Effectiveness of a triple-drug regimen for global elimination of lymphatic filariasis: a modelling study

*Michael A Irvine, Wilma A Stolk, Morgan E Smith, Swaminathan Subramanian, Brajendra K Singh, Gary J Weil, Edwin Michael,
T Deirdre Hollingsworth*

Summary

Background Lymphatic filariasis is targeted for elimination as a public health problem by 2020. The principal approach used by current programmes is annual mass drug administration with two pairs of drugs with a good safety profile. However, one dose of a triple-drug regimen (ivermectin, diethylcarbamazine, and albendazole) has been shown to clear the transmissible stage of the helminth completely in treated individuals. The aim of this study was to use modelling to assess the potential value of mass drug administration with the triple-drug regimen for accelerating elimination of lymphatic filariasis in different epidemiological settings.

Methods We used three different transmission models to compare the number of rounds of mass drug administration needed to achieve a prevalence of microfilaraemia less than 1% with the triple-drug regimen and with current two-drug regimens.

Findings In settings with a low baseline prevalence of lymphatic filariasis (5%), the triple-drug regimen reduced the number of rounds of mass drug administration needed to reach the target prevalence by one or two rounds, compared with the two-drug regimen. For areas with higher baseline prevalence (10–40%), the triple-drug regimen strikingly reduced the number of rounds of mass drug administration needed, by about four or five, but only at moderate-to-high levels of population coverage (>65%) and if systematic non-adherence to mass drug administration was low.

Interpretation Simulation modelling suggests that the triple-drug regimen has potential to accelerate the elimination of lymphatic filariasis if high population coverage of mass drug administration can be achieved and if systematic non-adherence with mass drug administration is low. Future work will reassess these estimates in light of more clinical trial data and to understand the effect on an individual country's programme.

Funding Bill & Melinda Gates Foundation.

Introduction

Lymphatic filariasis is a neglected tropical disease caused by filarial nematodes that is prevalent in large parts of the tropics and subtropics.[1] Currently, 790 million people are at risk of the disease and 68 million are infected, with a further 20 million suffering from chronic morbidity.[2–4] In 2000, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched by WHO with the primary goal of global elimination of filariasis through mass drug administration of pairs of anthelmintic drugs (albendazole in combination with either ivermectin or diethylcarbamazine).[5] The campaign has seen unprecedented scale-up, with 22 countries currently undergoing mass drug administration at full geographic coverage and a further 18 countries in surveillance after mass drug administration. This programme was made possible by donation of diethylcarbamazine citrate by Eisai, albendazole by GlaxoSmithKline, and ivermectin by Merck.

Current guidelines require at least five rounds of mass drug administration, resulting in a microfilaraemia prevalence of less than 1%, as measured using a transmission assessment survey across an implementation unit, preceded by an initial pre-transmission assessment survey at particular sites.[6,7] These programmes have resulted in huge health gains internationally among low-income populations.[6] However, in 2014, 11 countries had yet to begin their mass drug administration programmes; moreover, some districts or other focused areas in several countries have not yet reached elimination targets despite 10 years or more of mass drug administration.[8] Several factors can lead to a programme failing to reach its targets—eg, high prevalence of filariasis, poor population coverage, partial effectiveness of drug regimens, inadequate dose received, non-adherence because of fear of side-effects, and failure for medicine to be delivered.[9–12] For these scenarios, new strategies are needed to achieve the elimination goals by 2020.

Findings of a clinical trial suggested that, by combining the three drugs used to treat lymphatic filariasis (ivermectin, diethylcarbamazine, and albendazole), improved efficacy for clearing the transmissible stage of the filarial parasite *Wuchereria bancrofti* (microfilariae) and sterilising adult filarial worms could be achieved.[13] The safety and efficacy of this promising regimen for widespread use is the subject of ongoing study. However, the triple-drug

Research in context

Evidence before this study
We searched PubMed on Sept 20, 2016, with the terms "ivermectin", "DEC", "albendazole", and "lymphatic filariasis". All studies that included ivermectin, diethylcarbamazine, and albendazole in a trial of individual clinical effectiveness for lymphatic filariasis infection were included. Findings showed that the triple-drug regimen resulted in a much stronger and more prolonged clearance of microfilaraemia. The aim of this study was to use simulation modelling to assess the potential effect of a three-drug regimen of ivermectin, diethylcarbamazine, and albendazole for accelerating elimination of lymphatic filariasis in different epidemiological settings.

Added value of this study
We used three transmission models to simulate the effect of triple-drug mass drug administration in different scenarios and with different levels of coverage to estimate the added benefit of

using ivermectin, diethylcarbamazine, and albendazole over standard two-drug regimens. Our analysis allowed us to extrapolate results from early clinical trial data to predict the likely outcome of subnational triple-drug mass drug administration programmes in different epidemiological settings.

