



Delays in lymphatic filariasis elimination programmes due to COVID-19, and possible mitigation strategies

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Received 25 August 2020; revised 22 December 2020; editorial decision 4 January 2021; accepted 11 January 2021

Background: In view of the current global coronavirus disease 2019 pandemic, mass drug administration interventions for neglected tropical diseases, including lymphatic filariasis (LF), have been halted. We used mathematical modelling to estimate the impact of delaying or cancelling treatment rounds and explore possible mitigation strategies.

Methods: We used three established LF transmission models to simulate infection trends in settings with annual treatment rounds and programme delays in 2020 of 6, 12, 18 or 24 months. We then evaluated the impact of various mitigation strategies upon resuming activities.

Results: The delay in achieving the elimination goals is on average similar to the number of years the treatment rounds are missed. Enhanced interventions implemented for as little as 1 y can allow catch-up on the progress lost and, if maintained throughout the programme, can lead to acceleration of up to 3 y.

Conclusions: In general, a short delay in the programme does not cause a major delay in achieving the goals. Impact is strongest in high-endemicity areas. Mitigation strategies such as biannual treatment or increased coverage are key to minimizing the impact of the disruption once the programme resumes and lead to potential acceleration should these enhanced strategies be maintained.

Keywords: acceleration, COVID-19, elimination, lymphatic filariasis, mitigation, modelling

Introduction

Lymphatic filariasis (LF), a disease caused by parasitic filarial worms, was identified as potentially eradicable in 1993.¹ It has been targeted for elimination as a public health problem by the World Health Organization (WHO), with initial goals set for 2020, which are now being revised for 2030.² The main strategy to achieve elimination as a public health problem is through mass drug administration (MDA). The most common drugs used by the LF control and elimination programmes are either a combination of diethylcarbamazine citrate and albendazole (DA) or ivermectin and albendazole (IA) in areas where onchocerciasis is endemic. Geographically this means that IA is used in most of Africa,

while DA is used in other parts of the world, including the Indian subcontinent. Currently MDA programmes are ongoing in 46 countries.³

MDA campaigns are generally carried out annually, for a minimum of 5 y (five rounds), with the aim of achieving at least 65% coverage. Afterwards, a series of transmission assessment surveys must reveal a low likelihood of current transmission to achieve elimination as a public health problem. In areas where *Wuchereria bancrofti* is endemic, this is generally associated with reaching a threshold of 1% microfilaria (mf) prevalence or 2% antigenemia prevalence in areas where the dominant vector for transmission is *Anopheles* or *Culex*. Historically a 0.5% mf threshold was used in areas with *Aedes*-transmitted LF, now using a 1%

antigenemia threshold. Areas where *Brugia* is endemic use a 2% antibody prevalence.⁴

The current global coronavirus disease 2019 (COVID-19) pandemic has had a huge impact worldwide, with >10 million confirmed cases in the first half of 2020 and more than half a million deaths. This impact is compounded by its indirect effects on other diseases and health programmes. In view of the current global COVID-19 pandemic, and the need to practice physical distancing, the WHO issued the recommendation on 1 April 2020 to put all community-based surveys, active case-finding activities and mass treatment campaigns for neglected tropical diseases on hold until further notice.⁵ For the LF control and elimination programmes that had an MDA round planned, this has meant the stopping of all activities. It thus becomes important to assess the impact of delays in MDA delivery on the 2030 goals and to consider strategies to strengthen programmes after the lockdown to mitigate the negative impact of disruption.

Strategies that have been considered for accelerating progress towards the 2020 goals (now 2030) could be used to mitigate these delays, such as biannual rounds of treatment or increased coverage.^{6–8} Recent clinical trials and mathematical modelling studies have shown that the combination of all three drugs, commonly known as the triple drug (IDA), can substantially improve progress towards the goal.^{7,9–13} The use of IDA has been recommended by the WHO to accelerate global elimination efforts.¹⁴ However, only countries without onchocerciasis can deploy IDA in their programmes, due to risks of adverse events.

A suite of three different mathematical models has recently been used to compare strategies to accelerate global elimination of LF,⁷ as well as to assess the likelihood of resurgence after reaching the 1% mf prevalence threshold.⁸ Those same models are used here to estimate the impact of MDA delays in the expected progress towards the 1% mf threshold, establish mitigation strategies that are sufficient to catch up on the missed/delayed rounds and assess the acceleration provided from mitigation strategies that can be maintained longer term. Mitigation and acceleration strategies considered here include enhancing coverage from 65% to 80%, deploying the treatment twice per year (biannual treatment) and, for areas using DA, the benefit of switching to the triple drug.

