OPEN LETTER

The roadmap towards elimination of lymphatic filariasis by 2030: insights from quantitative and mathematical modelling [version 1; peer review: 2 approved]

NTD Modelling Consortium Lymphatic Filariasis Group

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Abstract

The Global Programme to Eliminate Lymphatic Filariasis was launched in 2000 to eliminate lymphatic filariasis (LF) as a public health problem by 1) interrupting transmission through mass drug administration (MDA) and 2) offering basic care to those suffering from lymphoedema or hydrocele due to the infection. Although impressive progress has been made, the initial target year of 2020 will not be met everywhere. The World Health Organization recently proposed 2030 as the new target year for elimination of lymphatic filariasis (LF) as a public health problem. In this letter, LF modelers of the Neglected Tropical Diseases (NTDs) Modelling Consortium reflect on the proposed targets for 2030 from a quantitative perspective. While elimination as a public health problem seems technically and operationally feasible, it is uncertain whether this will eventually also lead to complete elimination of transmission. The risk of resurgence needs to be mitigated by strong surveillance after stopping interventions and sometimes perhaps additional interventions.

Keywords

Lymphatic filariasis, Elimination, NTD Modelling Consortium, mass drug administration, modelling, Sustainable Development Goals, feasibility

This article is included in the 2030 goals for neglected tropical diseases collection.

Open Peer Review

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Background

Lymphatic filariasis (LF) is a mosquito-borne neglected tropical disease (NTD) that is caused by the filarial parasites *Wuchereria bancrofti*, *Brugia malayi* and *B. timori* and occurs worldwide in tropical and subtropical areas. Infection can lead to lymphoedema, elephantiasis and hydrocele; all severely disabling, chronic conditions. Recognizing the huge socio-economic burden caused by LF and considering advances in diagnosis and treatment, the World Health Assembly adopted Resolution 50.29 in 1997, calling for global elimination of LF as a public health problem[1]. To achieve this goal, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched in 2000, with the following specific targets for 2020: 1) to interrupt transmission by annual mass drug administration (MDA) with two-drug combinations of donated antifilarial drugs, and 2) to alleviate the suffering of those affected with lymphoedema and hydrocele by offering a basic package of care[2]. The fight against LF and other NTDs was further reinforced by the London Declaration on Neglected Tropical Diseases in 2012[3] and by the adoption of the United Nations sustainable development goals (SDGs) for 2030, which include the goal to end the epidemic of neglected tropical diseases[4].

Important progress towards the goals has been made, with eleven countries having validated elimination of LF as a public health problem by 2017[2], meaning that criteria for both GPELF targets were met. In addition, ten countries were under post-treatment surveillance after having reached criteria for stopping MDA in all endemic districts, and 32 had scaled-up MDA to all districts in need of treatment. However, there were also five countries that had not yet started MDA in any of the endemic districts and thirteen countries that are treating only part of the districts in need of MDA. Moreover, in many countries, the recommended basic package of care for people with lymphoedema or hydrocele is not yet universally available. Clearly, GPELF's 2020 targets will not be met everywhere.

In consultation with the global NTD community, the World Health Organization (WHO) is currently developing new targets and milestones beyond 2020, which should be aligned with the sustainable development goals (SDGs) and should be ambitious, evidence-based and realistic[5]. Endemic country representatives, implementing partners, donors and other stakeholders were invited to provide feedback on WHO proposed milestones and targets during two rounds of online consultations (April–July 2019). For LF, WHO proposes to keep the global elimination of LF as a public health problem as the main goal, with an adapted timeline. By 2030, all countries should have completed their MDA programs, should be implementing post-MDA or post-validation surveillance, and should have implemented a minimum package of care for LF morbidity[6].

Members of the NTD Modelling Consortium were also included in the consultation process. The NTD Modelling Consortium was set up in 2014 with funding from the Bill & Melinda Gates Foundation to support ongoing efforts to control and eliminate NTDs by high-quality quantitative modelling[7]. Within this consortium, modelers working on various NTDs joined forces to address the most pressing policy questions and to accelerate innovations in the mathematical modelling of NTDs by exchanging ideas and insight. Among the consortium's key outputs is a detailed assessment across NTDs, including LF, of whether WHO's 2020 goals can be met with current strategies and where acceleration strategies are required[8,9].

In this Open Letter, we - LF specialists associated with the NTD Modelling Consortium - reflect on the proposed targets for 2030, drawing from our collective experience and modelling work by ourselves and others: how can the proposed targets be measured, are they technically and operationally feasible, what is needed to sustain the achievements, what are the main uncertainties, and what are the main risks to be mitigated in order to achieve and maintain the stated goals? A summary of key points is provided in Table 1.

Models for lymphatic filariasis

Mathematical models for infectious disease provide a mechanistic, quantitative representation of the processes involved in transmission and control, and they can be used to predict the

Table 1. Modelling insights and the feasibility of the proposed WHO 2030 targets for LF and the main challenges.