Implications of all the available evidence
The triple-drug regimen has the potential to accelerate achievement of elimination goals for lymphatic filariasis, particularly in areas with high baseline prevalence. However, a more effective treatment will not overcome issues of poor population coverage or high systematic non-adherence in subsets of the population, because of the long lifespan of adult filarial worms. Therefore, a paradigm shift might be needed in how these programmes are rolled out to realise the potential of the triple-drug regimen and to relieve the burden of this debilitating disease.

regimen would not be suitable for all areas where lymphatic filariasis is endemic because of contra-indications for diethylcarbamazine in regions where onchocerciasis is endemic and for ivermectin in areas where loiasis is endemic. Nevertheless, a triple-drug regimen of ivermectin, diethylcarbamazine, and albendazole holds great promise.

The additional value of the triple-drug regimen at the population level—for reaching elimination targets more quickly and with fewer rounds of mass treatment compared with standard two-drug regimens—is a crucial factor in the consideration of any change in use and must be investigated for expected-use cases and scenarios. Mathematical modelling can play a part by simulating different scenarios and assessing the likely effect of a triple-drug regimen under different assumptions.

We used three state-of-the-art lymphatic filariasis trans-mission models to assess the likely effect of the triple-drug regimen of ivermectin, diethylcarbamazine, and albendazole in several scenarios, to understand the extent of any potential benefit of the triple-drug regimen over the standard two-drug strategy, and to investigate the conditions under which this benefit is most pronounced. Three models provide far greater robustness and quantification of uncertainty in prediction versus use of one model. Five broad scenarios are considered from various plausible settings in which both the dominant vector species and the baseline prevalence of microfilariae are varied to reflect the current global situation of lymphatic filariasis endemicity. These scenarios include areas where no previous mass drug administration campaign has been undertaken and those where five rounds of mass drug administration were insufficient to reduce the prevalence of infection to the target of less than 1% needed for stopping mass drug administration.

Methods
Study design
Clinical trial findings suggest that microfilariae clearance by ivermectin, diethylcarbamazine, and albendazole is likely to be 100%.[13] Ongoing studies will refine this estimate; therefore, our analysis is for the most optimistic effect. In view of the evidence from the clinical trial, we made two plausible efficacy assumptions for the new triple-drug regimen on adult worms (appendix p 2). First, we assumed that the combination of ivermectin, diethylcarbamazine, and albendazole has the same macrofilaricidal properties as albendazole and diethyl-carbamazine (55%) and the remaining worms are sterilised permanently; this assumption was denoted IDA1. Second, we assumed that ivermectin, diethylcarba-mazine, and albendazole has the same macrofilaricidal properties as albendazole and diethylcarbamazine (55%); this assumption was referred to as IDA2. These assumptions are compared with a counterfactual regimen of albendazole and diethylcarbamazine because we are only considering areas that are not co-endemic with onchocerciasis, which would prohibit use of diethylcarbamazine.

A pertinent question is, with a 100% effective regimen, whether one round of treatment would be sufficient in driving the prevalence of microfilariae below 1% (appendix p 1). To assess the effect of one round of treatment, we used a simple model of infection in which every individual has either microfilaraemia or no infection (amicrofilaraemia), and the combined regimen of ivermectin, diethylcarbamazine, and albendazole is assumed to permanently clear microfilaraemia with 100% efficacy (IDA1). This estimate was compared with the counterfactual regimen (albendazole and diethylcarbamazine), assuming no transmission and 23·1% clearance of microfilariae.[14]

Procedures

We compared three models of lymphatic filariasis transmission to analyse the projected efficacy of the triple-drug regimen of ivermectin, diethylcarbamazine, and albendazole: LYMFASIM, EPIFIL, and TRANSFIL (appendix pp 4–11).[15–18] LYMFASIM and TRANSFIL are stochastic microsimulations including detailed descriptions of individuals' burden as well as systematic non-adherence. EPIFIL is a deterministic, age-structured, population-based model of lymphatic filariasis infection including a juvenile, adult worm, and microfilariae stage as well as a larval stage in the mosquito population. All models have been fitted previously to various age-structured microfilaraemia data (age-structured cross-sectional data, trends in prevalence of microfilariae during interventions, association between prevalence of microfilariae and biting rate) and have been compared robustly with other data—eg, circulating filarial antigen prevalence.[15,16,19–21] We assessed the models at their standard parameter settings so that every model's most confident predictions could be used, as they would have been if no direct comparison with other models were available. We then compared predictions for several standardised scenarios and elucidated the causes of differences.

We presented the effect of ivermectin, diethyl-carbamazine, and albendazole in three typical scenarios, capturing a range of transmission settings (appendix p 3). First, we used an Asian setting with a 5% baseline prevalence of microfilariae, where *Culex* species are dominant (eg, India, Sri Lanka, and Indonesia). Second, we used an African setting that is not co-endemic with onchocerciasis or loiasis, with 10% baseline prevalence of microfilariae, where *Anopheles* species are dominant and bednet use is 0% or 50% (eg, Madagascar, Zambia, and Zimbabwe). Third, we used a setting of Papua New Guinea, with 40% prevalence of microfilariae, where *Anopheles* species are dominant and bednet use is 0% or 50%.

