Abstract: Despite many current interventions against neglected tropical diseases (NTDs) being highly cost effective, new strategies are needed to reach the World Health Organization's control and elimination goals. Here we argue for the importance of incorporating economic evaluations of new strategies in decisions regarding resource allocation. Such evaluation should ideally be conducted using dynamic transmission models that capture inherent nonlinearities in transmission and the indirect benefits ('herd effects') of interventions. A systematic review of mathematical models that have been used for economic analysis of interventions against the ten NTDs covered by the London Declaration reveals that only 16 out of 49 studies used dynamic transmission models, highlighting a fundamental - but addressable - gap in the evaluation of interventions against NTDs.
Danielle Loughlin,
Editor
*Trends in Parasitology*

Dear Dr Loughlin,

Thank you very much for considering our manuscript entitled “*Neglected tools for neglected diseases: mathematical models in economic evaluations*”.

We are very grateful to the referees and editors for their comments, and have endeavoured to address them in the revised manuscript which we now submit.

We look forward to hearing from you.

Yours sincerely,

[Hugo Turner

Dr Hugo C. Turner (corresponding author on behalf of all authors)
Neglected tools for neglected diseases: mathematical models in economic evaluations

Corresponding Author's Institution: Imperial College London, Faculty of Medicine, School of Public Health

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Summary

Despite many current interventions against neglected tropical diseases (NTDs) being highly cost effective, new strategies are needed to reach the World Health Organization’s control and elimination goals. Here we argue for the importance of incorporating economic evaluations of new strategies in decisions regarding resource allocation. Such evaluation should ideally be conducted using dynamic transmission models that capture inherent nonlinearities in transmission and the indirect benefits (‘herd effects’) of interventions. A systematic review of mathematical models that have been used for economic analysis of interventions against the ten NTDs covered by the London Declaration reveals that only 16 out of 49 studies used dynamic transmission models, highlighting a fundamental – but addressable - gap in the evaluation of interventions against NTDs.

Key words: NTDs; neglected tropical diseases, mathematical modelling; analysis theoretical models; epidemiology; control programmes; cost effectiveness; cost benefit; economic evaluation studies.
Neglected Tropical Diseases: Reaching the 2020 control and/or elimination goals

The neglected tropical diseases (NTDs) are a group of chronic, disabling, and disfiguring conditions that occur especially among the rural poor and disadvantaged urban populations [1]. These diseases cause a substantial health and economic burden on poor populations in Africa, Asia, and Latin America [1]. Latest estimations indicate NTDs cause approximately 534,000 deaths, and are responsible for 56.6 million disability-adjusted life-years (DALYs) lost, each year [2-4], although these numbers are likely to be significantly underestimated [2].

In January 2012 the United Kingdom Coalition against Neglected Tropical Diseases subscribed to the London Declaration for the control and/or elimination of ten of the highest burden NTDs by the year 2020 (Table 1) [5]. These goals were inspired by the World Health Organization’s (WHO) 2020 road map for accelerating work to overcome the global burden of NTDs [6].

The reports by the Disease Control Priorities Project (DCPP) include estimates of the cost effectiveness of interventions against diseases in the developing world (http://www.dcp-3.org/). These reports illustrate that many of the current interventions against NTDs are highly cost effective and, in several instances, are even more so than interventions against the so-called ‘big three’; malaria, tuberculosis and human immunodeficiency virus (HIV) [7, 8].

Despite this, it is also recognised that novel strategies and tools will be needed to reach the NTD control and elimination goals [5]. However, the majority of cost-effectiveness estimates (such as those presented by the DCPP [8]) are only relevant to interventions currently in use in specific epidemiological and programmatic settings, and are often not informative to the decision-making process of switching to new strategies in different settings.
In the context of the London Declaration, models will be needed to perform economic evaluations to investigate what changes in policy are required to meet the WHO 2020 goals in the most cost-effective way. The aim of this paper is to (a) highlight why this area of research should be addressed with dynamic, rather than the more commonly used static transmission models, and (b) to outline what we feel are key research needs for this area.

Mathematical models for economic evaluation

The use of mathematical models to perform economic evaluations of new health care interventions is an important tool for deciding how to allocate public-health resources [9]. Accurately parameterised mathematical models have the advantage of enabling investigation of the cost-effectiveness of various strategies in a range of different epidemiological and programmatic scenarios, and can therefore help optimise the use of resources. This is particularly important for NTDs, which are most prevalent in resource-poor settings and historically have suffered from a lack of funding (for control implementation and research), visibility, and political advocacy. Modellers must work effectively with funders and politicians who will often want to demonstrate impact quickly rather than delaying decision making while comprehensive evaluations are undertaken. Consequently, models must be flexible and versatile enough to capture the effects and accompanying uncertainties of past and ongoing intervention activities.

Static infection models

The most widely used models for economic evaluations are so-called static (infection) models, such as decision-tree and Markov models [10-13]. Such models are relatively straightforward to develop, and tend to have low computational demands, facilitating rapid simulations and accompanying sensitivity analyses [14]. In static models, individual hosts acquire infection at a rate—the so-called force of infection—which is uncoupled from the
abundance of infection (i.e. for microparasites, the number and density of infected individuals; for macroparasites, the number and density of parasites) in the population or community as a whole [10, 15, 16]. This may be an appropriate framework for non-communicable diseases, but it is not for infectious diseases where the rate of infection is inextricably linked to: a) the abundance of infection among all individuals in a population and, b) on how these individuals are connected and able to transmit infection to one another (e.g. by direct contact, by vectors, or by exposure to contaminated material in the environment).