Current WHO Goal	Elimination as a public health problem (<1% microfilaria prevalence) by 2020.
2030 Target	Global elimination as a public health problem by 2030.
Is the new target technically feasible under the current disease strategy?	Yes, provided that coverage is high enough, systematic non-adherence is low, and mass drug administration (MDA) has already started.
If not, what is required to achieve the target? (updated strategy, use of new tools, etc.)	For late-starting programs: optimize coverage, use annual MDA with triple drug or biannual MDA.
Are current tools able to reliably measure the target?	Yes. Elimination as a public health problem is defined as achieved when countries have passed three consecutive transmission assessment surveys (TAS 1-3) with a pre-defined methodology.
What are the biggest unknowns?	Where and when will passing TAS lead to elimination of transmission? Are additional interventions (e.g. vector control) required to main the achievements?
What are the biggest risks?	Risk of resurgence after passing TAS and stopping MDA.

impact of interventions or to forecast future events. Several LF models are applied within the NTD modelling consortium, named EPIFIL, LYMFASIM and TRANSFIL, each with their own strengths and limitations. All models dynamically simulate LF transmission and the impact of interventions in a closed population, usually representing a village or town. However, the models are different in details, employed modelling technique, and how they are mostly applied. EPIFIL is a deterministic, population-based model, which is nowadays implemented within a Monte Carlo-based Bayesian melding framework to fit the model to local data, while capturing the remaining uncertainties in estimated parameters[10,11]. LYMFASIM[12,13] and TRANSFIL[14] are both individual-based, stochastic models, meaning that individuals in the population are explicitly represented with their own characteristics to capture within-population heterogeneities. These models can be computationally intensive, making calibration a time-consuming process, and usually the value of most parameters is fixed in model applications. Models and modelling methods are continuously improved and refined to deal with new research questions. Recent advances include the development of model-ensembling approaches (to combine predictions from multiple models)[15] and efforts to capture geospatial heterogeneities[10,16]. Outside of the modelling consortium, a geospatially-explicit model was recently developed for American Samoa, that captures the connectedness between sites via migrating humans[17]. For an explanation of modelling terminology, we refer to a recently published glossary[18].

Insights gained from modelling analyses

Measuring the target

WHO considers LF to be eliminated as a public health problem, if periodic transmission assessment surveys (TAS, with a predefined survey design) show that the average infection prevalence has been reduced and sustained below a critical threshold, expecting that transmission will eventually cease and the risk of resurgence is minimal[19]. In areas with bancroftian filariasis transmitted by *Anopheles* or *Culex*, the critical threshold has been set at 1% microfilaria (mf) prevalence in the community or 2% antigen prevalence in 6–7 year-old children; slightly lower values are used where *Aedes* is the main vector of bancroftian filariasis; for brugian filariasis, 2% antibody prevalence is used as critical threshold. Passing TAS does not necessarily mean that infection prevalence is below the threshold across the entire district; small foci with low-level residual transmission can be missed by TAS-like surveys, and additional effort is needed to detect microfoci[20]. Uncertainty about the dynamics of, and association between, different infection indicators[21] makes it difficult to quantify the risk of resurgence associated with signals of residual transmission.

Timeline to achieve the target and technical feasibility

Models have been used to examine timelines to achieving elimination as a public health problem, usually defined as mf prevalence below 1%. Modelling suggests that achieving the 1% mf prevalence target is technically feasible with the standard WHO-recommended strategy of annual MDA with a two-drug combination (diethylcarbamazine + albendazole (DA) or ivermectin +albendazole (IA)). However, the required treatment duration strongly depends on baseline endemicity and achieved coverage (here defined as percentage treated out of the total population) and may often exceed the initially anticipated 5–6 years[9]. Poor coverage severely impedes elimination programs, especially when a large group of people is systematically not treated in repeated MDA rounds (also called systematic non-adherence or systematic non-compliance)[9,22]. The risk of not achieving the 2030 targets is highest in areas with late-start MDA, high local baseline prevalence, and/or insufficient coverage.

Models were also used to explore to what extent elimination can be accelerated by using alternative strategies. Firstly, the required treatment duration can be minimized by optimizing the coverage and preventing systematic non-adherence[9,23,24]. This will enhance the impact per round and reduce the risk that residual transmission persists in an untreated population subgroup. This is particularly important for areas with a history of poor coverage. Secondly, treatment duration can likely be reduced by treating with more efficacious treatment regimens, such as a triple-drug combination of ivermectin, diethylcarbamazine and albendazole (IDA). This triple-drug combination was shown to be more efficacious than the standard two-drug regimens[25] and our modelling suggested that the required treatment duration can be reduced by a third by using IDA instead of DA[9,26]. However, using IDA is not a solution for poor coverage. Additionally, IDA is not safe in areas endemic for onchocerciasis or loiasis, and therefore cannot be used in large parts of Africa. The use of DEC-medicated salt can also be highly efficacious, but will require a completely different treatment delivery approach[27]. Thirdly, models predicted that the required treatment duration can also be reduced considerably by treating biannually (i.e. twice per year) instead of annually if coverage remains the same, assuming that a) the second round reaches some people who were missed in the first round and b) people treated twice benefit from additional chemotherapeutic effects on worms and mf[9,23,24]. However, these predictions were not confirmed by recent community intervention trials and concerns exists on feasibility of biannual campaigns in low-resources settings. Lastly, models showed that complementary vector control (enhanced coverage of insecticide-treated bednets) has little impact on the required programme duration for reducing mf prevalence below 1%, but will help to reduce risk of resurgence[24,26]. In 2017, WHO issued new guidelines on the use of alternative MDA regimens for LF elimination, informed by empirical data and modelling[28]. They recommend the use of IDA in onchocerciasis and loiasis-free areas that have not started MDA or have not yet had four rounds with effective coverage (i.e. >65% of the total population), and for areas that failed to meet epidemiological thresholds for elimination as a public health after five or more treatment rounds with effective coverage. The use of biannual MDA is not recommended.

