



OPEN LETTER

REVISED **How modelling can help steer the course set by the World Health Organization 2021-2030 roadmap on neglected tropical diseases [version 2; peer review: 2 approved]**

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Abstract

The World Health Organization recently launched its 2021-2030 roadmap, *Ending the Neglect to Attain the Sustainable Development Goals*, an updated call to arms to end the suffering caused by neglected tropical diseases. Modelling and quantitative analyses played a significant role in forming these latest goals. In this collection, we discuss the insights, the resulting recommendations and identified challenges of public health modelling for 13 of the target diseases: Chagas disease, dengue, *gambiense* human African trypanosomiasis (gHAT), lymphatic filariasis (LF), onchocerciasis, rabies, scabies, schistosomiasis, soil-transmitted helminthiasis (STH),

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Invited Reviewers

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report

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report

Taenia solium taeniasis/ cysticercosis, trachoma, visceral leishmaniasis (VL) and yaws. This piece reflects the three cross-cutting themes identified across the collection, regarding the contribution that modelling can make to timelines, programme design, drug development and clinical trials.

Keywords

Mathematical, Statistical, Targets, Public Health, Elimination, Transmission, Cross-cutting, NTD





This article is included in the [2030 goals for neglected tropical diseases](#) collection.

Invited Reviewers

1 2

report

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

Following reviewer advice, the largest change is the addition of a new paragraph in challenges, that broaches two non-mutually exclusive issues; 1) model-use hierarchy, from broad large-scale guidance to ground-level implementation and 2) model access at localised levels to aid decision making.

Other changes include the clarification of misleading text.

Any further responses from the reviewers can be found at the end of the article

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A renewed roadmap for a new decade

The World Health Organization's (WHO) 2021-2030 Neglected Tropical Disease (NTD) Roadmap was launched on January 28th, 2021, renewing the commitment of the global NTD community to end the suffering caused by these diseases¹. The development of the roadmap was guided by extensive global stakeholder consultation, including consultation with mathematical and statistical modellers. Modellers were asked to assess the technical feasibility of proposed goals, to identify major challenges for achieving the new goals from a transmission dynamics perspective, possible acceleration strategies, and key outstanding research questions². Technical commentaries have been published as a collection in Gates Open Research³⁻¹⁵, which detail these insights for 13 NTDs: Chagas disease, dengue, *gambianse* human African trypanosomiasis (gHAT), lymphatic filariasis (LF), onchocerciasis, rabies, scabies, schistosomiasis, soil transmitted helminthiasis (STH), *Taenia solium* taeniasis/cysticercosis, trachoma, visceral leishmaniasis (VL) and yaws.

Neglected tropical diseases continue to affect over one billion people¹⁶ as the result of the considerable inequalities in global healthcare systems that fail to support those most in need¹⁷. The burden of NTDs falls largely on the poorest communities, resulting in an unrelenting cycle of poverty that is driven by negative social, health and economic impacts of infection on individuals and families, augmenting existing social divides. For infections with a substantial zoonotic component, morbidity and mortality among livestock also affect people's livelihood with economic impacts that transcend medical implications. Notable progress to reduce the burden of NTDs has been made as a result of the commitments made in 2012 through the WHO 2020 NTD Roadmap¹⁸ and the London Declaration on NTDs¹⁹. As a result, 500 million people no longer require interventions against several NTDs and 40 countries, territories and areas have eliminated at least one disease¹. These wins are the outcome of concerted and consolidated efforts from endemic communities and invaluable volunteers, governments, donor agencies and the pharmaceutical industry. Despite such early gains, reaching the endgame presents some of the greatest challenges – namely

sustaining those early gains whilst identifying and averting small numbers of sparsely distributed cases. The 2030 roadmap is shaped around three pillars that aim to support global efforts to maintain the gains, address the challenges and ultimately combat NTDs¹: 1. Accelerating programmatic action. 2. Intensifying cross-cutting approaches and 3. Shifting operating models and culture to facilitate in country ownership.