Materials and methods

Employed mathematical models

We used three well-described published mathematical models of LF transmission to enhance our understanding of the disruption caused by COVID-19 to ongoing control and elimination efforts. We included the following models, developed and applied by members of the Neglected Tropical Disease Modeling Consortium: EPIFIL,^{15,16} a deterministic population-based model, and LYMFASIM^{17,18} and TRANSFIL,^{19,20} both stochastic individual-based models. All models capture the basic processes relevant to the transmission dynamics of LF, including parasite life cycle, vector density and biting rate and human exposure to the vectors. The formulation and parameterization of these models is detailed in

the references (see the supplementary material for an updated implementation of the three models).

Scenarios considered

Countries may be at different stages in their control programme. In this analysis we assumed that two annual MDA rounds achieving 65% coverage were completed before the interruption caused by COVID-19 (disruptions at other points in the programme yield broadly similar results and are discussed in the supplementary material). Two settings were considered, one relevant for most of Africa, with *Anopheles*-driven transmission and annual treatment with IA, and a second representing India-like populations, with *Culex*-driven transmission and treatment with DA. The assumptions of drug effectiveness in terms of macro- and microfilaricidal effect and sterilization of adult worms was taken from Stolk et al.⁷ (see also the supplementary material). Vector control is commonly recommended to enhance MDA but is generally outside the control of the LF programmes. To be conservative, we considered that there was no bed net coverage, although we acknowledge that bed net coverage is present in many African areas.²¹ Additional simulations considering bed nets and indoor residual spraying (IRS) are shown in the supplementary materials.

To assess the impact of delayed MDA, we explored four scenarios where the MDA rounds are postponed either 6, 12, 18 or 24 months, which causes a gap of 1.5, 2, 2.5 and 3 y, respectively (Figure 1). A 6-month interruption represents one postponed round and 12- or 24-month interruptions represent one or two cancelled rounds, respectively, whereas an 18-month interruption represents one delayed and one postponed round.

To manage and minimize the impact of the delay in delivering the next round of MDA, national programmes could implement alternative enhanced strategies after resuming activities. Here we explored the impact of various MDA-based mitigation strategies: enhanced achieved coverage (up from 65% to 80%); switching to biannual rounds, treating every 6 months; and, in areas where appropriate (our India-like setting), the deployment of the triple drug. In all simulated scenarios, MDA continues until the 1% mf threshold is achieved, up to 2045 (the end of the simulation window).

Analysis of simulation results

We generated a large number of simulations (simulation bank) and extracted uniformly 10 000 runs per scenario for each model across a wide range of baseline prevalences (assumed to be in 2018) from 1% to 40%. All simulations across the three models are considered as an ensemble, with equal weighting. We projected forward from the baseline under the different treatment regimes in each scenario and extracted the simulated mf prevalence in the population each year. We summarized some results following a general classification of low-, medium- and high-prevalence areas. These were mapped to the non-contiguous microfilaria prevalences of 5–10%, 15–20% and 25–30%, respectively. To select the simulations for each prevalence bracket we extracted 1000 runs from each model uniformly from the simulation bank.

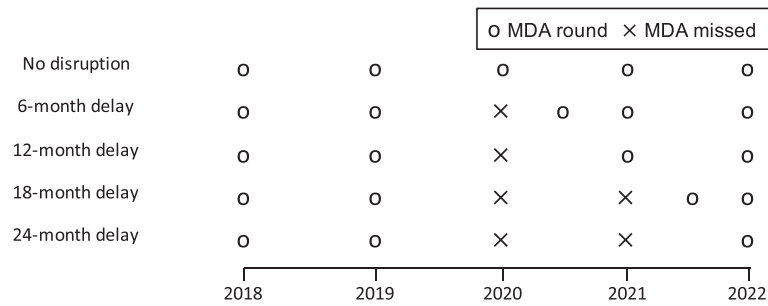


Figure 1. Timing of the MDA rounds assuming the programme starts in 2018 and the COVID-19 disruption occurs in 2020. Four delay scenarios (6, 12, 18 and 24 months) and a no-disruption scenario were considered. A treatment round is merely postponed if it is delayed for 6 months but it is cancelled if delayed for 12 months (resulting in one cancelled round in the 12- and 18-month delay scenarios and two cancelled rounds in the 24-month delay scenario).