Consequently, although static models are suitable for the evaluation of interventions that do not markedly affect the targeted parasites transmission cycle, such as those that relieve disease symptoms and sequelae but do not treat infection, or those that target a very small fraction of the vector, host, or parasite population (leaving a large infectious reservoir), they are rarely suitable for evaluating interventions that reduce levels of infection transmission in a population. **In such circumstances, static models will underestimate the impact of an intervention.**

**Dynamic transmission models**

Dynamic transmission models couple the rate of infection and the population abundance of infection by explicitly modelling the transmission cycle of the disease in question [14, 15, 17]. They involve a substantial time investment to develop, can be computationally intensive [14] and can be more difficult to parameterise (and consequently generally have greater inherent uncertainty) than static models. However, and critically, dynamic transmission models capture the so-called ‘herd effect’ (or indirect effects) of interventions targeting particular population groups. Such interventions include vaccination campaigns and school-based mass drug administration (MDA) programmes, whereby all individuals within a
population can benefit from the intervention, albeit in a differential manner, regardless of whether they are within the target group or not. Figure 1 illustrates this concept by showing that a school-based MDA programme treating children for *Ascaris lumbricoides* can have a notable indirect (herd) benefit for the untreated adults whose worm burden is also reduced over time, due to population-wide reductions in transmission. The impact of these indirect herd effects will accumulate over time as reductions in transmission affect reductions in incidence which, in turn, manifest more slowly in reduced population levels of infection. Consequently, the extent that static models underestimate the impact of transmission reducing interventions will increase over time. By the same token, static models may provide a reasonable approximation to dynamic models over a relatively short time frame. Therefore, accounting for the herd effect can be crucial to the validity, robustness and policy relevance of conclusions drawn from cost-effectiveness evaluations of interventions against transmissible diseases in general, and of NTDs in particular [14, 15, 18].

Aside from dynamic models being general applicability and appropriate for cost-effectiveness evaluations of transmissible diseases, including NTDs, they also have a number of more specific advantages over their static counterparts. First, they can be used to compare in an unbiased manner, the effectiveness of interventions which elicit very different effects on the dynamics of infection/transmission [19]. For example, ivermectin which is used a potent microfilaricide used to control River Blindness, elicits a pronounced yet transient reduction in numbers of microfilariae (the parasite transmission stage) [20], whilst doxycycline, a macrofilaricide, sterilises and kills adult worms, causing a more gradual but sustained reduction in worm burden (and microfilariae) [21-23]. Furthermore, potential prophylactic helminth vaccines [24], may induce notable long-term benefits while possibly having a relatively small initial impact compared to MDA.
Second, dynamic models can be used to evaluate the possibility of infection elimination under specific intervention strategies or intervention combinations (i.e. the reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required [25]). For this purpose, dynamic models should generally be stochastic, capturing the reality of random chance in demographic and transmission processes. This is because such random variation becomes increasingly important in determining whether a disease is eliminated as infection is decreased to very low levels, a process known as ‘stochastic fade-out’. By contrast, in (non-stochastic) deterministic models, all events occur in a pre-specified way depending on the parameter values and initial conditions of the model, ignoring the effects of chance. Stochastic models are particularly relevant to NTDs as goals shift from control to elimination because new interventions are likely to be more expensive than current tools and may only be deemed cost-effective if they lead to elimination faster, avoiding future costs [26].

Lastly, the transmission of macroparasites (such as the causative agents of guinea worm, schistosomiasis, river blindness, lymphatic filariasis and soil-transmitted helminthiasis) is often governed by density-dependent processes (Box 1) [27-29] which makes the effect of control interventions on transmission often highly non-linear (Figure 2), i.e. decreasing the mean parasite load by 50%, may not decrease transmission by 50%. This means that the indirect benefits of treatment on the reduction in transmission will depend on the number and distribution of parasites between hosts [17, 30]. Consequently, these macroparasites often require dynamic transmission models tracking the intensity of the different parasite life-stages accurately to account for the impact of interventions against them [17].

Density-dependent processes may also be important regulators of microparasite population dynamics. Particularly important is the Allee effect (a positive or facilitating density-
dependent process), which gives rise to a so-called ‘breakpoint’ population density below which the infection cannot persist [31]. A study that fitted a dynamic transmission model to data on the prevalence of ocular *Chlamydia trachomatis* (aetiological agent of trachoma) before and after MDA in 24 Ethiopian villages indicated that the transmission probability was decreasing non-linearly—and more rapidly than would be expected without assistance from an Allee effect—as the prevalence of infection in the community declined [32]. Thus, the microparasite population would be less likely to recover after cessation of MDA, highlighting the potential importance of accounting for these effects when evaluating elimination strategies.

**Current models used for economic evaluations of NTD interventions**

We conducted a systematic review of mathematical modelling studies that include an economic analysis of intervention strategies for the ten NTDs under the London Declaration (Table 1). We performed a computer-assisted search of the bibliographic databases Medline, ISI Web of Knowledge, and PubMed. We imposed no language or date restrictions. The reference lists within retrieved publications were searched for articles that were not identified in our database searches. The criteria for inclusion and exclusion of studies, and the search terms are shown in Figure 3. It is beyond the scope of this paper to conduct an in-depth comparison of all studies for each disease, and thus we mainly focus on compiling a list of studies, stratified by whether they employ static infection or dynamic transmission models. A review of the methodological quality (other than model type) of economic evaluations for parasitic diseases is published elsewhere [33].

We found 49 model-based economic evaluations of NTD interventions, with half on Chagas disease and schistosomiasis. Only 16 of the identified studies used dynamic transmission models, the majority by the same small group of authors (Table 1). This is not to imply that
using a static model was always the wrong choice; this depends on both the intervention and
the parasite under investigation. However, it does highlight a methodological predilection,
which, although reasonable in certain circumstances, will increasingly become inappropriate
in the context of the elimination goals set by the London Declaration for many of the NTDs.

It is noteworthy that this bias towards static models for economic evaluations is not confined
to NTDs but a common theme in the economic analysis literature. A review by Kim and
Goldie (2008) on the cost-effectiveness of a range of different vaccination programmes also
found that most of the models used were static [14].