The use of mathematical and statistical modelling in NTD research and policy has until recently, and with a few exceptions (e.g., onchocerciasis²⁰), lagged behind other groups of infectious diseases that receive more focus and funding (often, diseases that impact wealthier individuals and nations, or those perceived to potentially impact these). However, this is changing with the advent of groups like the NTD Modelling Consortium²¹, who have developed the Policy-Relevant Items for Reporting Models in Epidemiology of Neglected Tropical Diseases (PRIME-NTD) principles, as a guide to communicate the quality and relevance of modelling to stakeholders²⁰. This has added clout to the call for modelling in the policy arena as well as setting a high bar of best practice for the wider modelling community. Having now gained significant traction, the use of modelling in NTD policy has contributed to new intervention tools²², vector control strategies²³⁻²⁶, shaped policy responding to COVID-19-related programme disruptions²⁷⁻³⁵ and has aided in the development of WHO guidelines^{36,37}. For this positive relationship to continue, it is imperative to invest in a mutual understanding through ongoing conversation between policy-makers and modellers, to determine what kind of questions are the “right” questions, how to interpret uncertainty and what the models can and cannot be used for.

This piece introduces a collection of papers borne of a meeting in Geneva, in April 2019 attended, among others, by the NTD Modelling Consortium and convened by the WHO: *Achieving NTD control, Elimination and Eradication Targets Post-2020; Modelling Perspectives & Priorities*². As new management targets and strategies took shape, the meeting provided policy makers and modellers the space to ask and answer specific questions regarding the proposed 2030 goals and the intended strategies to achieve them. Although the roadmap covers a range of diseases with diverse epidemiologies and differing management recommendations, the priority questions identified by modelers and stakeholders during the 2019 meeting and echoed by the authors of the technical commentaries shared three similar themes that should be considered in NTD modelling moving forward: timelines, programme design, and clinical study design.

Timelines

Goals are only worth setting in the context of time. It is therefore not surprising that many of the technical commentaries in this collection identified timelines as a priority issue. The public health and economic benefits of reaching goals are innumerable but can only be achieved by the target year through appropriate mobilisation of diverse resources. Modelling in the forms of past inference and forward projections can align

many moving parts (for example epidemiological, demographic, and social considerations) to inform our understanding of the reasons why programmes succeed or fail^{38,39}. Forecasts have played a crucial role in understanding whether the 2020⁴⁰ and associated collection^{41,42}, 2025⁴³ and 2030^{3-15,34} goals can be reached under current strategies with the caveat that long-term predictions naturally become more uncertain.

In some instances, whether a goal can or will be met on time is relatively easy to ascertain – for example it is a resounding no for leprosy and rabies, which are hindered by passive case control, long quiescent incubation periods, and inadequate investment in interventions^{15,44}. Alternatively, the goals for schistosomiasis¹¹, STH⁸, and onchocerciasis¹³ seem achievable in some or most settings, depending on localised parameters like baseline prevalence, and already experienced duration of and adherence to mass drug administration (MDA) programmes. In the case of *T. solium*, a lack of internationally agreed goals for elimination or control curtails the ability to effectively model timelines; for example, the 2021-2030 NTD roadmap proposes the overall milestone of achieving “intensified control in hyperendemic areas”, without agreeing on technical definitions for *T. solium* endemicity levels, or defining measurable criteria for attaining “intensified” control¹⁴.

Programme design

The diseases considered by the London Declaration and WHO roadmaps are at differing stages in their trajectories. Whilst some are on the cusp of achieving their goals, others face political and epidemiological barriers to progress. Both scenarios raise several priority questions regarding programme design, where ‘programme’ can mean intervention or surveillance. In addition to determining success or failure within the defined intervention time frames, modelling has provided insights into key factors of operational design like the treatment coverage necessary to reach goals in a given setting. Where it may not be possible, models can be used to test the efficacy of separate and combined chemotherapeutic³⁷ and non-pharmaceutical interventions^{23,45,46}, including combined interventions that target multi-host systems for zoonotic NTDs¹⁴. Additionally, deciding the optimal timing⁴⁷ or frequency^{48,49} of treatment, and knowing who to treat^{50,51} are essential to the success of all interventions. Of course, the intervention strategies most likely to lead to achievement of the goals may not be sustainable in terms of cost to individuals, governments, or donors. By partnering highly detailed transmission models with cost-effectiveness analysis, modelling can also contribute to tailored insights regarding the affordability and benefits versus costs of interventions⁵²⁻⁶². Models can also be used to explore integration between NTD programmes, or to understand the potential cross-utility of existing NTD programmes on other helminth species, such as exploring the additional benefit of national schistosomiasis control programmes using praziquantel on *T. solium* prevalence in co-endemic areas¹⁴. Understanding this cross-utility is vital to intensifying cross-cutting approaches – one of the three core pillars of the roadmap, that differentiates the framework from its predecessor.