To ascertain the effect of population coverage and systematic non-adherence on the increased effectiveness of ivermectin, diethylcarbamazine, and albendazole, we did a sensitivity analysis of these two factors in the TRANSFIL model. We chose population coverage levels of 55%, 65%, and 75%. We also considered high and low systematic non-adherence, in which a randomly chosen individual's decision on adhering to mass drug administration was the same as their decision in the previous round 25% of the time (low systematic non-adherence) or 75% of the time (high systematic non-adherence).

In areas where elimination campaigns are currently failing, several reasons could account for this occurrence, but it is difficult to measure the main drivers of this behaviour. We used TRANSFIL to investigate the additional effect of ivermectin, diethylcarbamazine, and albendazole under the three main hypotheses for why a campaign might be failing to achieve its goals after several rounds of mass drug administration (appendix p 3).

The first hypothesis is that the burden of disease in the population is highly aggregated, meaning that some individuals are disproportionately more exposed than others. The second hypothesis is that strong systematic non-adherence occurs when a group of individuals consistently do not receive treatment. The third hypothesis is that poor population coverage might be present for individuals who are more highly exposed. For each possible hypothesis, we undertook five rounds of mass drug administration with the standard regimen, after which either the standard regimen was continued or the elimination campaign switched to the triple-drug regimen of ivermectin, diethylcarbamazine, and albendazole.

Statistical analysis

The primary outcome measure was the number of rounds of mass drug administration needed to reduce the prevalence of microfilariae to below 1%, as recorded 1 year after implementation (transmission assessment survey). Because two models assessed in the analysis of scenarios are stochastic in nature (LYMFASIM and TRANSFIL), and two models account for parameter uncertainty (EPIFIL and TRANSFIL), there will be uncertainty between runs. Therefore, we ran every scenario and efficacy assumption for ivermectin, diethylcarbamazine, and albendazole 200 times.

We aggregated the probability of reducing the prevalence of microfilariae to below 1% over all three models, using an equal weighting for all models. We also recorded the probabilities for the individual models.

Role of the funding source

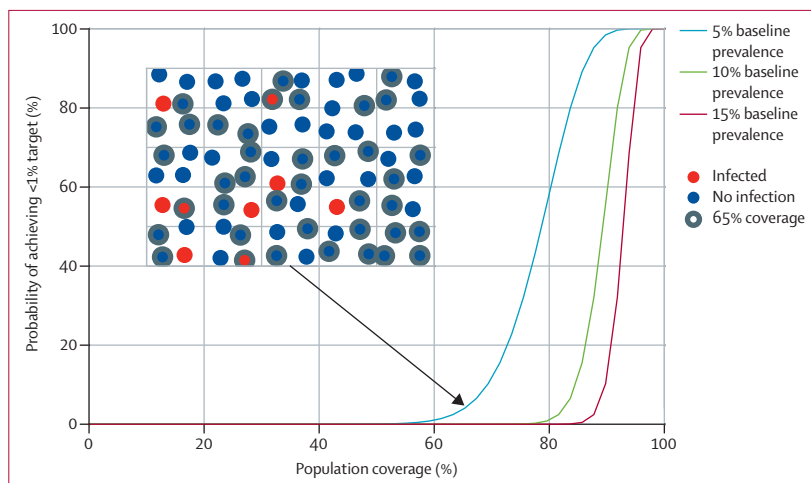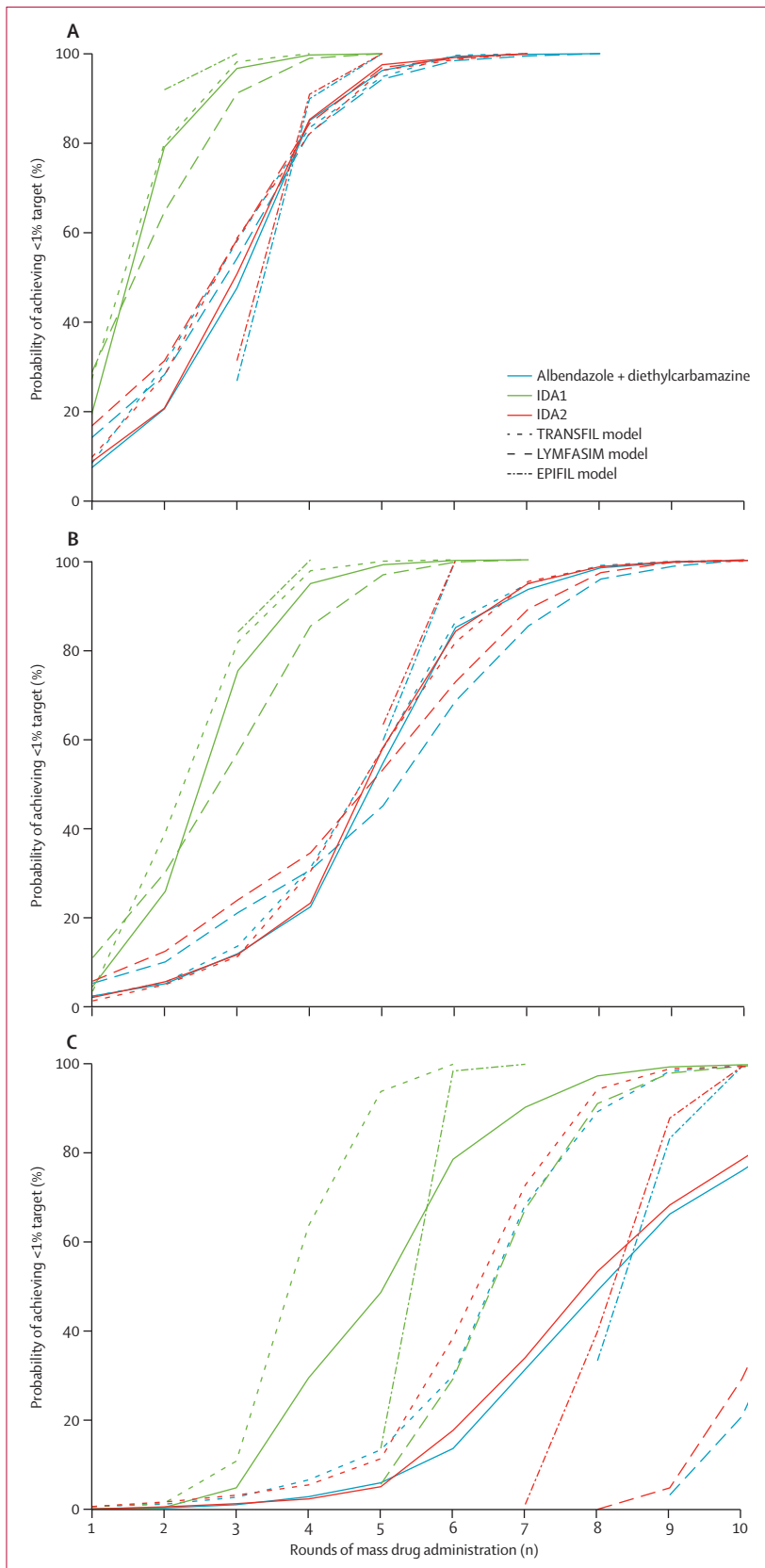The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Figure 1: **Effect of one round of triple-drug mass drug administration**
Plot shows the probability of achieving target prevalence (<1%) when baseline microfilariae prevalence is 5% (blue line), 10% (green line), and 15% (red line). (Inset) Illustration of setting with 5% prevalence (red spots), 95% not infected (amicrofilaraemia; blue spots), and 65% population coverage (black circles).