A research gap: dynamic models for economic evaluations

Although static models are suitable for the evaluation of interventions that do not markedly
affect the targeted parasite’s transmission cycle—such as when there is a large untargeted
reservoir of parasites or vectors, when evaluating over a short time horizon—they notably
underestimate the impact of, and thus are inappropriate for evaluating, interventions that
reduce levels of infection transmission in a population, such as MDA or vaccination
campaigns. This is particularly important when investigating elimination strategies. The lack
of dynamic models used for the economic evaluation of NTD interventions constitutes a
fundamental research gap and methodological shortcoming. This is of particular importance
in the context of NTDs which have comparatively little funding for research and policy
orientated analyses and are most prevalent in resource-poor settings. Thus, it is imperative
that appropriate analyses are conducted to guide the most cost-effective way of deploying
intervention tools and strategies [19]. Furthermore, it is important to consider that even with
the development of new drugs and other intervention tools, along with the optimisation of
existing strategies, there is unlikely to be a ‘silver bullet’ which is the optimum solution in
every situation. A more likely reality is more complicated, and one that will require different
combinations of existing strategies and the development of specific approaches depending on local conditions. For example, in areas with high pre-control endemicity of soil-transmitted helminths, it may be necessary to extend school-based deworming programmes to include adults in the community [34-36]. Dynamic transmission models can be useful tools in investigating the potential benefit and cost of different combinations of interventions in different programmatic and epidemiological scenarios, guiding the most cost-effective use of resources.

The role of dynamic models in clinical trials and enhancing Target Product Profiles

It would be beneficial to proposed trials of new interventions to recognise early in the planning process the important analytical role of dynamic models so that suitable data can be collected for parameterization and robust analysis and evaluation. In particular, data may need to be collected at a number of time points additional to those indicated for measuring primary outcomes to: a) understand the dynamics of the trialled drug’s action on the parasite and b) permit adjustment for the potential diluting effects of reinfection post drug treatment, an inevitable consequence for trials conducted in endemic settings with ongoing transmission. Furthermore, dynamic models can have a role in not only evaluating new interventions, but informing desired characteristics based on model-projected outcomes and benefits (i.e. the Target Product Profile) and helping to inform decisions on which candidates to take forward from pre-clinical to clinical development.

Development of dynamic models: Research needs and challenges

There are research requirements for the further development of dynamic models (discussed in [19, 37]) and for the accompanying and necessary economic evaluations. A summary of the key research needs is given below.
Empirical and programmatic data

A key impediment to the evaluation of NTD interventions, both in terms of economic and public-health outcomes, is the lack of longitudinal data available from large-scale and long-term control programmes [19] which are made available to modellers and analysts for model parameterization and impact evaluation. This relative paucity of empirical studies is in itself another major research gap for NTDS.

Robust economic evaluations can be fairly ‘data hungry’, ideally requiring programmatic data on pre-control endemicity from a variety of areas with different epidemiology and programmatic attributes, including levels of therapeutic coverage and systematic non-compliance over time, and the duration and type of the intervention(s) employed. In addition there needs to be an improved interaction and dialogue between modellers and those who coordinate the data collection side of control programme. More epidemiological mapping is also necessary to understand: a) the distribution of infections (and co-infections) at different programmatic levels (districts, regions etc.), potentially allowing a more geographically targeted approach to control [38], and b) how seasonal variations in transmission may vary among areas, which may influence the benefit and optimum timing of different interventions.

Programmatic data will also be crucial to validate current and future model projections and, with individual data, to understand better the impact of individual heterogeneities in responses to interventions (such as individual drug responses) on population-level benefits and cost-effectiveness.

Transmission breakpoints and surveillance strategies

Transmission breakpoints theoretically arise due to the operation of positive density dependencies (Box 1) and refer to the density (e.g. number of macroparasites per host or number of hosts infected with microparasites per unit population) below which the parasite
population cannot sustain itself and enters terminal decline [17]. Understanding the behaviour of the host–parasite system in the vicinity of these transmission breakpoints is a priority area of research [19], particularly on how different interventions may be associated with different risks of infection resurgence after they are stopped or scaled down. Also, it will be important to consider when interventions can be safely stopped based on the relationship between transmission breakpoints and operational thresholds for intervention cessation (and starting post-intervention surveillance). Economic modelling can also be helpful in informing the most cost-effective operational threshold for intervention cessation and identifying the methods for scaling down or stopping interventions, accounting for the sensitivity of the current diagnostic methods (and the potential economic value of new, more accurate ones).

Dynamic models can also be useful in investigating patterns of potential infection resurgence following cessation of control and in designing cost-effective surveillance strategies to detect this. This area will become increasingly important as progress towards the 2020 NTD goals is made.

**Health impacts**

A notable gap in research is the development of dynamic models linking infection to mortality and morbidity [19], a prerequisite for performing cost-unity analysis. More research is needed to ascertain how disease burden relates to present, past, and cumulative experience of infection (and co-infection) [19]. There is also a growing need for further development/application of more comprehensive disability metrics such as the quality-adjusted life year (QALY) which can more effectively capture the disease burden of NTD infections [39]. Moreover, it is important that other benefits of NTD control strategies, such as increased school attendance, cognitive development, increased productivity, and the prevented economic burden [40, 41] are considered.
Costs

Comprehensive costs of NTD interventions should be incorporated into the modelling analyses, in particular the relative cost of alternative/complementary strategies, which may change with scale and can be influenced by other related intervention activities. For example, the relative increase in the programme cost of increasing the treatment frequency of MDA, or using complementary focal vector control, will likely change depending on the scale that the strategy is adopted within a given geographical area (e.g. across a whole district or just in high risk areas). Additionally, further investigation into what drives pronounced variation in the costs of interventions among countries [42, 43], and how this may influence the relative costs of alternative strategies, is urgently needed. The potential increase in costs as programmes are expanded to cover hard-to-reach groups also needs consideration [44]. Moreover, multiple perspectives should be investigated, not just from the health care providers (i.e. the control programmes and non-governmental organization (NGO) donors), but also that from the pharmaceutical companies that donate or discount drugs, as different intervention strategies will influence the costs associated with these parties in different ways.

Economic evaluation framework

Many alternative intervention strategies (such as increasing treatment frequency of MDA) will be aimed at accelerating progress towards elimination, rather than delivering additional health gains. Therefore, cost-effectiveness ratios alone, which compare interventions using cost per DALY averted (or an alternative measure of health gain, such as in terms of their value for money in obtaining health gains) will not necessarily be the most informative metric by which to judge the ‘best’ or most appropriate intervention strategy. This highlights a need for a new paradigm in economic evaluation frameworks which better appraise the long-term benefits of elimination. For example, in economic evaluations it is standard practice to discount both the costs and benefits occurring in the future. However, it has been suggested
that applying a constant discount rate may undervalue the future, an important consideration when evaluating elimination strategies [45]. These economic evaluation frameworks should potentially consider the implications of using non-constant discount rates (and /or using different rates for costs and effects) [45, 46]. It is also important that future economic evaluations incorporate appropriate multivariate sensitivity analysis to investigate the robustness of their results to changes in key assumptions, as well as exploring the generalisability of their results outside of the particular programmatic and epidemiological context. Univariate sensitivity analysis (i.e. only changing one parameter value at a time) may not capture important correlations in the effects induced by different parameters [33].