These are all very practical features of intervention programmes that can in principle be planned for, but underlying features of target populations and human nature can undermine this. Survey data in recent years have made it evident that whilst the aim may be to deliver treatment at a certain geographical and therapeutic coverage, it is not analogous with consumption, as treatment is systematically not ingested by some^{63,64}, or is not disseminated to the full intended group, reducing the true coverage. There are a variety of reasons for this^{65,66}, but it is likely that similar mechanisms impact participation in surveillance, therefore biasing the estimates of prevalence, particularly when treatment and surveillance are co-occurring (e.g., gHAT^{9,67}, rabies^{15,68}). Modelling shows that the impact of this variable effective coverage depends on the pathogen in question and transmission intensity^{64,69-71} but it undoubtedly has an impact on reaching public health goals^{72,73}, and on the reliability of the projected intervention intensity needed to reach them. It has also been suggested (in the context of VL though applicable beyond), that modelling results – and therefore policy based on them – may be erroneous without better capturing socio-economic and human behaviour risk factors, including feedback loops of behaviour change as a result of perceived risk⁷⁴. This also highlights the need for ongoing surveillance and the use of modelling throughout to provide real-time insight into post-intervention population-level infection dynamics.

Once a strategy has been deemed effective and prevalence targets are attained, it is likely that these interventions either transition, such as going from MDA to identified case management, or they stop all together. Establishing robust surveillance strategies at this point is vital, but obviously not everyone can be regularly sampled and not every incident infection case will be detected. Stochastic events like reinfection and reintroduction are risks that can drive resurgence. Modelling can support the identification of the optimal surveillance strategy and determine which prevalence or intensity indicators need to be monitored to ensure the desired public health goal⁷⁵⁻⁷⁷, although challenges remain in developing long-term strategies⁷⁸. Modelling can make useful contributions in developing sustainable, effective interventions and surveillance strategies and should therefore be included in any programmatic design from the start. As embodied by the 2021-2030 NTD roadmap, impactful interventions cannot be achieved by working in silos, but instead require continuous communication between all parties of an interdisciplinary team.

Drug development and clinical study design

Though modelling is increasingly used in public health decision making, the use of modelling to direct clinical trial design and drug development is not so common, and even less so for NTDs. Chemotherapeutic interventions are the cornerstone of large-scale intervention strategies to reach goals like elimination as a public health programme or elimination of transmission. Though treatment options are limited for the likes of STH, LF and trachoma, they are themselves considered sufficiently effective at reducing prevalence and

transmission. There is therefore a cautiously sanguine view that consistent application and uptake is enough to reach target public health goals^{1,4,5}. However, confidence in the existing treatment for onchocerciasis (targeted for elimination of transmission) is less apparent because the standard ivermectin dose only kills skin dwelling transmission stages with sub-optimal efficacy against adult stages. Modelling suggests this will not be sufficient to reach public health goals^{13,79}, pressing the need for novel chemotherapeutics. However, financial returns on investments into NTDs are limited and therefore largely unappealing, particularly because of the heavy reliance by endemic nations on donations from pharmaceutical producers. Increased use of mathematical modelling could reduce the financial waste associated with the drug-development-to-distribution-pipeline⁷⁹. If we consider this pipeline in three parts; pre-clinical, clinical trial and distribution, it is clear that modelling can provide valuable insight at each stage. Onchocerciasis and LF have recently benefited from pharmacokinetic-pharmacodynamics modelling, translating pre-clinical non-human experimental results into quantitative insights relevant to human treatment⁸⁰. Clinical trial simulations are designed to include all aspects of a clinical trial protocol including (but not limited to) recruitment criteria, drug properties/effectiveness and follow-up times⁸¹, providing valuable guidance that translates into more effective, efficient, cost-efficient and robust clinical trials. In addition to providing insight into the optimal distribution of new drugs⁸², rethinking the distribution of existing drugs to achieve public health targets can also be guided by modelling^{37,48}.