Detailed predictions of when elimination of LF as a public health problem can be achieved in African countries, under current or alternative strategies, have been published elsewhere[24]. Accurate prediction is often difficult due to geospatial variation in and uncertainty about baseline endemicity and achieved coverage levels. Programmatic data on coverage are often unreliable due to different factors (e.g. not everyone who receives

a tablet may also swallow, uncertainty about the overall population size makes it difficult to estimate coverage as percentage, health workers and/or programme managers at different levels may be incentivized to report inflated coverage figures). Data from sentinel sites can be used to validate and constrain models[29].

Operational feasibility

A key challenge will be ensuring high effective coverage. This can be done, as shown in various studies[30–32], but preventing systematic non-adherence remains important. Although models suggest that treating biannually can be very effective to accelerate elimination, there can be a reluctance to adopt biannual MDA due to costs and logistics, so it may not always be feasible to implement. Moreover, biannual MDA at a lower coverage could exaggerate the effects of systematic non-adherence, whereas increasing coverage will decrease heterogeneity[14]. Focusing resources on achieving high coverage for annual treatment may be more resource-effective than biannual MDA with lower coverage[23].

Loiasis co-endemicity presents a severe impediment for LF elimination programs, as both diethylcarbamazine and ivermectin can cause severe side effects in people highly infected with loiasis. The World Health Organization-recommended strategy for such areas is twice-yearly MDA with albendazole alone. Early modelling of twice-yearly albendazole, guided by limited empirical data, suggests that the required treatment duration under this strategy will be longer than for annual MDA with IA or DA[9]. Test (for loiasis)-and-not-treat (those with too high *L. loa* mf) could be an alternative strategy, if LoaScopes or other rapid diagnostics to test for loiasis become available[33]. As only a small proportion of the population has to be excluded because of high *L. loa* mf density[34], this strategy will likely be successful in almost the same timespan as with standard MDA if adherence is equally good. However, this strategy may be relatively costly[35].

Ability to sustain achievement of the goal

An important question is what measures are needed after the cessation of MDA to sustain the achievements. Field studies showed that low-level transmission can continue after passing TAS[36]. Indeed, TAS can be passed with some residual infection remaining and, moreover, small foci with residual infection may be missed by TAS methodology (see above). Residual infection remaining after MDA cessation can lead to resurgence and reintroduction in areas that had been freed of LF, as was shown by a modelling framework for LF in American Samoa[17], although these findings are not necessarily generalizable to other areas with different transmission conditions. Therefore, even after validating elimination of LF as a public health problem by passing the 3rd TAS, some form of post-validation surveillance is required for early detection of possible resurgence. Quantitatively-informed guidance is needed for post-validation surveillance and for measuring elimination of transmission.

The risk of some residual infection remaining after stopping MDA will vary within treatment areas due to geospatial variation in baseline endemicity, transmission conditions (vector species, biting rate, heterogeneity in the exposure to vectors, etc.), or uptake of interventions. The risk of resurgence depends on the abundance of residual infections and the epidemiological setting. Theoretically, there is threshold prevalence below which the mating probability of any given adult worm is too low to sustain transmission, so that transmission will eventually cease to occur (elimination of transmission) even in the absence of further interventions. This breakpoint depends on specifics of the epidemiological setting, including vector species characteristics, vector abundance or local biting rate, heterogeneity in exposure to mosquito bites within the human population, density dependence in transmission processes, etc. For example, fewer vectors (e.g. through control) increase the threshold[10,11,37], whereas assortative mixing will decrease the threshold[38]. Modelling work has been conducted to assess breakpoint thresholds for mf prevalence, antigen prevalence and third-stage larvae (L3) prevalence in the vector population. Mf prevalence threshold values can be far below 1% and vary from site to site[11,24,29], and are unmeasurable in the current TAS framework. L3 prevalence in mosquitoes could be the most sensitive indicator of transmission[11], and sequential sampling approaches based on infection in vectors could be more sensitive[29]. Xenomonitoring gives a real-time indication of parasite presence and levels in communities[39–41]. When prevalence is above the breakpoint, transmission can still die out stochastically. However, the risk of failure increases with increasing prevalence[42].

Better understanding of spatial variations in transmission and uptake of interventions is critical for understanding which settings are at greatest risk of resurgence. Strengthening vector control during the endgame could reduce this risk and overcome site-to-site variation in timelines to elimination[11].

Considerations of cost

A recent systematic review found that the WHO recommended strategies for LF elimination are consistently cost-effective or cost-saving across a wide range of settings and assumptions[43]. Model projections suggest that 175 million disability-adjusted life years (DALYs) were potentially averted by the first 15 years of the GPELF, saving a possible $100.5 billion (USD) over the lifetime of the benefited cohorts[44]. Models suggest that the increased biannual treatment costs will be compensated for by shorter timescales[23]. In poor coverage areas, enhancing coverage is the most cost-effective way to accelerate success[23].

What are the main risks that need to be mitigated to achieve and maintain the stated goals?

Countries that have not started MDA will require accelerated scale-up to achieve 2030 goals[45]. The current TAS-design is likely insufficient to guarantee the eventual elimination of transmission in all the different settings; hence, clear post-MDA and post-validation surveillance guidelines are required. Some experience on this is available from low-endemic areas. Some highly endemic areas are a long way from reaching the epidemiological targets for elimination as a public health problem. Weak post-validation surveillance (e.g. due to lack of guidance, resources or motivation to find cases) may lead to late detection of resurgence and the achievement of <1% mf prevalence may be lost.

Immediate priorities for future modelling

Priorities for future modelling have been identified in discussions with representatives from WHO. Table 2 lists these

Table 2. Priorities questions identified in discussion with WHO and how modelling can help to address them.