The implications of integrated control

NTD interventions are increasingly becoming integrated to target more than one disease or groups of diseases at once, and there is a growing need for modelling studies evaluating alternative interventions to account for this. For instance, onchocerciasis and lymphatic filariasis intervention activities (as well as those for schistosomiasis and soil-transmitted helminthiases) are often carried out simultaneously, and therefore a change in strategy for one (such as increasing the treatment frequency) will likely have an additional impact on the other diseases in co-endemic areas. There is also an increasing drive to integrate chemotherapy-based NTD interventions with complementary socioeconomic and nutritional improvements such as WASH (water, sanitation, and hygiene) and school-feeding. However, the implications of this integration on the optimum control and monitoring and evaluation strategy (for the combination of targeted diseases) [47] and programme costs have not been fully investigated.

Model validation and comparisons

More funding and resources need to be made available for model validation; before undertaking detailed evaluations of competing intervention strategies, one must be able to
demonstrate that a model adequately describes epidemiological patterns both in endemic parasite (pathogen) populations and, crucially, in populations perturbed by control activities. This process is often held back by a lack of appropriate longitudinal data from sentinel populations. Indeed, the gathering of such data is often not prioritized highly enough despite being essential to robust policy-relevant model-based evaluations.

To inform policy in a reliable and robust manner, it will be essential that model comparison exercises are performed [19], exploring the reasons for any disparity between the results and conclusions of different models on the economic value of different control strategies.

By explicitly considering transmission, dynamic models have greater inherent uncertainty than their static counterparts, in both parameterization and structure. This makes their validation even more important. However, adequately reflecting uncertainty in our understanding of infections and their transmission dynamics has an important role in model-based decision making; policy makers should be presented with both the expectation and the accompanying uncertainty associated with epidemiological and economic projections alike.

Concluding Remarks

The lack of economic evaluations using dynamic transmission models demonstrates an important research gap and methodological shortcoming in the evaluation of NTD control and elimination interventions. This is particularly important in the context of the London Declaration, where dynamic models will be nessecessary to investigate what changes to policy are required to meet the 2020 NTD control and elimination goals. Despite being easier to develop, and more commonly used, static infection models are generally ill-suited for this undertaking, potentially generating inaccurate results leading to poor policy decisions on intervention strategies.
We believe that reaching the 2020 NTD goals will not only depend on the continuing and burgeoning implementation of existing intervention strategies, and the development of new more effective intervention tools, but also on the concomitant development of judiciously formulated and well parameterized dynamic transmission models with which to undertake economic evaluations. Such evaluations will inform policy by determining the optimum way in which intervention tools should be deployed in fundamentally resource-poor settings.

In order for this to happen effectively, a wide range of research needs should be addressed including, but not limited to: i) more empirical studies and greater availability of programmatic data to further parameterise/develop these dynamic transmission models, and to improve estimated health effects, ii) the advancement of economic evaluation frameworks and collection of detailed cost data that account for integrated NTD control programmes, and iii) rigorous model validation and comparison.

Acknowledgements:
We thank Zulma Cucunubá Pérez and Pierre Nouvellet for their comments and feedback on the Chagas disease models.

Abbreviations:
Disability-adjusted life-years (DALYs); Disease Control Priorities Project (DCPP); Human immunodeficiency virus (HIV); Mass drug administration (MDA); Neglected tropical diseases (NTDs); Non-governmental organization (NGO); Quality-adjusted life year (QALY); Water, Sanitation, and Hygiene (WASH); World Health Organization (WHO).
References


35. Truscott, J., et al., Can chemotherapy alone eliminate the transmission of soil transmitted helminths? Parasit Vectors, 2014. 7(1), 266.


Frick, K.D., et al., *Modeling the economic net benefit of a potential vaccination program against ocular infection with Chlamydia trachomatis.* Vaccine, 2004. 22(5-6), 689-696.


<table>
<thead>
<tr>
<th>Glossary</th>
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<tbody>
<tr>
<td><strong>Cost-effectiveness analysis:</strong> a method for assessing the relative gains in health generated by a health intervention compared to the costs.</td>
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<tr>
<td><strong>Disability-Adjusted Life-Years (DALYs):</strong> a time-based measure of disease burden accounting for years of life lost due to premature mortality and healthy years of life lost due to disability[48].</td>
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<tr>
<td><strong>Density dependent process:</strong> a demographic or transmission process whose rate is regulated by the density of parasites in the host or population.</td>
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<td><strong>Dynamic transmission model:</strong> a model that links the rate at which individual hosts acquire new infections with the abundance of infection among all hosts in a population.</td>
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<td><strong>Elimination of infection:</strong> reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent reestablishment of transmission are require.</td>
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<tr>
<td><strong>Neglected Tropical Diseases (NTDs):</strong> a group of chronic, disabling, and disfiguring conditions that occur especially among the rural poor and disadvantaged urban populations.</td>
</tr>
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<td><strong>Macroparasites:</strong> parasites that are large enough to be seen with the naked eye (e.g. parasitic worms) and which do not multiply directly within the definitive host.</td>
</tr>
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<td><strong>Static transmission model:</strong> a model that assumes the rate at which individual hosts acquire new infections is independent of the abundance of infection among all hosts in a population.</td>
</tr>
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<td><strong>Herd effect:</strong> the indirect benefit afforded to individuals not directly targeted by an intervention that arises from the reduction in transmission that ensues from an effective intervention.</td>
</tr>
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<td><strong>Transmission breakpoint:</strong> the (non-zero) parasite density below which a parasite population cannot maintain itself and is driven into terminal decline and eventual elimination.</td>
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Box 1 Density-dependent processes

A process is density-dependent when the rate at which it occurs is determined by the number (density) of parasites within the host or in the parasite population as a whole. These processes can either restrict or enhance transmission and can act at multiple points in a parasite’s life cycle [29].