Challenges

Modelling has certainly addressed many of the key questions asked of modellers at the 2019 meeting². However, cross-disease challenges remain⁸³. The most common of these, highlighted by all groups involved in the meeting report² and this collection, is undoubtedly a lack of data or poor data quality. This could be because certain parameters simply cannot be measured; because of vast heterogeneity or because they have yet to be collected⁸⁴. A previous collection details the data needs to improve modelling^{51,84–94}, across the NTDs, so great detail will not be provided here. However, for example, VL has a highly variable incubation period, unknown duration of asymptomatic infection and estimates for the duration of lasting immunity are ill-defined^{6,85,95}, introducing uncertainty into the temporal dynamics underlying any projections. Chagas disease, gHAT and leprosy also suffer from relatively long, but indeterminate incubation periods^{9,12,21} impacting case detection and adding greater uncertainty in epidemiological estimates fitted to by models^{85,96}. Asymptomatic or pre-symptomatic infection is common of many NTDs and presents a significant challenge to their management. For example, asymptomatic VL infections cannot be treated, whereas it is possible to treat asymptomatic gHAT but only if it is able to be detected. Identifying their respective proportions in an infected population, particularly in the absence of high surveillance coverage, means accounting for this group using roundabout methods and proxy diagnostics^{6,9}.

Many diagnostics are indirect, proxy measures of case detection, often with less than perfect sensitivity or specificity^{97,98}, and have a direct effect on perceived prevalence and individual burdens of infection^{99,100}. Given that models are only as good as the data to which they are fitted, this has a significant impact on the utility of model results. For example, in the instances of STH and intestinal schistosomiasis (*Schistosoma mansoni*), WHO targets are given in terms of eggs per gram of faecal matter as detected with the Kato-Katz method, which notoriously suffers from poor sensitivity, particularly for low intensity infections¹⁰¹, invariably underestimating prevalence. Where a multi-host system is present for zoonotic NTDs, though it is possible to measure infection through direct observation of parasite stages in the animal host(s)¹⁴, via necropsy or other methods¹⁰², it is likely that this approach is inappropriate for monitoring and evaluating the likes of *T. solium* control programmes, due to the large animal sample sizes required to detect a statistically meaningful impact on transmission, especially in low prevalence settings¹⁴. Molecular xenomonitoring (testing vectors for the parasite instead of human hosts) for LF and onchocerciasis has shown promise¹⁰³ but operational research gaps remain, impacting large-scale utilisation¹⁰⁴. Reconciling these different streams of imperfect diagnostic data will be key to their utility in modelling and indeed to reaching and sustaining public health goals.

The operational units over which epidemiological data are collected, and projections made are also often over somewhat arbitrary administrative borders that infectious diseases do not adhere to. For rabies, non-spatial models are inadequate for capturing the low-endemicity incidence rates¹⁵ such that more data-intensive modelling approaches are required. In addition to questionable detection success, VL surveillance has operated over geographical units that are too large to evaluate the success of control methods⁶, despite modelling showing that transmission is highly localised over smaller spatial scales (i.e. 85% of inferred transmission distances $\leq 300\text{m}$)¹⁰⁵. Similarly for onchocerciasis, modelling shows that the rate at which interventions can be scaled down depend strongly on the spatial units of assessment^{13,106}. Clustering of *T. solium* porcine cysticercosis around human taeniasis carriers, particularly evident in South American communities, demonstrates the need for spatially explicit models in certain settings^{14,107}, such as the recently developed CystiAgent model for Peru¹⁰⁸, capable of testing spatially structured interventions. From this it is evident that whilst spatial heterogeneity requires nuanced model structure, the leading challenge here is the paucity of data at the spatial level necessary to parameterise the models for spatially relevant insights. This will become ever more important as all NTDs move towards low-prevalence and spatially-heterogeneous incidence patterns.

The assumptions made to overcome these uncertainties often differ across models – which then produce differing results. This is somewhat overcome by the practice of model comparison^{109,110}, which highlights important biological and population processes that impact epidemiological trajectories, Understanding

where these differences in modelling results come from and what these differences can tell us is critical to the interpretation of modelling results. This waves a clear flag for collaborative opportunities between modellers, field epidemiologists and clinicians, to generate the necessary data to inform model parameters, or provide setting-specific insight, improving projections and the cross-discipline understanding of model results. Indeed, the optimal working relationship is a synergistic pathway, where the model's needs drive data collection, the data shapes further model iterations, and these then inform policy and the outcomes at the programmatic and clinical level^{51,83–94}. Improving communication between these groups is critical to achieving the desired public health gains²⁰.