Priority question / issue identified in discussion with WHO	How can modelling address this?
1. Identify countries where intensification of interventions is required to reach the target of elimination as a public health problem by 2030.	Use models to make spatially-explicit predictions of the end-year of MDA, considering baseline endemicity (as estimated by a geospatial model) and history of MDA (start year, frequency, achieved coverage). Compare model-based spatially-explicit predictions of the end-year of MDA with the end-year as estimated by WHO using other approaches.
2. What is the probability that there are still locations with mf prevalence >1%, in spite of passing TAS? How frequently does this occur and what are the drivers of this? Identify countries and subnational areas at highest risk.	Apply the models to simulate trends in infection in large number of villages together forming an evaluation unit, assuming that the same MDA was applied in all villages (MDA regimen, duration of MDA) and assuming variation in both baseline endemicity and achieved MDA coverage. Sample settings and children within settings according to TAS methodology. Assess under which circumstances and how frequently there are still locations with >1% mf prevalence, despite passing TAS. Investigate the same under modified TAS sampling schemes (e.g. improving site selection, adjusting critical threshold, using different diagnostics).
3. Are current criteria for stopping MDA and the design of post-MDA surveillance appropriate after treatment with IDA (instead of DA)? If not, how should they be adapted?	Similar to 2), but focusing specifically on sites using IDA instead of DA. Work with data collected in clinical and field trials of IDA to model dynamics of antigen in response to IDA in different settings and the simulate sampling.
4. What are the best ways to design post-validation surveillance to detect resurgence with limited resources?	Simulating dynamics of transmission once the <1% mf population prevalence has been met to estimate probability of and timeline to true elimination of transmission or resurgence. Identify the main drivers and early indicators of elimination of transmission and resurgence.

MDA, mass drug administration; TAS, transmission assessment surveys; IDA, ivermectin, diethylcarbamazine and albendazole; DA, diethylcarbamazine and albendazole.

priorities and briefly characterizes how modelling can help to address them.

Data availability

No data are associated with this article.

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References

1. Resolution WHA50.29: **Elimination of lymphatic filariasis as a public health problem.** Geneva: World Health Organization, 1997. (accessed 12 Sept 2019).
Reference Source

2. **Global Programme to Eliminate Lymphatic Filariasis: Progress report, 2017.** *Wkly Epidemiol Rec.* 2018; **93**(44): 589–602.
Reference Source

3. **London Declaration on Neglected Tropical Diseases.** 2012; (accessed 26 Aug 2019).
Reference Source

4. United Nations: **General Assembly Resolution A/Res/70/1: Transforming our world: the 2030 agenda for sustainable development (21 October 2015).** Seventieth session of the General Assembly; 2015.
Reference Source

5. World Health Organization: **WHO launches global consultations for a new Roadmap on neglected tropical diseases.** 2019. (accessed 26 Aug 2019).
Reference Source

6. World Health Organization: **NTD Roadmap 2021-2030.** Proposed goals and milestones for each NTD. 2019. (accessed 26 Aug 2019).
Reference Source

7. Hollingsworth TD, Adams ER, Anderson RM, *et al.*: **Quantitative analyses and modelling to support achievement of the 2020 goals for nine neglected tropical diseases.** *Parasit Vectors.* 2015; **8**(1): 630.
PubMed Abstract | Publisher Full Text | Free Full Text

8. Hollingsworth TD: **Counting Down the 2020 Goals for 9 Neglected Tropical Diseases: What Have We Learned From Quantitative Analysis and Transmission Modeling?** *Clin Infect Dis.* 2018; **66**(suppl_ 4): S237–S44.
PubMed Abstract | Publisher Full Text | Free Full Text

9. Stolk WA, Prada JM, Smith ME, *et al.*: **Are Alternative Strategies Required to Accelerate the Global Elimination of Lymphatic Filariasis? Insights From Mathematical Models.** *Clin Infect Dis.* 2018; **66**(suppl_ 4): S260–S6.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Gambhir M, Bockarie M, Tisch D, *et al.*: **Geographic and ecologic heterogeneity in elimination thresholds for the major vector-borne helminthic disease, lymphatic filariasis.** *BMC Biol.* 2010; **8**: 22.
PubMed Abstract | Publisher Full Text | Free Full Text

11. Singh BK, Michael E: **Bayesian calibration of simulation models for supporting management of the elimination of the macroparasitic disease, Lymphatic Filariasis.** *Parasit Vectors.* 2015; **8**(1): 522.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Subramanian S, Stolk WA, Ramaiah KD, *et al.*: **The dynamics of *Wuchereria bancrofti* infection: a model-based analysis of longitudinal data from Pondicherry, India.** *Parasitology.* 2004; **128**(Pt 5): 467–82.
PubMed Abstract | Publisher Full Text

13. Stolk WA, de Vlas SJ, Borsboom GJ, *et al.*: **LYMFASIM, a simulation model for predicting the impact of lymphatic filariasis control: quantification for African villages.** *Parasitology.* 2008; **135**(13): 1583–98.
PubMed Abstract | Publisher Full Text

14. Irvine MA, Reimer LJ, Njenga SM, *et al.*: **Modelling strategies to break transmission of lymphatic filariasis--aggregation, adherence and vector competence greatly alter elimination.** *Parasit Vectors.* 2015; **8**: 547.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Smith ME, Singh BK, Irvine MA, *et al.*: **Predicting lymphatic filariasis transmission and elimination dynamics using a multi-model ensemble framework.** *Epidemics.* 2017; **18**: 16–28.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Irvine MA, Kazura JW, Hollingsworth TD, *et al.*: **Understanding heterogeneities in mosquito-bite exposure and infection distributions for the elimination of lymphatic filariasis.** *Proc Biol Sci.* 2018; **285**(1871): pii: 20172253.
PubMed Abstract | Publisher Full Text | Free Full Text