Negative density dependence
Negative (down-regulatory, constraining or restricting) density-dependence occurs when the rate at which a process occurs decreases with increasing parasite density. For example, the per capita rate of larval development within the vectors of filarial nematodes often decreases as parasite density increases [28]. Interventions that lead to a reduction in parasite abundance can cause a relaxation of these negative density-dependent restrictions, increasing per capita rates of transmission, making parasite populations resilient to perturbation, and leading to a lower than hoped impact of an intervention.

Positive density dependence
Positive (facilitating or enhancing) density-dependent processes occur when rates increase with increasing parasite intensity. The Allee effect is an example of a positive density dependency. A more specific example is the probability that a female worm is mated within the definitive host [49] increases with parasite density as there is a greater chance of worms of different sexes finding each other and mating. Positive density-dependence can make elimination of a parasite population more likely as they can cause the reproductive success of a parasite to decrease with decreasing parasite densities giving rise to breakpoints below which the population cannot sustain itself and enters terminal decline.
Table 1: A summary of identified modelling studies presenting economic evaluations across the diseases considered by the London Declaration on NTDs.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total</th>
<th>Static Models</th>
<th>Dynamic Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea worm</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leprosy</td>
<td>2</td>
<td>0</td>
<td>2 [50, 51]</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>3</td>
<td>1 [52]</td>
<td>2 [53, 54]</td>
</tr>
<tr>
<td>Trachoma</td>
<td>4</td>
<td>3 [55-57]</td>
<td>1 [58]</td>
</tr>
<tr>
<td>Sleeping sickness</td>
<td>5</td>
<td>5 [59-63]</td>
<td>0</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>13</td>
<td>6 [64-69]</td>
<td>7 [70-76]</td>
</tr>
<tr>
<td>River blindness</td>
<td>2</td>
<td>0</td>
<td>2 [77, 78]</td>
</tr>
<tr>
<td>Soil-transmitted helminthiases</td>
<td>3</td>
<td>1 [79]</td>
<td>2 [80, 81]</td>
</tr>
<tr>
<td>Chagas</td>
<td>12</td>
<td>12 [82-93]</td>
<td>0</td>
</tr>
<tr>
<td>Visceral leishmanias</td>
<td>5</td>
<td>5 [94-98]</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>49</strong></td>
<td><strong>33</strong></td>
<td><strong>16</strong></td>
</tr>
</tbody>
</table>
Figure 1: The model projected indirect benefit of treating children (2-14 year olds) for *Ascaris lumbricoide* for untreated adults. The results were obtained using a fully aged structured deterministic dynamic transmission model, described in more detail in [35, 36]. Results assume a low transmission setting (a basic reproduction number, $R_0$, of 2) and a high coverage (80%).

Figure 2: Schematic representation of the nonlinear relationship between parasite density and transmission. The blue line indicates the situation for a linear relationship between parasite density and transmission; the red line illustrates the potential impact of negative density dependence processes on the relationship.

Figure 3: Selection criteria for inclusion and exclusion of modelling studies presenting economic evaluations of neglected tropical disease interventions. The search terms included all of the variants of the following terms: mathematical model; dynamic model static model; decision trees; cost benefit analysis; cost effectiveness analysis; economics, and economic evaluation.
Dear Editor,

Thank you very much for considering our manuscript. We greatly appreciate the reviewer’s and editor’s suggestions for improvement and have endeavoured to address the issue raised (see below).

Editor’s Comments

Editor’s comment 1. Abstract. I have below a suggested modification to the abstract that bears in mind the recommendation of the piece being most suitable as an Opinion article that brings forth the authors' perspective on a topic:

Despite many current interventions against neglected tropical diseases (NTDs) being highly cost effective, new strategies are needed to reach the World Health Organization’s control and elimination goals. Here we argue for the importance of incorporating economic evaluations of new strategies in decisions regarding resource allocation. Such evaluation should ideally be conducted using dynamic transmission models that capture inherent nonlinearities in transmission and the indirect benefits (‘herd effect’) of interventions. A systematic review of mathematical models that have been used for economic analysis of interventions against the ten NTDs covered by the London Declaration reveals that only 16 out of 49 studies used dynamic transmission models, highlighting a fundamental – but addressable – gap in the evaluation of interventions against NTDs.

Authors’ response

Thank you, for the suggested edits. We have incorporated them into the manuscript.

Editor’s comment 2. Aims of the article in the introductory section. Please add a brief paragraph at the end of the introductory section of the article that states the aims of the article (i.e. what key point does the article put forward and why is this important to discuss?). This will provide a framework so that the reader can approach the next sections of the article with these aims in mind.

Authors’ response

We have added the following to the end of the Introduction:

“In the context of the London Declaration, models will be needed to perform economic evaluations to investigate what changes in policy are required to meet the 2020 NTD goals in the most cost-effective way. The aim of this paper is to (a) highlight why this area of research should be addressed with dynamic, rather than the more commonly used static transmission models, and (b) to outline what we feel are key research needs for this area.”
Editor’s comment 3. Concluding remarks. Please include in the Concluding Remarks section a brief summary of the key points you raised in the "Research Needs" section.

Authors’ response

We have incorporated the following into the Concluding remarks.

“In order for this to happen effectively, a wide range of research needs should be addressed including, but not limited to: i) more empirical studies and greater availability of programmatic data to further parameterise/develop these dynamic transmission models, and to improve estimated health effects, ii) the advancement of economic evaluation frameworks and collection of detailed cost data that account for integrated NTD control programmes, and iii) rigorous model validation and comparison.”

Editor’s comment 4. Highlights. I have a suggested revision to the manuscript's highlights below, mainly aimed at highlighting the "Research Needs" section.

Highlights

• New strategies are needed to reach the WHO NTD control and elimination goals.
• Economic evaluations using mathematical models could improve resource allocation.
• Dynamic models are needed to account for nonlinearities in transmission.
• Challenges and research needs to address this gap are outlined.