A

B

C

Albendazole + diethylcarbamazine
IDA1
IDA2
TRANSFIL model
LYMFASIM model
EPIFIL model

Rounds of mass drug administration (n)

Figure 2: **Effect of triple-drug regimen in areas with no previous mass drug administration**
Plots show the probability of achieving target prevalence (<1%) with two-drug (blue line) and triple-drug (green and red lines) regimens. Solid lines indicate a model-averaged estimate and dashed lines are estimates from the individual models. (A) Low prevalence setting (Asia, *Culex* spp, 5% baseline prevalence of microfilariae, no long-lasting insecticide-treated nets). (B) Moderate prevalence setting (Africa, not co-endemic with onchocerciasis, *Anopheles* spp, 10% baseline prevalence of microfilariae, no long-lasting insecticide-treated nets). (C) High prevalence setting (Papua New Guinea, *Anopheles* spp, 40% baseline prevalence of microfilariae, no long-lasting insecticide-treated nets). IDA1=ivermectin, diethylcarbamazine, and albendazole as efficacious as two-drug regimen and 100% worm sterilisation. IDA2=ivermectin, diethylcarbamazine, and albendazole as efficacious as two-drug regimen.

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Figure 1 shows the effect of one round of ivermectin, diethylcarbamazine, and albendazole. Even in settings with a low baseline prevalence of microfilariae, the existing target of 65% population coverage is unlikely to reduce the prevalence to below 1% with one round of ivermectin, diethylcarbamazine, and albendazole. At a microfilariae prevalence of 5%, a slight overlap can be seen between individuals who are infected and those who are treated at a coverage of 65% (figure 1, inset), resulting in too small a reduction in prevalence. As population coverage increases, the probability of reducing micro-filariae to less than 1% rises markedly; however, the probability is only more than 80% when population coverage exceeds 80%. By comparison, the counterfactual regimen of albendazole and diethylcarbamazine had negligible probability (<0·1%) of reducing prevalence of microfilariae to target levels for any level of population coverage (data not shown).

