Courtenay, O.**, **Crump, R. E.**, de Vlas, S. J., Dobson, A., **Dyson, L.**, **Farkas, H.**, Galvani, A. P., Gambhir, M., Gurarie, D., **Irvine, M. A.**, **Jervis, S.**, **Keeling, M. J.**, Kelly-Hope, L., King, C., Lee, B. Y., Le Rutte, E. A., Lietman, T. M., Ndeffo-Mbah, M., Medley, G. F., Michael, E., Pandey, A., Peterson, J. K., Pinsent, A., Porco, T. C., Richardus, J. H., Reimer, L., **Rock, K. S.**, Singh, B. K., Stolk, W., Swaminathan, S., Torr, S. J., Townsend, J., Truscott, J., Walker, M., Zoueva, A. and NTD Modelling Consortium (2015) *Quantitative analyses and modelling to support achievement of the 2020 goals for nine neglected tropical diseases*. Parasites & Vectors, 8 (1). pp. 630. doi:10.1186/s13071-015-1235-1

[3.2] Rock, K. S., **Torr, S. J.**, Lumbala, C. and **Keeling, M. J.** (2015) *Quantitative evaluation of the strategy to eliminate human African trypanosomiasis in the Democratic Republic of Congo*. Parasites & Vectors, 8 (1). pp. 532. doi: 10.1186/s13071-015-1131-8
[3.3] Huang, C., **Crump, R. E.**, **Brown, P.**, **Spencer, S. E. F.**, Miaka, E. M., Shampa, C., **Keeling, M. J.** and **Rock, K. S.** (2020) *Shrinking the gHAT map: identifying target regions for enhanced control of gambiense human African trypanosomiasis in the Democratic Republic of Congo*. medRxiv [Preprint]. doi:10.1101/2020.07.03.20145847
[3.4] Mahamat, M. H., Peka, M., Rayaisse, J.-B., **Rock, K. S.**, Toko, M. A., Darnas, J., Brahim, G. M., Alkatib, A. B., Yoni, W., Tirados, I., Courtin, F., **Brand, S. P. C**., Nersy, C., Alfaroukh, I. O., **Torr, S. J.**, Lehane, M. J. and Solano, P. (2017) *Adding tsetse control to medical activities contributes to decreasing transmission of sleeping sickness in the Mandoul focus (Chad)*. PLOS Neglected Tropical Diseases, 11 (7). pp. e0005792. doi:10.1371/journal.pntd.0005792
[3.5] NTD Modelling Consortium Discussion Group on *Gambiense* Human African Trypanosomiasis (inc. **Rock, K. S.**) (2020). *Insights from quantitative and mathematical modelling on the proposed 2030 goal for gambiense human African trypanosomiasis (gHAT)*. Gates Open Research 3 (1553). doi: 10.12688/gatesopenres.13070.2
[3.6] Irvine, M. A., Stolk, W. A., Smith, M. E., Subramanian, S., Singh, B. K., Weil, G. J., Michael, E. and **Hollingsworth, T. D.** (2017) *Effectiveness of a triple-drug regimen for global elimination of lymphatic filariasis: a modelling study*. The Lancet Infectious Diseases, 17 (4). pp. 451-458. doi:10.1016/S1473-3099(16)30467-4

Grants

[G1] Hollingsworth, T. D. (PI), **Keeling, M. J.**, Medley, G. F., **Courtenay, O.**, **Adams, E. R.** and **Torr, S.**, *NTD Modelling Consortium*. **Sponsor:** Task Force for Global Health, Inc., Novartis and Children's Investment Fund Foundation (UK) **Duration:** Jan 2015 - Aug 2017 **Award:** USD7,863,475
[G2] Hollingsworth, T. D. (PI)**, Keeling, M. J.**, **Rock, K. S.**, **Courtenay, O.** and **Spencer, S.**, *NTD Modelling Consortium: moving towards elimination*. **Sponsor:** Bill & Melinda Gates Foundation [OPP1184344] **Duration:** Nov 2017 – Nov 2021 **Award:** USD7,948,142
[G3] Rock, K. S. (PI), Hollingsworth, T. D., **Keeling, M. J.**, **Madan, J.** and Tediosi, F., *HAT Modelling and Economic Predictions for Policy (HAT MEPP)*. **Sponsor:** Bill & Melinda Gates Foundation [OPP1177824] **Duration:** Nov 2017 - Feb 2021 **Award:** USD2,295,928
[G4] Rock, K. S. (PI), **Keeling, M. J.**, **Dyson, L.**, **Madan, J.**, **Spencer, S.** and Tediosi, F. *Modelling for the HAT Endgame*. **Sponsor:** Bill & Melinda Gates Foundation [INV-005121] **Duration:** Nov 2020 – Aug 2024 **Award:** USD2,199,618
[G5] Hollingsworth, T. D. (PI), **Keeling, M. J.** and **Spencer, S.**, *Projections on eliminating NTDs (integrating mapping with modeling)*. **Sponsor:** Bill & Melinda Gates Foundation [OPP1156227] **Duration:** Nov 2016 - Oct 2018 **Award:** USD2,887,280