Authors’ response

Thank you for these excellent edits. We have incorporated them into the manuscript highlights.
Referees Comments

Reviewer #1:
The authors observed that dynamic transmission models were used in only 16/49 model-based economic evaluation studies in the field of NTDs, argue that this is a fundamental research gap, and present an agenda for research. I am not convinced that this paper needs to be published now in this journal, for the following reasons:

1.1. In 2012, PLoS-NTDs publishd a series of research agenda's on helminthic diseases (as subgroup of NTDs), including one on modelling (Basanez et al). At this point, I would rather want to see new research than yet another (and not particulary renewing) review / research agenda.

Authors’ response 1.1
We feel it is important to highlight that the PLoS-NTDs review to which the Reviewer refers is only on helminthiases, where as in this paper we cover all of the NTDs considered by the London Declaration (including leprosy, trachoma, sleeping sickness, Chagas disease, and visceral leishmaniasis). Furthermore, this paper focuses on the use of models for economic evaluations (a relatively minor aspect of the PLoS NTDs review) which we believe, especially in the context of the London Declaration, will have an increasingly important role – and more so than in the past – for decision making and resource prioritisation, including investigating the most cost-effective changes to policy to meet the World Health Organization’s 2020 elimination goals.

We have endeavoured to make our assertions clearer by making changes to the Introduction and Conclusions sections of the manuscript, and by explicitly setting out the goals of the paper. Following the Editor’s suggestion, we have also changed the manuscript into an Opinion piece, rather than a Review.

1.2. The review component of this paper is very small and superficial. The authors observed that dynamic transmission models were used in only 16/49 model-based economic evaluation studies in the field of NTDs; other studies used static models. The authors acknowledge that the use of static models may not always have been the wrong choice (depending on both the intervention and the parasite under investigation), but fail to evaluate whether the choice of models has been appropriate or not.

Authors’ response 1.2
We agree with the Reviewer that the review component is relatively minor and not an integral part of the manuscript. Therefore, after discussions with the Editor, and following her recommendation, we have changed the article to an Opinion piece. In this new context, we believe that the level of detail given on the methodologies used by the articles identified by our systematic review is sufficient to support our assertion that dynamic transmission models are seldom used for the economic analysis of interventions against NTDs.

1.3. The authors present the lack of economic evaluations using mathematical models as a major, even fundamental, research gap. I would argue that there is a research gap on almost everything when it comes to the neglected diseases. I am not convinced that economic evaluations in general or economic evaluations with dynamical models are more neglected than other research aspects (at least, not by the "evidence" presented here). The more important research questions may simply be on different aspects. For me, the lack of
empirical studies in general is the more fundamental gap. Although I do agree, that mathematical models are not used to their maximum potential to inform both new research projects and control policies.

Authors’ response 1.3

We agree with the Reviewer that research on NTDs in general remains relatively overlooked and underfunded, albeit to a lesser extent now than in the past. Yet we firmly believe that to maintain the unprecedented commitment and drive by the global health community to rid the world’s most impoverished people of these diseases, it is crucial that resources are most effectively deployed and that wasteful, ineffective, or ill-suited intervention strategies are avoided. The coupling of economic evaluations to dynamic transmission models provides an essential analytical framework to achieve this broad strategic goal. We do agree with the Reviewer that the lack of empirical studies is indeed a pressing research gap, and have made greater reference to this in the text (including in the Concluding remarks).

Empirical and programmatic data

“A key impediment to the evaluation of NTD interventions, both in terms of economic and public-health outcomes, is the lack of longitudinal data from large-scale, long-term control programmes [18] which are made available to modellers and analysts for model parameterization and impact evaluation. This relative paucity of empirical studies is in itself another major research gap for NTDs.”

Concluding remarks

……

“In order for this to happen effectively, a wide range of research needs should be addressed including, but not limited to: i) more empirical studies and greater availability of programmatic data to further parameterise/develop these dynamic transmission models, and to improve estimated health effects, ii) the advancement of economic evaluation frameworks and collection of detailed cost data that account for integrated NTD control programmes, and iii) rigorous model validation and comparison.”

Reviewer #2:

This is a well written paper that argues for dynamic modelling for NTD. This is the same argument as used for vaccination programmes (see work by W. John Edmunds et al), but for a different audience. Although the paper makes a good case, it is largely from the point of view of the modellers (of which I am one). I think that I missed a novel insight, or good evidence that "proper" modelling would change the situation dramatically. As far as I can see, the case needs to be made for more analysis and data against just intervening. I have listed some points below that the authors might wish to consider when re-writing.

Authors’ response

We thank the referee for these appreciative comments.

Comment 2.1) P4 L3 - "public health resources" - perhaps a hyphen to distinguish between public-health resources and public health-resources. Also it might be worth including a
sentence or two about the relationship between political and economic objectives and the role of public health. Most of the current impetus to control NTD is from international perspective (World Bank, WHO, BMGF etc), and this perspective matters when considering the economics of control. They might, for example, be more interested in making an impact quickly rather than spending a long time doing the research to find the most cost-effective intervention for a particular situation. Modelling costs, not only in terms of direct resources, but also in terms of potential delays to decision making - is it worth this cost from the perspective of the funders?

**Authors’ response 2.1**

We have added the hyphen as suggested to allay any ambiguity and discussion regarding relationship between political and economic objectives.

“The use of mathematical models to perform economic evaluations of new health care interventions is an important tool for deciding how to allocate public-health resources [9]. Accurately parameterised mathematical models have the advantage of enabling investigation of the cost effectiveness of various strategies in a range of different epidemiological and programmatic scenarios, and can therefore help optimise the use of resources. This is particularly important for NTDs, which are most prevalent in resource-poor settings and historically have suffered from a lack of funding (for control implementation and research), visibility, and political advocacy. Modellers must work effectively with funders and politicians who will often want to demonstrate impact quickly rather than delaying decision making while comprehensive evaluations are undertaken. Consequently, models must be flexible and versatile enough to capture the effects and accompanying uncertainties of past and ongoing intervention activities.”

Comment 2.2) - Static models are fine if they are only considering a one-time intervention in a narrow time window. The failure comes when they don't consider the time effects - future incidence is dependent on current incidence (which is dependent on current prevalence). Inclusion of the time dimension in the discussion of static infection models would be welcome.

**Authors’ response 2.2**

We agree and have added more discussion regarding time dimension into the manuscript.