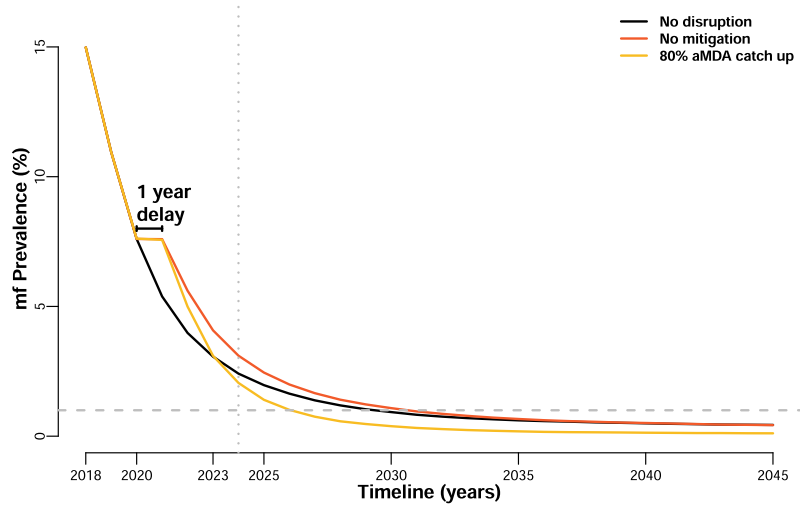


Figure 2. Example of yearly mf prevalence trends over time. Black line shows a no-disruption scenario (counterfactual), with a baseline prevalence of 15%. Red line shows a no-mitigation scenario, where a 1-y delay takes place in 2020. The yellow line shows a scenario where 80% MDA is implemented from 2021 onward as a catch-up (and acceleration) strategy. The vertical dotted line indicates the catch-up point (the first year where the yellow line is below the black line). The horizontal dashed line marks the 1% mf prevalence threshold, which is reached earlier in the acceleration (yellow) scenario. In this example it takes three rounds of MDA with 80% coverage to catch-up. All three solid lines are an average of 1000 simulations with TRANSFIL, with a baseline prevalence in 2018 of 14–16%.

We used a counterfactual no-disruption scenario (i.e. the initial five rounds take place as expected; Figure 1) to assess for how long the enhanced strategies need to be implemented in order to catch up with the expected progress of the programme. We calculated the year in which the prevalence in the different interventions is equal to or less than the counterfactual scenario, as that would indicate that the enhanced strategy managed to mitigate the disruption caused by the gap in treatment (see Figure 2 for an illustrative example). After the initial 5-y programme, we assume that the treatment strategy used after resuming activities is continued until the 1% mf threshold is met. We can then use these same runs to quantify the gains should these alternative strategies be maintained beyond catching up (see Figure 2). To summarize results over the prevalence range, we calculated the moving average with a window size of 4000 simulations (sorted by preva-

lence) and the volatility as the unweighted standard deviation in the same window size.

Results

The expected delay in reaching the 1% mf threshold is broadly similar across the baseline prevalence (here considered in 2018; Figure 3 [top]). Across the full baseline prevalence range explored, the delay in reaching the 1% goal (and thus the increase in the length of the programme that needs to be considered) is estimated to be on average slightly less than the delay of the MDA round. For example, a 1-y delay in distributing the MDA round causes on average almost 1-y delay in the *Culex* DA setting and a bit less than a 1-y delay in the *Anopheles* IA setting (Figure 3 [top]). Areas with a prevalence <5% are close to the