17. Xu Z, Graves PM, Lau CL, *et al.*: **GEOFIL: A spatially-explicit agent-based modelling framework for predicting the long-term transmission dynamics of lymphatic filariasis in American Samoa.** *Epidemics.* 2019; **27**: 19–27.
PubMed Abstract | Publisher Full Text

18. Porgo TV, Norris SL, Salanti G, *et al.*: **The use of mathematical modeling studies for evidence synthesis and guideline development: A glossary.** *Res Synth Methods.* 2019; **10**(1): 125–33.
PubMed Abstract | Publisher Full Text | Free Full Text

19. World Health Organization: **Global Programme to Eliminate Lymphatic filariasis: monitoring and epidemiological assessment of mass drug administration. A manual for national elimination programmes.** Geneva, Switzerland: World Health Organization, 2011.
Reference Source

20. Harris JR, Wiegand RE: **Detecting infection hotspots: Modeling the surveillance challenge for elimination of lymphatic filariasis.** *PLoS Negl Trop Dis.* 2017; **11**(5): e0005610.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Irvine MA, Njenga SM, Gunawardena S, *et al.*: **Understanding the relationship between prevalence of microfilariae and antigenaemia using a model of lymphatic filariasis infection.** *Trans R Soc Trop Med Hyg.* 2016; **110**(2): 118–24.
PubMed Abstract | Publisher Full Text | Free Full Text

22. Dyson L, Stolk WA, Farrell SH, *et al.*: **Measuring and modelling the effects of systematic non-adherence to mass drug administration.** *Epidemics.* 2017; **18**: 56–66.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Stolk WA, ten Bosch QA, de Vlas SJ, *et al.*: **Modeling the impact and costs of semiannual mass drug administration for accelerated elimination of lymphatic filariasis.** *PLoS Negl Trop Dis.* 2013; **7**(1): e1984.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Michael E, Singh BK, Mayala BK, *et al.*: **Continental-scale, data-driven predictive assessment of eliminating the vector-borne disease, lymphatic filariasis, in sub-Saharan Africa by 2020.** *BMC Med.* 2017; **15**(1): 176.
PubMed Abstract | Publisher Full Text | Free Full Text

25. King CL, Suamani J, Sanuku N, *et al.*: **A Trial of a Triple-Drug Treatment for Lymphatic Filariasis.** *N Engl J Med.* 2018; **379**(19): 1801–10.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Irvine MA, Stolk WA, Smith ME, *et al.*: **Effectiveness of a triple-drug regimen for global elimination of lymphatic filariasis: a modelling study.** *Lancet Infect Dis.* 2017; **17**(4): 451–8.
PubMed Abstract | Publisher Full Text

27. Smith ME, Singh BK, Michael E: **Assessing endgame strategies for the elimination of lymphatic filariasis: A model-based evaluation of the impact of DEC-medicated salt.** *Sci Rep.* 2017; **7**(1): 7386.
PubMed Abstract | Publisher Full Text | Free Full Text

28. World Health Organization: **Guideline: alternative mass drug administration regimens to eliminate lymphatic filariasis.** Geneva: World Health Organization, 2017.
Reference Source

29. Michael E, Smith ME, Katabarwa MN, *et al.*: **Substantiating freedom from parasitic infection by combining transmission model predictions with disease surveys.** *Nat Commun.* 2018; **9**(1): 4324.
PubMed Abstract | Publisher Full Text | Free Full Text

30. Krentel A, Damayanti R, Titaley CR, *et al.*: **Improving Coverage and Compliance in Mass Drug Administration for the Elimination of LF in Two 'Endgame' Districts in Indonesia Using Micronarrative Surveys.** *PLoS Negl Trop Dis.* 2016; **10**(11): e0005027.
PubMed Abstract | Publisher Full Text | Free Full Text

31. Hodges MH, Smith SJ, Fussum D, *et al.*: **High coverage of mass drug administration for lymphatic filariasis in rural and non-rural settings in the Western Area, Sierra Leone.** *Parasit Vectors.* 2010; **3**: 120.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Weerasooriya MV, Yahathugoda CT, Wickramasinghe D, *et al.*: **Social mobilisation, drug coverage and compliance and adverse reactions in a Mass Drug Administration (MDA) Programme for the Elimination of Lymphatic Filariasis in Sri Lanka.** *Filaria J.* 2007; **6**: 11.
PubMed Abstract | Publisher Full Text | Free Full Text

33. Kamgno J, Nana-Djeunga HC, Pion SD, *et al.*: **Operationalization of the test and not treat strategy to accelerate the elimination of onchocerciasis and lymphatic filariasis in Central Africa.** *Int Health.* 2018; **10**(suppl_1): i49–i53.
PubMed Abstract | Publisher Full Text | Free Full Text

34. Kamgno J, Pion SD, Chesnais CB, *et al.*: **A Test-and-Not-Treat Strategy for Onchocerciasis in *Loa loa*-Endemic Areas.** *N Engl J Med.* 2017; **377**(21): 2044–52.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Lenk EJ, Moungui HC, Boussinesq M, *et al.*: **A test-and-not-treat strategy for onchocerciasis elimination in Loa *loa co*-endemic areas: cost analysis of a pilot in the Soa health district, Cameroon.** *Clin Infect Dis.* 2019; pii: ciz461.
PubMed Abstract | Publisher Full Text

36. Rao RU, Nagodavithana KC, Samarasekera SD, *et al.*: **A comprehensive assessment of lymphatic filariasis in Sri Lanka six years after cessation of mass drug administration.** *PLoS Negl Trop Dis.* 2014; **8**(11): e3281.
PubMed Abstract | Publisher Full Text | Free Full Text