“However, and critically, dynamic transmission models capture the so-called ‘herd effect’ (or indirect effects) of interventions targeting particular population groups. Such interventions include vaccination campaigns and school-based mass drug administration (MDA) programmes, whereby all individuals within a population can benefit from the intervention, albeit in a differential manner, regardless of whether they are within the target group or not. Figure 1 illustrates this concept by showing that a school-based MDA programme treating children for *Ascaris lumbricoides* can have a notable indirect (herd) benefit for the untreated adults whose worm burden is also reduced over time, due to population-wide reductions in transmission. The impact of these indirect herd effects will accumulate over time as reductions in transmission affect reductions in incidence which, in turn, manifest more slowly in reduced population levels of infection. Consequently, the extent that static models underestimate the impact of transmission reducing interventions will increase over
time. By the same token, static models may provide a reasonable approximation to
dynamic models over a relatively short time frame.”

“Although static models are suitable for the evaluation of interventions that do not
markedly affect the targeted parasites transmission cycle—such as when there is a
large untargeted reservoir of parasites or vectors, \textit{when evaluating over a short time
horizon}—they notably underestimate the impact of, and thus are inappropriate for
evaluating, interventions that reduce levels of infection transmission in a population,
such as MDA or vaccination campaigns. This is particularly important when
investigating elimination strategies.”

Comment 2.3) - Dynamic models generally have greater inherent uncertainty because of the
difficulties of parameterization and structure. This model uncertainty is probably a better
measure of real uncertainty than that which can be gained from static models. The paper
would be improved by explicitly mentioning uncertainty in decision making based on models
- the models should not only get the expectation right, they should get the risk of different
outcomes right as well.

Authors’ response 2.3

We agree with the Reviewer on this very important point and we have incorporated it in the
revised manuscript.

\textit{Model validation and comparisons}

“By explicitly considering transmission, dynamic models have greater inherent
uncertainty than their static counterparts, in both parameterization and structure. This
makes their validation even more important. However, adequately reflecting
uncertainty in our understanding of infections and their transmission dynamics has an
important role in model-based decision making; policy makers should be presented
with both the expectation and the accompanying uncertainty associated with
epidemiological and economic projections alike.”

Comment 2.4)-Elimination. The London Declaration et al. have generally confused the
concept of elimination. Some of what is written here presumes the original definition
"Reduction to zero of the incidence of a specified disease (/infection) in a defined
geographical area as a result of deliberate efforts; continued intervention measures are
required”. However, the current 2020 goals are written as "elimination as a public health
problem” which is defined as control in the original definition. What is written here is
conflating the confusion. Precision of these ideas will become an increasingly important issue
as incidence is reduced. I think that you should at least define here what you mean, and that
should include the reference the Dahlem conference that defined it. I actually think that this
confusion over the term elimination is exactly what models are good at avoiding.
Authors’ response 2.4

We have added into the manuscript and the glossary the definition of elimination as articulated at the Dahlem conference (along with the reference). We have also removed reference to the London Declaration in this section to avoid confusion.

“Second, dynamic models can be used to evaluate the possibility of infection elimination under specific intervention strategies or intervention combinations (i.e. the reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required [Added Suggested reference]. For this purpose, dynamic models should generally be stochastic, capturing the reality of random chance in demographic and transmission processes. This is because such random variation becomes increasingly important in determining whether a disease is eliminated as infection is decreased to very low levels, a process known as ‘stochastic fade-out’. By contrast, in (non-stochastic) deterministic models, all events occur in a pre-specified way depending on the parameter values and initial conditions of the model, ignoring the effects of chance. Stochastic models are particularly relevant to NTDs as goals shift from control to elimination because new interventions are likely to be more expensive than current tools and may only be deemed cost effective if they lead to elimination faster, avoiding future costs [24].”

Comment 2.5) - You have argued (quite well) above that a static model is almost always wrong. Static models are always wrong for vaccination, and will seriously under-estimate the impact for any other intervention.

Authors’ response 2.5

We agree with the Reviewer that it is important to state explicitly that static models will underestimate the impact of interventions which reduce transmission in a population and are being evaluated over a considerable timespan. As the Reviewer suggests, this is particularly relevant to vaccination campaigns but also to MDA programmes. We have modified that text in several places to emphasize this important point.

“Consequently, although static models are suitable for the evaluation of interventions that do not markedly affect the targeted parasite’s transmission cycle, such as those that relieve disease symptoms and sequelae but do not treat infection, or those that target a very small fraction of the vector, host, or parasite population (leaving a large infectious reservoir), they are rarely suitable for evaluating interventions that reduce levels of infection transmission in a population. In such circumstances, static models will underestimate the impact of an intervention.”

“Although static models are suitable for the evaluation of interventions that do not markedly affect the targeted parasite’s transmission cycle—such as when there is a large untargeted reservoir of parasites or vectors or when evaluating over a very narrow time horizon—they notably underestimate the impact of, and are thus inappropriate for evaluating, interventions that reduce levels of infection transmission in a population, such as MDA or vaccination campaigns. This is particularly important when investigating elimination strategies.”

Comment 2.6) - Have transmission breakpoints ever been demonstrated, or are they only a theoretical construct? Are they actually useful in control terms? More important, I suggest, is the modeling of potential patterns of resurgence, and the surveillance required to detect them.
Authors’ response 2.6

To demonstrate a transmission breakpoint one would have to first suppress, with an effective intervention strategy, a parasite population to extremely low but detectable levels and then, withholding the intervention, observe the residual parasite population decline to local extinction. By these criteria, transmission breakpoints have not been demonstrated and consequently remain largely theoretical. Yet they remain an integral part of deterministic transmission models (much less so in stochastic models) which could otherwise not strictly be used to make predictions on elimination, although empirical programmatic thresholds are sometimes used as an alternative given the theoretical and unproven nature of the breakpoints. In practice, theoretical breakpoints are not used as an explicit goal for intervention campaigns and we agree with the Reviewer on the more important practical issue of modelling patterns of potential resurgence and the necessary surveillance to detect this after cessation of an intervention. We have added this to the research needs section.

Transmission breakpoints and surveillance strategies

“Transmission breakpoints theoretically arise due to the operation of positive density dependencies (Box 1) and refer to the density…….”