In the Asian scenario, with a low (5%) baseline prevalence of microfilariae, the probability of achieving the target of less than 1% prevalence of microfilariae was moderately high with both the triple-drug and two-drug regimens (figure 2A). After three rounds of mass drug administration, averaged across models, the probability of achieving the target prevalence with the existing two-drug regimen was 48%, compared with a 95% probability with the triple-drug regimen. However, after five rounds (the current standard protocol), the difference between the regimens was smaller (95% with the two-drug regimen *vs* 100% with the triple-drug regimen). Larger gains were observed for the African scenario, with a moderate (10%) baseline prevalence of microfilariae (figure 2B). Here, the probability of achieving the less than 1% target prevalence after five rounds of mass drug administration was 55% for the two-drug regimen compared with 98% for the most optimistic, three-drug, 100% worm sterilisation assumption (IDA1). In the Papua New Guinea scenario, with the highest (40%) baseline prevalence of microfilariae, the probability of achieving

the target prevalence of less than 1% was greater with five rounds of the triple-drug regimen than with the standard two-drug regimen (6% with the two-drug regimen *vs* 50% with the triple-drug regimen; figure 2C). When the number of rounds of mass drug administration rose to six, the triple-drug regimen increased the chances of reaching the target prevalence by a factor of five (16% *vs* 80%). Varying the proportion of worm sterilisation (90–100%) did not greatly affect the probability of reaching the threshold target (appendix p 15).

Compared with the standard two-drug regimen, the number of rounds of mass drug administration needed to achieve the less than 1% target prevalence, and the probability of a large number of rounds being needed by chance for a particular parameter set (fewer outliers in the box plots; appendix pp 12, 13), was much lower with the triple-drug regimen. The amount of variation is different for every model, but the results are qualitatively consistent. The reduction in the range of rounds between the standard two-drug regimen and the triple-drug regimen was between four and five rounds for low, moderate, and high prevalence settings. This finding can also be seen as reducing the likelihood of needing more than five rounds of mass drug administration.

Changing population coverage has a strong effect on reducing the number of rounds needed to achieve less than 1% prevalence of microfilariae, for both the triple-drug regimen of ivermectin, diethylcarbamazine, and albendazole and the two-drug regimen of albendazole and diethylcarbamazine (figure 3). Increasing coverage from 65% to 75% reduces the number of rounds needed to have a 95% probability of reaching the target prevalence, from seven to three rounds for the two-drug regimen and from three to two rounds for the triple-drug regimen. High systematic non-adherence has a striking effect on the outcome of mass drug administration with poor levels of coverage (55%) increasing the number of rounds needed to achieve 95% probability from seven to ten rounds for the two-drug regimen and four to eight rounds for the triple-drug regimen (appendix p 14). However, at higher levels of coverage (75%), the effect is less severe, with the number of rounds needed for 95% probability increasing by one for both the two-drug and three-drug regimens.

The additive effect of using long-lasting insecticide-treated nets with mass drug administration was investigated for the scenarios from Africa and Papua New Guinea, where *Anopheles* spp is the dominant vector (figure 4). Use of bednets had only a marginal effect on the number of rounds of mass drug administration needed to reach the 1% microfilariae prevalence

Figure 3: **Relative effects of population coverage and systematic non-adherence**
Plots show the probability of achieving target prevalence (<1%) with two-drug (blue line) and triple-drug (green line) regimens with high and low systematic non-adherence (dashed lines) when population coverage is (A) poor (55%), (B) standard (65%), and (C) high (75%). IDA1=ivermectin, diethylcarbamazine, and albendazole as efficacious as two-drug regimen and 100% worm sterilisation.
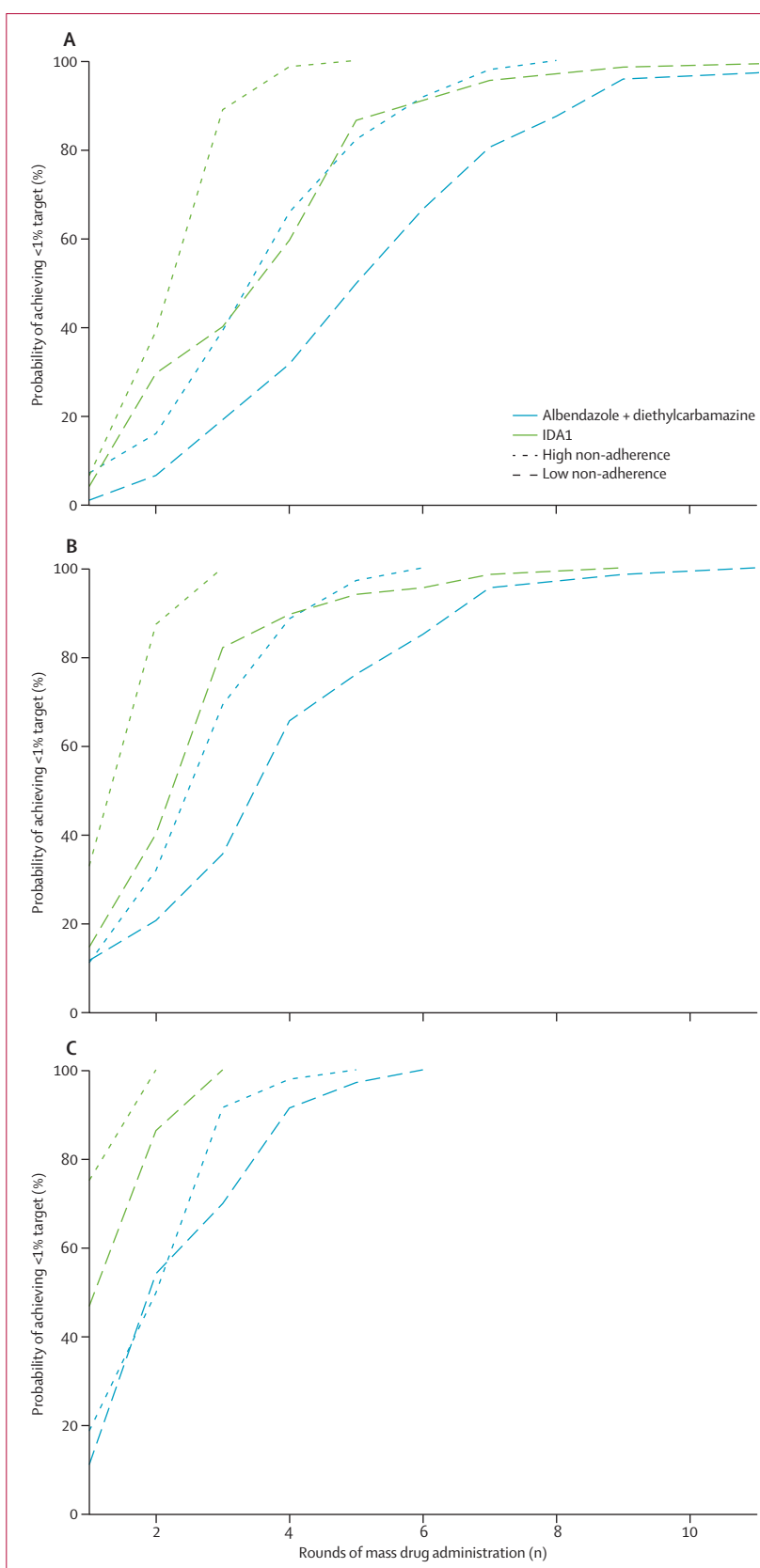
threshold in both the moderate and high prevalence settings.