37. Duerr HP, Dietz K, Eichner M: **Determinants of the eradicability of filarial infections: a conceptual approach.** *Trends Parasitol.* 2005; **21**(2): 88–96.
PubMed Abstract | Publisher Full Text

38. de Vos AS, Stolk WA, de Vlas SJ, *et al.*: **The effect of assortative mixing on stability of low helminth transmission levels and on the impact of mass drug administration: Model explorations for onchocerciasis.** *PLoS Negl Trop Dis.* 2018; **12**(10): e0006624.
PubMed Abstract | Publisher Full Text | Free Full Text

39. Rao RU, Samarasekera SD, Nagodavithana KC, *et al.*: **Programmatic Use of Molecular Xenomonitoring at the Level of Evaluation Units to Assess Persistence of Lymphatic Filariasis in Sri Lanka.** *PLoS Negl Trop Dis.* 2016; **10**(5): e0004722.
PubMed Abstract | Publisher Full Text | Free Full Text

40. Zaky WI, Tomaino FR, Pilotte N, *et al.*: **Backpack PCR: A point-of-collection diagnostic platform for the rapid detection of Brugia parasites in mosquitoes.** *PLoS Negl Trop Dis.* 2018; **12**(11): e0006962.
PubMed Abstract | Publisher Full Text | Free Full Text

41. Cook DAN, Pilotte N, Minetti C, *et al.*: **A superhydrophobic cone to facilitate the xenomonitoring of filarial parasites, malaria, and trypanosomes using mosquito excreta/feces. [version 1; peer review: 2 approved]** *Gates Open Res.* 2017; **1**: 7.
PubMed Abstract | Publisher Full Text | Free Full Text

42. Stolk WA, Stone C, de Vlas SJ: **Modelling lymphatic filariasis transmission and control: modelling frameworks, lessons learned and future directions.** *Adv Parasitol.* 2015; **87**: 249–91.
PubMed Abstract | Publisher Full Text

43. Gedge LM, Bettis AA, Bradley MH, *et al.*: **Economic evaluations of lymphatic filariasis interventions: a systematic review and research needs.** *Parasit Vectors.* 2018; **11**(1): 75.
PubMed Abstract | Publisher Full Text | Free Full Text

44. Turner HC, Bettis AA, Chu BK, *et al.*: **The health and economic benefits of the global programme to eliminate lymphatic filariasis (2000–2014).** *Infect Dis Poverty.* 2016; **5**(1): 54.
PubMed Abstract | Publisher Full Text | Free Full Text

45. Kastner RJ, Stone CM, Steinmann P, *et al.*: **What Is Needed to Eradicate Lymphatic Filariasis? A Model-Based Assessment on the Impact of Scaling Up Mass Drug Administration Programs.** *PLoS Negl Trop Dis.* 2015; **9**(10): e0004147.
PubMed Abstract | Publisher Full Text | Free Full Text

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Version 1

Reviewer Report 05 November 2019

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Disclaimer:

- The findings and conclusions in this report are those of the reviewer and do not necessarily represent the views of the CDC.

Summary:

- This open letter written by the Lymphatic Filariasis Group of the NTD Modelling Consortium contains a review of the mathematical models developed for lymphatic filariasis (LF) and their accomplishments to date. As stated in the background, the modelers in this consortium take the opportunity to reflect on the proposed 2030 goal targets, especially the perceived risks of not achieving global elimination of LF as a public health problem.

General comments:

- For a high-level review, sufficient detail is provided by the authors on the models. The article is clear and well-written and quantitative details are largely contained within the "Models for lymphatic filariasis" section. As a prior reviewer noted (Graves, 2019[1]), most of the career modelers for LF are included in this group, which can sometimes make it more challenging for incorporating different viewpoints, especially those based on models from outside of the Consortium. That said, the authors do an excellent job of highlighting model findings and how they have been translated into practice.

- The authors presented thoughtful plans for dealing with residual microfoci (or hotspots) of LF infection and their relation to cessation criteria for MDA. There is recent evidence of residual microfoci (or hotspots) of LF infection after many years of treatment (Biritwum *et al.*, 2016[2], Lau *et al.*, 2017[3] and Ahorlu *et al.*, 2018[4]). Priorities 2 and 3 of the modeling priorities would provide useful information on hotspot frequency, especially regarding evaluating sampling schemes. Additionally, it may be interesting for the modeling Consortium to test whether survey and response (Harris and Wiegand, 2017[5]) or surveillance and response (Bergquist *et al.*, 2015[6]) is a

viable strategy in post-TAS LF countries for eliminating hotspots and as a possible design for post-validation surveillance (priority question #4).

- I was surprised not to see a priority question on improved coverage. A theme throughout this letter is the need for sufficient chemoprophylaxis coverage and the authors importantly note that intervention modifications are not a substitute for poor coverage. Thus, coverage remains the biggest risk to achieving the 2030 targets. Ideally, mathematical modeling can be utilized to provide more tangible recommendations for programs to increase coverage. The authors note some of the successes; I wonder whether it is possible for modeling to provide insight on the best strategies to increase community participation (King *et al.*, 2011[7] and Deardorff *et al.*, 2018[8]) or to assess the feasibility and cost of broad implementation of special surveys that have been shown to increase coverage and compliance (Krentel *et al.*, 2016[9]).