The integration of modelling across public health hierarchy is also crucial but is an ongoing challenge. Whilst leading global health bodies like the WHO use modelling results to generate broad guidance at the international level, the truth is that this one-size-fits-all approach is unlikely to sufficiently describe intervention needs in every setting, such that local decision makers may be unsure why interventions – as advised by modelling – have not reached public health targets, when to stop MDA⁷⁹, or why resurgence occurs. This is not necessarily a failure of the modelling process, but of the framework in which modelling results are used and the way in which model results are accessed. One way to overcome this, and indeed many of the above challenges, is to provide in-country/ local decisions makers with modelling tools, making clear what data are needed to provide location-specific insights. Such tools do exist and efforts to extend the availability of these are ongoing where research and public health funding allow; for gHAT across the Democratic Republic of Congo, modelling has been used to identify target health zones, accompanied by an interactive visual tool¹¹¹. A tool for LF is also available¹¹², however the authors highlight the advantages and disadvantages associated with such tools. For example, the level of expertise needed to harness the tool and interpret the results will depend on the level of automation¹¹³ – which itself creates further trade-offs between usability and correct model specification, with fewer parameters available for change within an interface, limiting calibration to local settings. There is also an increased risk of incorrect interpretation including poor understanding of uncertainty and where it comes from, which could lead to reduced trust in the results and modelling methods. It is therefore imperative to balance the availability of tools at local scales with the expertise to use the models correctly.

Conclusion

The increased use of mathematical and statistical modelling over the last decade has helped move the field of NTDs into a more quantitative space, providing the link between epidemiological concepts and observed reality. For modelling to continue to fill this role and influence decision-making, ongoing conversations and engagement between all parties will be paramount. These will, in turn, overcome the continuous challenges of data quality and access, and the consequent model assumptions

required. As programme and disease management move towards a country-ownership framework under the new roadmap, it will be key that modelling follows suit, overcoming systematic notions of knowledge ownership and challenging associated power dynamics^{114–116}. In this way, future modelling will work to support this new NTD landscape.

Data availability

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Open Peer Review

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Reviewer Report 04 February 2022

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Angus McLure 

National Centre for Epidemiology and Population Health, Australian National University, Acton, ACT, Australia

The changes implemented by the authors have addressed my (minor) reservations.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease modelling broadly, with some experience with LF but not the other NTDs covered by this letter.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 04 January 2022

<https://doi.org/10.21956/gatesopenres.14570.r31306>

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Margaret C. Baker 

Georgetown University, Washington, DC, USA

This article is an introduction to the series of articles that have been published describing the role of mathematical modelling in the development of the goals and objectives set by the World Health

Organization in the 2021-2030 roadmap for NTDs. The article provides a good overview of the series which in turn provides welcome visibility into how mathematical models informed the development of the 2030 roadmap. The article makes the case for use of modeling in regards to informing: 1) Programmatic timelines, 2) Program design and 3) Drug development.

With regard to the first 2 items (timelines and program design), the case is clearly made for the potential of modeling to inform these, at least at a global level. What is less clear is how modeling can inform decision making at a national level to answer similar questions. This would require the use of an interactive tool that can be used by NTD program managers and their partners to input their parameters (e.g. disease agent, vector species, baseline prevalence, different intervention details, etc). They would in turn be provided with predictions on timelines and answers to questions such as: what would be the impact of: increasing coverage? Reducing those never treated by x %? Adding complimentary control methods? Increasing frequency of treatment? Such tools are available for other health areas like maternal and neonatal health (e.g http://www.healthpolicyplus.com/ns/pubs/18466-18842_MHTools.pdf; <http://www.mandate4mnh.org/>; Jones-Hepler *et al.*, 2017¹)

With regards to drug development I am not aware of the need for new drugs for LF or trachoma (the references provided did not collaborate and these are not listed as challenges in the Roadmap).