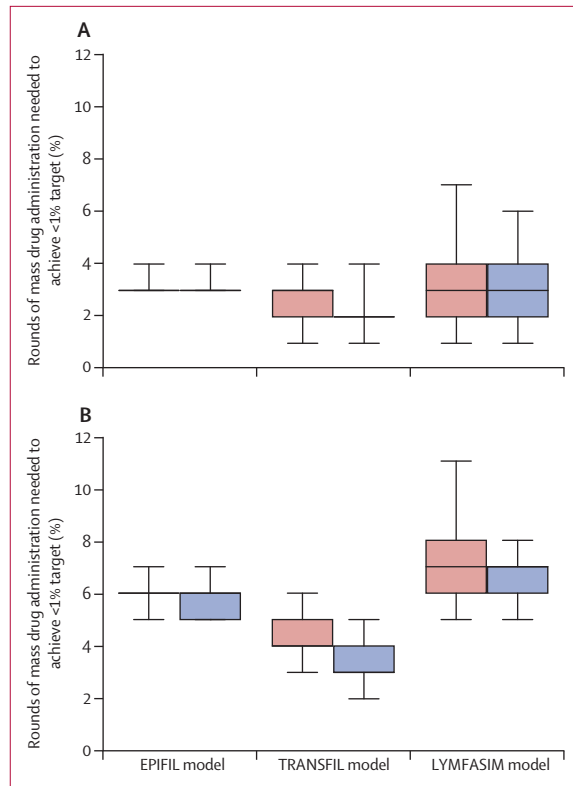The table shows the number of rounds of mass drug administration needed to achieve a prevalence of

Figure 4: Effect of bednets on efficacy of triple-drug regimen
Boxplots show data for settings where *Anopheles* spp are the dominant vector. Red boxes denote scenarios without bednets and blue boxes denote scenarios with bednets. Solid black line represents the median round; coloured box represents the IQR; whiskers represent the 5th and 95th percentiles. (A) Moderate prevalence setting (Africa, *Anopheles* spp, 10% prevalence of microfilariae, no previous mass drug administration). (B) High prevalence setting (Papua New Guinea, *Anopheles* spp, 40% prevalence of microfilariae, no previous mass drug administration).

	High heterogeneity in exposure	Systematic non-adherence	Poor population coverage of highly exposed individuals
Low prevalence setting			
Albendazole and diethylcarbamazine	1 (1–2)	2 (1–3)	4 (1–13)
Ivermectin, diethylcarbamazine, and albendazole	1 (1–2)	1 (1–3)	4 (1–8)
Moderate prevalence setting			
Albendazole and diethylcarbamazine	2 (1–8)	3 (1–9)	10 (1–14)
Ivermectin, diethylcarbamazine, and albendazole	1 (1–3)	2 (1–6)	6 (1–14)

Data are median number of rounds (95% CI). Based on simulations with TRANSFIL in a low prevalence setting (Asia, *Culex* spp, 5% prevalence of microfilariae, no previous mass drug administration, no long-lasting insecticide-treated nets) and a setting with moderate prevalence (Africa, not co-endemic with onchocerciasis, *Anopheles* spp, 10% prevalence of microfilariae, no previous mass drug administration, no long-lasting insecticide-treated nets).