“Dynamic models can also be useful in investigating patterns of potential infection resurgence following cessation of control and in designing cost-effective surveillance strategies to detect this. This area will become increasingly important as progress towards the 2020 NTD goals is made.”

Comment 2.7) Research Needs - personally I think that the validation of models is a step that is too often ignored and has a negative impact on the use of models. There needs to be more funding for the relatively boring task of showing why a particular model should be believed. However, validation is usually held back by lack of appropriate data.

Authors’ response 2.7

We agree with the Reviewer’s salient remark that model validation using appropriate data is an important research need and we have added this point into the research needs section of the revised manuscript.

Model validation and comparisons

“More funding and resources need to be made available for model validation; before undertaking detailed evaluations of competing intervention strategies, one must be able to demonstrate that a model adequately describes epidemiological patterns both in endemic parasite (pathogen) populations and, crucially, in populations perturbed by control activities. This process is often held back by a lack of appropriate longitudinal data from sentinel populations. Indeed, the gathering of such data is often not prioritized highly enough despite being essential to robust policy-relevant model-based evaluations.

Comment 2.8) - this relates back to the previous point. Why is this an "important research gap"? The prevalence of all NTD has been dramatically reduced - have models been important in this process? As a modeler, I can see the strong philosophical argument, but in
the case of NTD I am not sure that the use of modeling has been validated.

Authors’ response 2.8

We agree with the Reviewer that hitherto modelling has not played a hugely prominent role in influencing NTD control strategies (with some notable exceptions such as in onchocerciasis control) and in this sense its relevance to policy has not been truly accomplished. However, in the context of the London Declaration, and as tools to investigate what changes to policy and resource allocation need to be made to meet the demanding 2020 NTD goals, we believe that models will play a more substantial and important role than in the past. Recognising this need, the B&MGF is considering the establishment of an NTD Modelling Consortium which would fuel the development, refinement and rigorous comparison and validation of dynamic models for the diseases under the London Declaration.

We have made changes to the Introduction and Conclusions sections of the manuscript to clarify this argument and the goals of the paper (see Authors’ response 2.9).

Comment 2.9) Better to avoid hyperbole (“vital” is used three times, ”crucial” twice, “critical” three times). Usually what is meant is ”potentially important”. I don't get a sense from the paper of where the authors believe modelling should sit in the process of decision making. What are they arguing for? This comes across as a bit of a general whinge rather than clearly providing evidence that using static models gets the answer wrong, and that this has had a bad outcome.

Authors’ response 2.9

We thank the Reviewer for his/her stylistic suggestions and caution against hyperbole. We have amended the following sentences to somewhat temper the vivacity of our arguments in the revised manuscript:

“Thus, the microparasite population would be less likely to recover after cessation of MDA, highlighting the potential importance of accounting for these effects when evaluating elimination strategies.”

“Comprehensive costs of NTD interventions should be incorporated into the modelling analyses, in particular the relative cost of alternative/complementary strategies, which may change with scale and can be influenced by other related intervention activities”

“Moreover, multiple perspectives should be investigated, not just from the health care providers (i.e. the control programmes and non-governmental organization (NGO) donors), but also that from the pharmaceutical companies that donate or discount drugs, as different intervention strategies will influence the costs associated with these parties in different ways.”

“Accounting for the herd effect is potentially important to the validity, robustness and policy relevance of conclusions drawn from cost-effectiveness evaluations of interventions against transmissible diseases in general, and of NTDs in particular [14, 15, 17].”

“Programmatic data should also be used to validate current and future model projections and, with individual data, to understand better the impact of individual
heterogeneities in responses to interventions (such as individual drug responses) on population-level benefits and cost-effectiveness.”

At the suggestion of the Editor, the article has now changed from a review to an opinion piece, allowing us greater freedom to make our central argument more explicitly; namely, that static models will not be appropriate to address the current research questions in the context of the WHO’s 2020 control and elimination targets and the London Declaration

Aim

“In the context of the London Declaration, models will be needed to perform economic evaluations to investigate what changes in policy are required to meet the WHO 2020 goals in the most cost-effective way. The aim of this paper is to (a) highlight why this area of research should be addressed with dynamic, rather than the more commonly used static transmission models, and (b) to outline what we feel are key research needs for this area.”

Concluding Remarks

“The lack of economic evaluations using dynamic transmission models demonstrates an important research gap and methodological shortcoming in the evaluation of NTD control and elimination interventions. This is particularly important in the context of the London Declaration, where dynamic models will be necessary to investigate what changes to policy are required to meet the 2020 NTD control and elimination goals. Despite being easier to develop, and more commonly used, static infection models are generally ill-suited for this undertaking, potentially generating inaccurate results leading to poor policy decisions on intervention strategies.

We believe that reaching the 2020 NTD goals will not only depend on the continuing and burgeoning implementation of existing intervention strategies, and the development of new more effective intervention tools, but also on the concomitant development of judiciously formulated and well parameterized dynamic transmission models with which to undertake economic evaluations. Such evaluations will inform policy by determining the optimum way in which intervention tools should be deployed in fundamentally resource-poor settings.

In order for this to happen effectively, a wide range of research needs should be addressed including, but not limited to: i) more empirical studies and greater availability of programmatic data to further parameterise/develop these dynamic transmission models, and to improve estimated health effects, ii) the advancement of economic evaluation frameworks and collection of detailed cost data that account for integrated NTD control programmes, and iii) rigorous model validation and comparison.”
Turner et al Neglected tools for neglected diseases: mathematical models in economic evaluations

**Highlights**

- New strategies are needed to reach the WHO NTD control and elimination goals.
- Economic evaluations using mathematical models could improve resource allocation.
- Dynamic models are needed to account for nonlinearities in transmission.
- Challenges and research needs to address this gap are outlined.
Figure 1

Mean number of female worms per host

- Red line: Worm burden in school-aged children (treated)
- Dotted line: Worm burden in adults (untreated)
Figure 2

Measures of Transmission

Parasite Density

10% reduction in transmission

50% reduction in transmission

50% reduction in parasite load
681 potentially relevant articles identified

593 articles initially excluded as they were not evaluating control interventions against the relevant diseases

88 articles retrieved for more detailed review

39 articles excluded after review, as they had either no modelling or economic component

49 modelling studies conducting economic analysis

33 static models

16 dynamic models