As a reviewer I was asked to comment on whether the article adequately referenced different views and opinions, to which I respond, only partially. The article is authored by modellers who have a much clearer insight into the pro modelling perspective. There are still many in the NTD community who remain skeptical - due to one of the challenges that is clearly presented in this article, that is the reliability of the data on which the models are built. It would be helpful to have all the assumptions, parameters, and data sources used in the models published online in one easy-to-access place. This would enable more informed discussions to take place, across a wider group of participants, as existing evidence is weighed in making policy decisions. It would also be helpful to have a summary from this of the biggest evidence gaps - to drive research and documentation of programmatic results.

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[Publisher Full Text](#)

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: PC NTDs, implementation science, design and evaluation of infectious disease control programs

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 28 Jan 2022

Jessica Clark, University of Oxford, Old Road Campus, Headington, UK

What is less clear is how modeling can inform decision making at a national level to answer similar questions. This would require the use of an interactive tool that can be used by NTD program managers and their partners to input their parameters (e.g. disease agent, vector species, baseline prevalence, different intervention details, etc). They would in turn be provided with predictions on timelines and answers to questions such as: what would be the impact of: increasing coverage? Reducing those never treated by x %? Adding complimentary control methods? Increasing frequency of treatment? Such tools are available for other health areas like maternal and neonatal health (e.g http://www.healthpolicyplus.com/ns/pubs/18466-18842_MHTools.pdf; <http://www.mandate4mnh.org/>; Jones-Hepler et al., 2017¹)

A similar point has been raised by reviewer 1. A new final paragraph of the *Challenges* section has been added. In short, the translation of international-level policy to local-level implementation does mean that local-level specific details are often overlooked, and general policy recommendations fail to meet all conditions of that setting. Whilst providing tools locally is an obvious path to improve national (or smaller) level control, it comes with a trade-off. In making the models more user-friendly, some of the complexities that allow for fine scale tuning of certain parameters may have to become fixed, such that the insight is less specific. There is also the matter of interpretation and understandings the limitations of the models. As such, local expertise is still necessary even in the hands of decision-makers.

With regards to drug development I am not aware of the need for new drugs for LF or trachoma (the references provided did not collaborate and these are not listed as challenges in the Roadmap).

This misunderstanding was a result of poor sentence structure. We have rectified this by rewriting the opening to the *Drug development and clinical study design* section.

As a reviewer I was asked to comment on whether the article adequately referenced different views and opinions, to which I respond, only partially. The article is authored by modellers who have a much clearer insight into the pro modelling perspective. There are still many in the NTD community who remain skeptical - due to one of the challenges that is clearly presented in this article, that is the reliability of the data on which the models are built. It would be helpful to have all the assumptions, parameters, and data sources used in the models published online in one easy-to-access place. This would enable more informed discussions to take place, across a wider group of participants, as existing evidence is weighed in making policy decisions. It would also be helpful to have a summary from this of the biggest evidence gaps - to drive research and documentation of programmatic results.

It is out with the scope of this article to provide a thorough overview of the data needs to improve modelling insights. There is however a PLoS NTD collection that was cited in the main text. To make this clearer, text has been added to the *Challenges* section, directing the reader to this in-depth collection. With regards to the assumptions, parameters and data sources; these are provided in every publication that presents modelling results, and the code for each model is public. These are not included here because there are no models specifically presented here.

Competing Interests: No competing interests were disclosed.

Reviewer Report 14 December 2021

<https://doi.org/10.21956/gatesopenres.14570.r31527>

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Angus McLure 

National Centre for Epidemiology and Population Health, Australian National University, Acton, ACT, Australia

This open letter summarises the contributions of (infectious) disease modelling to inform elimination efforts for Neglected Tropical Diseases (NTDs), highlighting key areas of contributions (timelines/forecasts/predictions, Programme/intervention/surveillance design, and drug development) and naming some of the key challenges. To be frank, it appears to me the kind of letter that doesn't fit very well into the peer-review paradigm as the goal is primarily to introduce a collection of papers. However, I have tried to answer the peer-review questions as posed and provide constructive feedback where I can. I should note that my relevant area of knowledge is mostly around LF and infectious disease modelling more broadly, so my review is skewed towards topics most relevant to LF.