- Also, I was unsure about how the spatially-explicit predictions mentioned in priority question #1 would be generated. The authors mention an agent-based model (Xu *et al.*, 2019[10]) in the “Models for lymphatic filariasis” section. Maybe the plan is to use the same model to address priority question #1. I encourage the NTD Modelling Consortium to see if geostatistical models can be used here. Model-based geostatistics (Diggle *et al.*, 2002[11]) have been implemented for prevalence mapping (Diggle and Giorgi, 2016[12]) and spatial statistical models have been used recently for LF (Moraga *et al.*, 2015[13], Eneanya *et al.*, 2018[14] and Giorgi *et al.*, 2018[15]). This includes a model integrating mathematical and statistical modeling (Moraga *et al.*, 2015[13]). The authors commented that, “better understanding of spatial variations in transmission and uptake of interventions is critical for understanding which settings are at greatest risk of resurgence,” in relation to vector control. Potentially geostatistical models could be used to find covariates associated with risk of resurgence and used to predict the probability resurgence for other locations.

Specific comments:

1. The first sentence of the last paragraph of the Background section seems like a run-on sentence.

2. Table 1, line 6, “main” should be “maintain”.

3. Table 2, title, “Priorities” should be “Priority”.

References

1. Graves PM: Peer Review Report For: The roadmap towards elimination of lymphatic filariasis by 2030: insights from quantitative and mathematical modelling [version 1; peer review: 1 approved]. *Gates Open Research*. 2019; **3** (1538). Publisher Full Text | Reference Source
2. Biritwum N, Yikpotey P, Marfo B, Odoom S, Mensah E, Asiedu O, Alomatu B, Hervie E, Yeboah A, Ade S, Hinderaker S, Reid A, Takarinda K, Koudou B, Koroma J: Persistent ‘hotspots’ of lymphatic filariasis microfilaraemia despite 14 years of mass drug administration in Ghana. *Transactions of The Royal Society of Tropical Medicine and Hygiene*. 2016; **110** (12): 690-695 Publisher Full Text
3. Lau CL, Sheridan S, Ryan S, Roineau M, Andreosso A, Fuimaono S, Tufa J, Graves PM: Detecting and confirming residual hotspots of lymphatic filariasis transmission in American Samoa 8 years after stopping mass drug administration.*PLoS Negl Trop Dis*. 2017; **11** (9): e0005914 PubMed Abstract | Publisher Full Text
4. Ahorlu C, Koka E, Adu-Amankwah S, Otchere J, de Souza D: Community perspectives on persistent

transmission of lymphatic filariasis in three hotspot districts in Ghana after 15 rounds of mass drug administration: a qualitative assessment. *BMC Public Health*. 2018; **18** (1). Publisher Full Text
5. Harris JR, Wiegand RE: Detecting infection hotspots: Modeling the surveillance challenge for elimination of lymphatic filariasis.*PLoS Negl Trop Dis*. 2017; **11** (5): e0005610 PubMed Abstract | Publisher Full Text
6. Bergquist R, Yang GJ, Knopp S, Utzinger J, Tanner M: Surveillance and response: Tools and approaches for the elimination stage of neglected tropical diseases.*Acta Trop*. 2015; **141** (Pt B): 229-34 PubMed Abstract | Publisher Full Text
7. King JD, Zielinski-Gutierrez E, Pa'au M, Lammie P: Improving community participation to eliminate lymphatic filariasis in American Samoa.*Acta Trop*. 2011; **120 Suppl 1**: S48-54 PubMed Abstract | Publisher Full Text
8. Deardorff KV, Rubin Means A, Ásbjörnsdóttir KH, Walson J: Strategies to improve treatment coverage in community-based public health programs: A systematic review of the literature.*PLoS Negl Trop Dis*. **12** (2): e0006211 PubMed Abstract | Publisher Full Text
9. Krentel A, Damayanti R, Titaley CR, Suharno N, Bradley M, Lynam T: Improving Coverage and Compliance in Mass Drug Administration for the Elimination of LF in Two 'Endgame' Districts in Indonesia Using Micronarrative Surveys.*PLoS Negl Trop Dis*. 2016; **10** (11): e0005027 PubMed Abstract | Publisher Full Text
10. Xu Z, Graves PM, Lau CL, Clements A, Geard N, Glass K: GEOFIL: A spatially-explicit agent-based modelling framework for predicting the long-term transmission dynamics of lymphatic filariasis in American Samoa.*Epidemics*. 2019; **27**: 19-27 PubMed Abstract | Publisher Full Text
11. Diggle P, Tawn J, Moyeed R: Model-based geostatistics. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*. 2002; **47** (3): 299-350 Publisher Full Text
12. Diggle P, Giorgi E: Model-Based Geostatistics for Prevalence Mapping in Low-Resource Settings. *Journal of the American Statistical Association*. 2016; **111** (515): 1096-1120 Publisher Full Text
13. Moraga P, Cano J, Baggaley RF, Gyapong JO, Njenga SM, Nikolay B, Davies E, Rebollo MP, Pullan RL, Bockarie MJ, Hollingsworth TD, Gambhir M, Brooker SJ: Modelling the distribution and transmission intensity of lymphatic filariasis in sub-Saharan Africa prior to scaling up interventions: integrated use of geostatistical and mathematical modelling.*Parasit Vectors*. 2015; **8**: 560 PubMed Abstract | Publisher Full Text
14. Eneanya OA, Cano J, Dorigatti I, Anagbogu I, Okoronkwo C, Garske T, Donnelly CA: Environmental suitability for lymphatic filariasis in Nigeria.*Parasit Vectors*. 2018; **11** (1): 513 PubMed Abstract | Publisher Full Text
15. Giorgi E, Schlüter D, Diggle P: Bivariate geostatistical modelling of the relationship betweenLoa loa prevalence and intensity of infection. *Environmetrics*. 2018; **29** (5-6). 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?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics, epidemiology, neglected tropical diseases, global health

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.