Table: Analysis of hypotheses for failing elimination campaigns

microfilariae less than 1% after the initial five rounds of mass drug administration, for every scenario related to stagnation of the elimination campaign. The triple-drug regimen was predicted to save one round of mass drug administration versus the two-drug regimen of albendazole and diethylcarbamazine, with a greater effect when campaign stagnation was attributable to poor population coverage of heavily infected individuals in a setting of moderate prevalence, reducing the medium number of rounds from ten to six.

Discussion

The triple-drug regimen of ivermectin, diethyl-carbamazine, and albendazole represents an exciting new development for GPELF and could potentially reduce significantly the number of doses of anthelmintic drugs needed by this WHO campaign. Several questions remain open surrounding the efficacy of this triple-drug regimen at the population level and with respect to its ability to reinvigorate campaigns that have stagnated, as well as overcome issues such as poor population coverage or adherence. Here, we have shown a first step towards understanding these issues by comparing several different generic scenarios between the current regimen of albendazole and diethylcarbamazine and the new regimen of ivermectin, diethylcarbamazine, and albendazole, using three current models of lymphatic filariasis infection.

Existing mass drug administration programmes are designed around what was perceived to be achievable effective population coverage (65%) and duration to match the life expectancy of the adult worm (5 years). However, the level of coverage might not be enough to achieve elimination targets in all settings.[15,22,23] Because ivermectin, diethyl-carbamazine, and albendazole could lead to permanent sterilisation or killing of adult worms, shorter timeframes for campaigns can be considered, particularly if population coverage is higher. A shorter timeframe has the potential to reduce issues such as programme fatigue and poor coverage by allowing a more focused intervention and extra effort to optimise coverage.

Although at least 65% population coverage is recom-mended, many intervention units report higher levels.[23] Notwithstanding issues related to true coverage, both systematic non-adherence and the drug regimen have less of an effect with high levels of coverage with respect to the probability of success for a campaign given a specified number of rounds (figure 3). This finding highlights that, with good population coverage, a campaign is able to overcome some of the possible stagnation issues.

In addressing the 2020 goals for elimination of lymphatic filariasis, our results indicate that a campaign will have a greater probability of success if switching to ivermectin, diethylcarbamazine, and albendazole provides the same level of coverage as would be expected under the existing two-drug regimen. In a setting with moderate baseline prevalence of microfilariae, the

probability of a campaign's success increases by 70%; however, in a low prevalence setting, the gains are modest, only increasing the chances of success by about 20%. In high prevalence settings, the chances of success in achieving 2020 targets are only 35%.

At all levels of population coverage, systematic non-adherence restricts the potential effect of ivermectin, diethylcarbamazine, and albendazole. This finding suggests that although more effective, the triple-drug regimen is still susceptible to issues that limit the effectiveness of current mass drug administration regimens.[24] However, ivermectin, diethylcarbamazine, and albendazole consistently outperformed the current two-drug regimen in all simulation studies, including scenarios with high systematic non-adherence. This finding shows that ivermectin, diethylcarbamazine, and albendazole can accelerate lymphatic filariasis elimination programmes across various situations.

For the three models, there was variation in the number of rounds needed to push prevalence below 1% for each of the model runs. Stochastic variation and fluctuation in population parameters can lead to situations in which reduction in prevalence is more difficult to achieve even when other variables—eg, the average infection rate—are constant. The extent of these more extreme cases was reduced when ivermectin, diethylcarbamazine, and albendazole was implemented, versus the current two-drug regimen of albendazole and diethylcarbamazine, particularly with high transmission. This finding is especially encouraging for areas with high baseline prevalence of microfilariae or for settings in which implementation of mass drug administration has so far been unable to reduce prevalence of lymphatic filariasis to threshold targets.[24]

Our study has several limitations. First, because only a small study sample has been published up to now with respect to individual efficacy of ivermectin, diethylcarbamazine, and albendazole, the efficacy of the triple-drug regimen is still uncertain. Second, we did not aim to capture any specific country scenario with our modelling analysis; rather, we used selected scenarios that were representative of conditions in endemic regions. Therefore, we aimed to investigate overall patterns. Finally, the outcome measure chosen in our study was the number of rounds of mass drug administration to achieve WHO pre-transmission assessment survey guidelines of less than 1% microfilaraemia to directly address policy-relevant questions about when specific settings are able to move into the post-mass drug administration phase. However, a further question asks what the probability of elimination is once a region has entered the transmission assessment survey phase, which is not addressed here.

In conclusion, our modelling results suggest that the triple-drug regimen of ivermectin, diethylcarbamazine, and albendazole has great potential for accelerating elimination of lymphatic filariasis in many settings, which is important in view of WHO's ambitious target for global elimination by 2020. This study shows that although greater gains can be made with ivermectin, diethylcarbamazine, and albendazole, the regimen cannot fully overcome some challenges that mass drug administration campaigns face, such as systematic non-adherence and poor population coverage. However, if effective coverage can be achieved, ivermectin, diethylcarbamazine, and albendazole should help countries achieve elimination of lymphatic filariasis more quickly across a diverse number of settings.