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

The scale of the challenge linked to neglected tropical diseases (NTDs) remains staggering: over 1,000,000,000 people remain at risk from around 10 NTDs (London Declaration on Neglected Tropical Diseases, 2012), yet to date only a single human transmissible disease – smallpox – has been eradicated by public health measures. Since 2015 Warwick's NTD modelling research has had an impact on policy formulation and implementation of gHAT elimination strategies in the DRC and Chad, two of the worst-affected countries in the world, saving or improving the quality of an approximate 740,000 lives. In the case of LF, work at Warwick was implemented in the revised 2017 WHO guidelines, which promotes mass drug administration (MDA) via a triple drug regimen. This guideline has resulted in 45,200,000 people across 11 countries being treated with triple drug therapy in 2019.

Impact on national governments: optimal strategies for gHAT elimination in DRC and Chad

Public health interventions against gHAT have been very successful: the annual number of cases fell from 25,841 in 2000 to 6,973 in 2010, and to 864 in 2019 **[5.1]**. Given this impressive progress, the WHO moved from a target of elimination of gHAT as a public health problem by 2020 to a target of elimination of transmission by 2030 **[5.1]**.

Because transmission is not directly observable from case and screening data, it must be inferred by combining this data with an appropriate model **[3.2-3.4]**. Since 2015, Rock has worked directly with the responsible public health agencies in Uganda, Cote d'Ivoire, Guinea, DRC and Chad to allow them to quantitatively gauge the impact of existing interventions on gHAT transmission. Of note, productive partnerships began in 2015 with the respective health ministries' Programme National de Lutte contre la Trypanosomiase Humaine Africaine (PNLTHA) in DRC and Chad, two of the countries worst-affected by gHAT.

DRC: PNLTHA is a specialised programme set up in the early 1990s to organise public health approaches to the disease control throughout the country. Its integrated approach includes active screening and treatment; vector control (reduction of human-tsetse fly contact); and epidemiologic surveillance, training and communication at community level.

The University of Warwick's modelling examined what combination of medical interventions (active and passive screening, as well as vector control) in the DRC would be required to meet elimination of transmission by 2030 in 168 health zones (each with an average population of 100,000) **[3.3, 5.2]**. The findings revealed six new priority health zones where large-scale vector control would be needed (Bagata, Bandundu, Bolobo, Kikongo, Kwamouth and Masi Manimba in former Bandundu province), in addition to continuing existing vector control in the Yasa Bonga health zone, in order to meet the elimination of transmission target. This contributed to PNLTHA's policy review in 2018 and the decision to implement scaled-up vector control between 2019 and 2022 **[5.2]**. These 7 health zones have some of the highest levels of gHAT in the world **[5.2]**, with an approximate total at-risk population of 700,000.

Vector control interventions for gHAT use 'Tiny Target' technology – a small (50x25cm), low cost (<$1), eco-friendly insecticide-impregnated panel of blue cloth that attracts tsetse and is planted using stakes near a body of water. In 2014 there were no such large-scale interventions in DRC, however numbers of Tiny Targets were intensified to their highest ever levels in 2020 in accordance with Warwick's modelling, with 43,000 deployments made per year spanning an area of 11,700km^2. Additionally, these deployments are planned to increase to 80,000 by 2022 **[5.2]**. The Director of PNLTHA-DRC says: "*The modelling results from [Dr Rock] and the HAT MEPP team have played a decisive role in guiding and verifying planning localised interventions against gHAT across the DRC and our confidence in achieving the elimination goal of 2030. We hope to continue this precious collaboration… and be guided by other results"* **[5.2]**.