Reviewer Report 02 October 2019

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The letter reviews a large body of work (primarily conducted by the authors) on mathematical models of lymphatic filariasis (LF) with aim to reflect on the feasibility of eliminating LF as a public health concern by 2030. The authors present few other views and opinions to date since the authors represent the main modelling groups contributing to the topic. However, an earlier paper by Rebollo and Bockarie 2017 Trends Parastol is not cited, nor do they discuss why the previous prediction of elimination by 2020 was overoptimistic. The letter discusses the key challenges and unknowns that have and will continue to complicate the achievement of this goal. The authors conclude that goal is technically feasible, outlining the major improvements and upscaling of interventions that would be required. They discuss how reducing prevalence below 1% (part of the WHO definition of eliminating LF as a public health concern) relates to local elimination of transmission and the challenges inherent in maintaining prevalence below this level and designing surveillance programs that are sensitive to detect possible resurgence in a timely manner. To the best of our knowledge, all factual statements are correct and nearly all are adequately supported by arguments from the literature. Furthermore, the next steps of modelling of LF are mostly explained clearly. We point out a few of the exceptions to this below.

Table 1: “Is the new target technically feasible under the current disease strategy? Yes, provided that coverage is high enough, systematic non-adherence is low, and mass drug administration (MDA) has already started.” I agree that the modelling evidence suggests that the new target is achievable given these requirements. However, the requirements seems to contradict what the authors state in the background section i.e. that MDA *has not begun* in some countries. For example, LYMFASIM, TRANSFIL, and EPIFIL predict that in African settings where *Loa loa* is coendemic, even biannual MDA will take on average more than 10 years to reduce Mf prevalence below 1% if initial Mf prevalence exceeds 15%, 25%, or 30% respectively (Stolk et al. 2018[2]). Furthermore, there are also several high conflict or challenging countries (e.g. PNG) that are unlikely to start MDA in all endemic IUs until well after 2020.

“Clearly, GPELF’s 2020 targets will not be met everywhere.” I agree with this statement. However, while the letter to this point clearly states that we are not there now, the letter to this point doesn’t argue why success can’t be pulled off at short notice. A line stating that areas that haven’t begun MDA will need X or more years would correct this.

“Uncertainty about the dynamics of, and association between, different infection indicators makes it difficult to quantify the risk of resurgence associated with signals of residual transmission.” I believe it would be more helpful to be more explicit by briefly elaborating on the ‘different infection indicators’ – e.g. Antigen vs Mf prevalence.

“L3 prevalence in mosquitoes could be the most sensitive indicator of transmission” The following reference calculates critical prevalence thresholds (breakpoint values) below which transmission will die out without further interventions. The breakpoint for prevalence of L3 larvae mosquitos are consistently lower than prevalence of Mf in humans. I believe this is what the authors mean by ‘sensitive indicator’. The context of the sentence is a discussion of breakpoint prevalence values, however the connection to breakpoints was not immediately clear to me on a first read through. Perhaps it is better to put this in terms consistent with the rest of the paragraph, i.e. something like “L3 prevalence in mosquitoes could be the most sensitive indicator of transmission that will lead to resurgence if unchecked, as the breakpoint for L3 prevalence is much lower than the breakpoint for Mf in humans.”

“However, using IDA is not a solution for poor coverage.” Though I think I agree with what the authors mean to communicate, it should be noted that if IDA is better than DA at all IDA surely can certainly go *some* way to makeup for poorer coverage. The authors should elaborate and cite examples or models that illustrate this.

“Thirdly, models predicted that the required treatment duration can also be reduced considerably by treating biannually (i.e. twice per year) instead of annually if coverage remains the same, assuming that a) the second round reaches some people who were missed in the first round and b) people treated twice benefit from additional chemotherapeutic effects on worms and mf” I do not understand the reason for stating these two assumptions here – aren’t these also assumptions of the other studies/models with more than one round of MDA?

Table 2 Row 1. I agree that spatially-explicit models can provide very useful insights, but given the flight range of mosquitos and typical human movements, wouldn’t these kinds of model be most helpful to identify *regions within countries* (rather than whole countries) where intensification of interventions is required to reach the target of elimination?

Finally, we have also noted a few minor language issues
Table 3 column two. I do not understand the last part of the sentence “and the simulate sampling”

“WHO is currently developing new targets and milestones beyond 2020, which should be aligned with the sustainable development goals (SDGs) and should be ambitious, evidence-based and realistic” Not clear whether the authors are asserting that these targets and milestones *should* be such and such, or whether the this is one of the intentions of WHO.

Table 1:”Are additional interventions (e.g. vector control) required to main the achievements?” main -> maintain

References

1. Rebollo MP, Bockarie MJ: Can Lymphatic Filariasis Be Eliminated by 2020?. *Trends Parasitol*. **33** (2): 83-92 PubMed Abstract | Publisher Full Text
2. Stolk W, Prada J, Smith M, Kontoroupis P, de Vos A, Touloupou P, Irvine M, Brown P, Subramanian S, Kloek M, Michael E, Hollingsworth T, de Vlas S: Are Alternative Strategies Required to Accelerate the Global Elimination of Lymphatic Filariasis? Insights From Mathematical Models. *Clinical Infectious Diseases*. 2018; **66** (suppl_4): S260-S266 Publisher Full Text

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Is the Open Letter written in accessible language?
Yes

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

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Disease modeling, epidemiology, parasitology

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.