Regarding the correctness of all statements, to my knowledge, nearly all the statements are correct. However, I would like to highlight one statement which seemed at odds with the literature. The line comes in paragraph 10: 'To reach goals like elimination as a public health

programme (trachoma, STH, schistosomiasis and LF) and elimination of transmission (onchocerciasis) novel drug development will be critical'. With regards to LF, I don't agree with this statement, i.e. I don't think new drug development is critical for the elimination of LF as a public health problem. Moreover the statement appears to contradict the Consortium's recent paper specifically on LF elimination targets (NTD Modelling Consortium Lymphatic Filariasis Group, 2019¹). From my knowledge of LF, the existing drugs (ivermectin, albendazole, and diethylcarbamazine) work well and as long as drugs are matched to the setting, side effects are not major concerns. The Consortium's existing work suggests that the 2030 goals can be achieved with these existing drugs if programmes can effectively deliver enough rounds of MDA before 2030. The main barrier to this elimination campaign is achieving high coverage (with the existing drugs) and reaching areas or people who have consistently low treatment coverage. Even a 100% effective and safe medicine won't help if some people or foci aren't being treated. Whether this criticism can be extended to the other diseases mentioned here is beyond my knowledge. This is the only point in the paper I have real reservations about.

I have indicated in my review that the letter only *partly* references differing views and opinions. Though I don't think this represents a major defect of the letter, I should explain why I chose this response. As the main thrust of the letter is that modelling has been and can continue to be useful for directing elimination efforts, presenting differing views and opinions would involve finding examples of where models have *misdirected* elimination efforts or sharing the opinions those who hold that 'models are a waste of time'. While I have certainly come across those who hold the latter view, they tend not to express their view in the form of citable literature, so the absence of their opinions is perhaps to be expected! However, as regards instances where models have misdirected elimination efforts, given the large volume of literature covered, there are probably examples of this — i.e. where a model recommended an intervention that turned out to be far from adequate. Whether these examples are publicly available and known to the authors is another question. If they know of good examples, the authors might consider including these, perhaps with a note about how these failures have informed future modelling work.

Having said all this, I think the 'challenges' section of the paper covers the major challenges reasonably enough. This section can perhaps be improved by giving more examples of how these challenges translate into things that models *cannot* or have not yet been able to do; currently the section feels a little too modelling-centric rather than programme-centric. An example of something models have not been able to do (that I am aware of) is around critical prevalence thresholds for LF/oncho elimination. Various models investigating these have found that the critical threshold varies substantially based on setting-specific assumptions. However, knowing that the threshold will be different in different settings doesn't really help you pick a target threshold that's appropriate for *your* setting. And since there haven't been resources in place to fit models to every setting, we have ended up with the very crude 1%/2% prevalence thresholds which will be unnecessarily low in some settings and too high in others (e.g. places with high and highly heterogenous biting rates). This to me is an example not of the failure of *modellers*, but a limitation of modelling as an approach to help inform *specific* interventions/programmes. You might argue that the 1%/2% thresholds are targets not *necessarily* meant to be identified with critical transmission tipping points. However my reading of the non-modelling literature and conversations with non-modellers suggests that many people believe that the 1%/2% target thresholds entail the interruption of transmission and that many believe that the universal application of these thresholds have a rigorous evidence base. Moreover, discussion of resurgence often blame failure to achieve the threshold rather than suggesting that the threshold

might be wrong for the setting. Again this perhaps points to a failure of communication rather than a failure of the modelling itself, but as this letter is about how modelling informs practice, this example (or better example along a similar line) may be relevant for inclusion (if they can manage to express it more succinctly than I have!).

A final minor point:

P10. Misplaced comma in "by endemic nations, on donations".

References

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Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease modelling broadly, with some experience with LF but not the other NTDs covered by this letter.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 28 Jan 2022

Jessica Clark, University of Oxford, Old Road Campus, Headington, UK

Regarding the correctness of all statements, to my knowledge, nearly all the statements are correct. However, I would like to highlight one statement which seemed at odds with the literature. The line comes in paragraph 10: 'To reach goals like elimination as a public health programme (trachoma, STH, schistosomiasis and LF) and elimination of

transmission (onchocerciasis) novel drug development will be critical'. With regards to LF, I don't agree with this statement, i.e. I don't think new drug development is critical for the elimination of LF as a public health problem. Moreover the statement appears to contradict the Consortium's recent paper specifically on LF elimination targets (NTD Modelling Consortium Lymphatic Filariasis Group, 2019¹). From my knowledge of LF, the existing drugs (ivermectin, albendazole, and diethylcarbamazine) work well and as long as drugs are matched to the setting, side effects are not major concerns. The Consortium's existing work suggests that the 2030 goals can be achieved with these existing drugs if programmes can effectively deliver enough rounds of MDA before 2030. The main barrier to this elimination campaign is achieving high coverage (with the existing drugs) and reaching areas or people who have consistently low treatment coverage. Even a 100% effective and safe medicine won't help if some people or foci aren't being treated. Whether this criticism can be extended to the other diseases mentioned here is beyond my knowledge. This is the only point in the paper I have real reservations about.