References
1. Rebollo MP, Bockarie MJ. Toward the elimination of lymphatic filariasis by 2020: treatment update and impact assessment for the endgame. *Exp Rev Anti Infect Ther* 2013; **11:** 723–31.
2. Molyneux D, Zagaria N. Lymphatic filariasis elimination: progress in global programme development. *Ann Trop Med Parasitol* 2002; **96:** 15–40.
3. Ramaiah K, Ottesen EA. Progress and impact of 13 years of the global programme to eliminate lymphatic filariasis on reducing the burden of filarial disease. *PLoS Negl Trop Dis* 2014; **8:** e3319.
4. Hooper PJ, Chu BK, Mikhailov A, Ottesen EA, Bradley M. Assessing progress in reducing the at-risk population after 13 years of the global programme to eliminate lymphatic filariasis. *PLoS Negl Trop Dis* 2014; **8:** e3333.
5. Ottesen E, Duke B, Karam M, Behbehani K. Strategies and tools for the control/elimination of lymphatic filariasis. *Bull World Health Organ* 1997; **75:** 491.
6. Ottesen EA, Hooper PJ, Bradley M, Biswas G. The global programme to eliminate lymphatic filariasis: health impact after 8 years. *PLoS Negl Trop Dis* 2008; **2:** e317.
7. 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:** 54.
8. WHO. Global programme to eliminate lymphatic filariasis: progress report, 2014. *Wkly Epidemiol Rec* 2014; **38:** 489–504.
9. Plaisier A, Stolk W, Van Oortmarssen G, Habbema J. Effectiveness of annual ivermectin treatment for *Wuchereria bancrofti* infection. *Parasitol Today* 2000; **16:** 298–302.
10. Ramaiah K, Das P, Appavoo N, et al. A programme to eliminate lymphatic filariasis in Tamil Nadu state, India: compliance with annual single-dose DEC mass treatment and some related operational aspects. *Trop Med Int Health* 2000; **5:** 842–47.
11. Krentel A, Fischer PU, Weil GJ. A review of factors that influence individual compliance with mass drug administration for elimination of lymphatic filariasis. *PLoS Negl Trop Dis* 2013; **7:** e2447.
12. Kumar A, Kumar P, Nagaraj K, Nayak D, Ashok L, Ashok K. A study on coverage and compliance of mass drug administration programme for elimination of filariasis in Udupi district, Karnataka, India. *J Vector Borne Dis* 2009; **46:** 237.

13 Thomsen EK, Sanuku N, Baea M, et al. Efficacy, safety, and pharmacokinetics of coadministered diethylcarbamazine, albendazole, and ivermectin for treatment of bancroftian filariasis. *Clin Infect Dis* 2016; **62:** 334–41.

14 El Setouhy M, Ramzy RM, Ahmed ES, et al. A randomized clinical trial comparing single-and multi-dose combination therapy with diethylcarbamazine and albendazole for treatment of bancroftian filariasis. *Am J Trop Med Hyg* 2004; **70:** 191–96.

15 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 Vector* 2015; **8:** 1–19.

16 Stolk WA, De Vlas SJ, Borsboom GJ, Habbema JDF. LYMFASIM, a simulation model for predicting the impact of lymphatic filariasis control: quantification for African villages. *Parasitology* 2008; **135:** 1583–98.

17 Chan M-S, Srividya A, Norman R, et al. Epifil: a dynamic model of infection and disease in lymphatic filariasis. *Am J Trop Med Hyg* 1998; **59:** 606–14.

18 Subramanian S, Stolk W, Ramaiah K, et al. The dynamics of *Wuchereria bancrofti* infection: a model-based analysis of longitudinal data from Pondicherry, India. *Parasitology* 2004; **128:** 467–82.

19 Singh BK, Michael E. Bayesian calibration of simulation models for supporting management of the elimination of the macroparasitic disease, lymphatic filariasis. *Parasit Vector* 2015; **8:** 1–26.

20 Jambulingam P, Subramanian S, de Vlas S, Vinubala C, Stolk W. Mathematical modelling of lymphatic filariasis elimination programs in India: required duration of mass drug administration and post-treatment level of infection indicators. *Parasit Vector* 2016; **9:** 501.

21 Singh BK, Bockarie MJ, Gambhir M, et al. Sequential modelling of the effects of mass drug treatments on anopheline-mediated lymphatic filariasis infection in Papua New Guinea. *PLoS One* 2013; **8:** e67004.

22 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.

23 Michael E, Singh BK. Heterogeneous dynamics, robustness/fragility trade-offs, and the eradication of the macroparasitic disease, lymphatic filariasis. *BMC Med* 2016; **14:** 14.

24 Babu B, Kar SK. Coverage, compliance and some operational issues of mass drug administration during the programme to eliminate lymphatic filariasis in Orissa, India. *Trop Med Int Health* 2004; **9:** 702–09.