Chad: Vector control was first implemented in 2014 in the swampy Mandoul region, which has an approximate population of 40,000, and where most gHAT cases occurred between 2000 and 2013. Adaptation of the Warwick model to Mandoul made it possible to quantify the effect of interventions (both improved passive screening and vector control). Modelling suggested that these combined measures led to a 72% reduction in transmission. Continuing implementation of these interventions saw cases gradually reduce from 715 in 2002 to fewer than 20 cases reported in 2018 and 2019 **[5.3]**

The Warwick modelling for Chad provided important validation that the approach in Mandoul was an optimal strategy **[5.3]**. The Director of PNLTHA-Chad highlighted the significance of such verification: "*Cost effective public health interventions are essential in all countries due to the huge demand for medical resources, which is especially important in a low-income country like Chad.*" With regards to meeting the 2030 elimination of transmission target for gHAT, the findings demonstrated it was "*essential to continue interventions every year in order to lead our country on the path of elimination*" **[5.3]**.

Continued BMGF funding: In a 2018 review meeting, 'Progress and Plans for Elimination and Eradication Programs for HAT and Guinea Worm', Rock met with Bill Gates and his team to present and discuss the HAT modelling work **[5.1]**. In 2020 Rock secured further grant funding, 'Modelling for the HAT Endgame' **[G4]**, with BMGF stating this was to "*assist in finding the most*

efficient strategy to success" for gHAT elimination, in the context of the WHO 2030 elimination target **[5.1]**.

Impact on international organisations: revised WHO guidelines on LF elimination

On the basis of her high-profile modelling work through the NTD Consortium **[3.1]**, in January 2017 Hollingsworth joined a guideline development group convened by WHO to re-examine its guidelines pertaining to LF elimination. Prior to 2017, mass drug administration (MDA) with double drug therapy of diethylcarbamazine and albendazole (DA) was recommended by the WHO as the preferred approach to LF elimination in endemic areas. In 2017, this group produced revised guidelines **[5.4]** that incorporated Hollingsworth's findings in recommending a switch to the 'IDA' triple drug therapy (ivermectin, trade name Mectizan, with diethylcarbamazine and albendazole). Warwick modelling allowed for the quantification of the number of annual triple therapy rounds required to meet elimination targets **[3.6]**, an assumption that is fundamental in evaluating treatment cost and hence the overall viability of the proposed regimen.

In response to the new WHO guidelines, the global pharmaceutical giant Merck Sharp & Dohme committed to donating an additional 100 million Mectizan (ivermectin) treatments annually up to 2025 to support the elimination of LF by triple-drug therapy **[5.5]**. In 2019, 201,000,000 treatments for LF were approved by Merck's Mectizan Donation Program (MDP), allowing the triple drug IDA programme to extend its coverage into 13 new countries and territories: American Samoa, Egypt, Fiji, Guyana, India, Kenya, Madagascar, Malaysia, Papua New Guinea, Samoa, Sao Tome & Principe, Timor Leste and Tuvalu **[5.5]**. In MDP's 2019 Annual Highlights, Program Director Dr Yao Sodahlon writes in his message: "*As of December 2019, the number of people no longer needing treatment with Mectizan and albendazole for elimination of LF as a public health problem increased to 163.3 million [163,300,000], from 150.9 million [150,900,000] the previous year… We will continue working [with our partners] to sustain high Mectizan treatment coverage and ensure that no one is left behind – regardless of who they are and where they live*" **[5.6]**.

In October 2020 WHO revealed that in 2019 45,200,000 people were treated with the triple-drug IDA regiment across 11 countries based on the revised guidelines **[5.7]**. This represents around 6 in every 1,000 people (based on the world's total population of 7.7 billion in 2019).

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

[5.1] Statement from the Bill and Melinda Gates Foundation
[5.2] Statement from the Director of PNLTHA-DRC (statement in French), with Rock *et al.* (2020) appended (underpinning research paper **[3.3]**)
[5.3] Statement from the Director of PNLTHA-Chad (statement in French)
[5.4] *Guideline: Alternative mass drug administration regimens to eliminate lymphatic filariasis* (WHO, 2017) https://tinyurl.com/yxpfn2pa
[5.5] *Mectizan Donation Program* webpage https://tinyurl.com/yy9cpwd8
[5.6] *Mectizan Donation Program* 2019 annual highlights https://tinyurl.com/1rqtdqvg
[5.7] *Lymphatic filariasis: reporting continued progress towards elimination as a public health problem* (WHO, 29.10.20) https://tinyurl.com/yyclylok