The reference to LF was with regards to the fact that it has been targeted for elimination as a public health problem, rather than the need for new therapeutics specifically for LF. However, we acknowledge that the sentence was misleading and have rewritten the opening to the *Drug development and clinical study design* section.

I have indicated in my review that the letter only partly references differing views and opinions. Though I don't think this represents a major defect of the letter, I should explain why I chose this response. As the main thrust of the letter is that modelling has been and can continue to be useful for directing elimination efforts, presenting differing views and opinions would involve finding examples of where models have misdirected elimination efforts or sharing the opinions those who hold that 'models are a waste of time'. While I have certainly come across those who hold the latter view, they tend not to express their view in the form of citable literature, so the absence of their opinions is perhaps to be expected! However, as regards instances where models have misdirected elimination efforts, given the large volume of literature covered, there are probably examples of this — i.e. where a model recommended an intervention that turned out to be far from adequate. Whether these examples are publicly available and known to the authors is another question. If they know of good examples, the authors might consider including these, perhaps with a note about how these failures have informed future modelling work.

The second paragraph of *Programme design* highlighted some of the ways in which inherent features of the target populations (largely related to behaviour – adherence, treatment access etc) can impact the model projections. This has been made more explicit with the addition of a specific example regarding VL.

Having said all this, I think the 'challenges' section of the paper covers the major challenges reasonably enough. This section can perhaps be improved by giving more examples of how these challenges translate into things that models cannot or have not yet been able to do; currently the section feels a little too modelling-centric rather than programme-centric. An example of something models have not been able to do (that I am aware of) is around critical prevalence thresholds for LF/oncho elimination. Various models investigating these have found that the critical threshold varies substantially based on setting-specific assumptions. However, knowing that the threshold will be different in different settings doesn't really help you pick a target threshold that's appropriate for your setting. And since there haven't been resources in place to fit models to every setting, we have ended up with the very crude 1%/2% prevalence thresholds which will be unnecessarily low in some settings and too high in others (e.g. places with high and highly heterogenous biting rates). This to me is an example not of the failure of modellers, but a limitation of modelling as an approach to help inform specific interventions/programmes. You might argue that the 1%/2% thresholds are targets not necessarily meant to be identified with critical transmission tipping points. However my reading of the non-modelling literature and conversations with non-modellers suggests that many people believe

that the 1%/2% target thresholds entail the interruption of transmission and that many believe that the universal application of these thresholds have a rigorous evidence base. Moreover, discussion of resurgence often blame failure to achieve the threshold rather than suggesting that the threshold might be wrong for the setting. Again this perhaps points to a failure of communication rather than a failure of the modelling itself, but as this letter is about how modelling informs practice, this example (or better example along a similar line) may be relevant for inclusion (if they can manage to express it more succinctly than I have!).

This is an interesting point and, if we have distilled it correctly, we completely agree. What you describe is perhaps not so much a failure of modelling, or something models cannot do, but is a symptom of the framework in which we apply mathematical modelling to NTDs. Large-scale international-level policy and guidance is the outcome of mathematical models that are indeed fit to data from specific locations, likely using more than one model, however it is unlikely that this insight will adequately describe all settings. So, there is a disparity across the public health hierarchy from international-level modelling use to a local level. The point you raise about non-modellers then using certain values as wrote is, as you rightfully state, an outcome of communication and understanding. This is a nuanced point connected to local access to, and use of, models. Reviewer two has raised the point that a discussion should be had in this letter around the topic of making models available as tools. These two comments are not mutually exclusive. We have therefore addressed them simultaneously in an new final paragraph of the *Challenges* section.

A final minor point:

P10. Misplaced comma in "by endemic nations, on donations".

This has been rectified, thank you.

Competing Interests: No competing interests were disclosed.