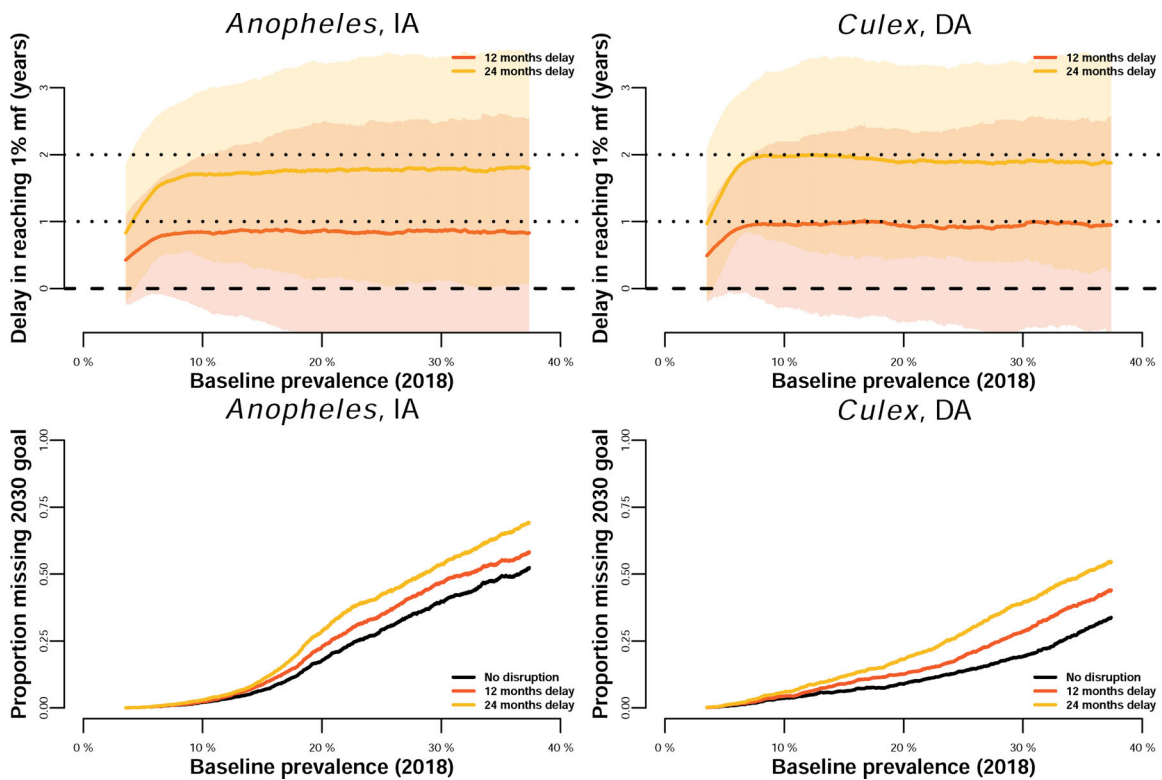


Figure 3. Moving average (window size of 4000) of the delay in reaching 1% mf prevalence (in years [top]) and the proportion missing the 2030 goals (bottom) for a wide range of baseline prevalences at the start of the current MDA programme in an *Anopheles*-transmitted setting treating with IA (left) and a *Culex*-transmitted setting treating with DA (right). The red and yellow lines illustrate scenarios with 12- or 24-month programme delays, respectively, after which annual MDA with 65% coverage continues. Shaded areas illustrate the standard deviation (volatility).

goal and thus the disruption is minimal. The proportion missing the 2030 goal is estimated to increase faster in *Anopheles* settings than in *Culex* settings as baseline prevalence increases (Figure 3 [bottom]).

A summary of the results across the four delays we considered for the two settings is shown in Table 1. The focuses here are the low-, medium- and high-prevalence areas as defined above (5–10%, 15–20% and 25–30% mf prevalence, respectively). Low-prevalence areas, irrespective of the delay considered, are on average likely to reach 1% mf before the 2030 endpoint; however, delays in the medium- and high-prevalence areas may require programmes to continue beyond 2030. Across the two settings and the prevalence brackets considered, a 6-month delay in the deployment of the MDA will lead on average to the programme not needing to be extended beyond the originally planned timelines (Table 1).

Alternative enhanced strategies, such as increasing efforts to achieve a higher coverage or increasing the treatment frequency, can help catch up to the time lost due to the COVID-19 disruption. Biannual rounds of MDA or switching to IDA, where possible, are on average faster methods to catch up than achieving a high coverage of 80% (Figure 4). Longer gaps in the programme would require more rounds of the enhanced campaigns to catch up (see supplementary materials).

Maintaining the strategies implemented to catch up and mitigate the disruption caused by COVID-19 will lead to acceleration

of the programmes, irrespective of the strategy used (Figure 5). A long disruption causing a 2-y delay (a 3-y gap between treatment rounds) can be caught up by these alternative strategies. All three strategies considered here (80% coverage achieved, biannual rounds or switching to IDA where possible) lead to qualitatively similar gains (Figure 5), which could be as big as reaching the goal 3 y earlier. The results shown here are for an India-like setting with *Culex* as the dominant vector and the deployment of DA as the drug combination. Results for *Anopheles*-transmitted settings, treated with IA, are broadly similar (see supplementary material).

Discussion

We have estimated the delays in LF elimination efforts due to the disruption caused by COVID-19 in two broadly defined settings using three well-established mathematical models of LF transmission.^{7,8} Moreover, we explored how alternative enhanced strategies could be used to catch up and recover from the disruption when programmes resume and potentially accelerate progress towards the 2030 goals if maintained longer term.

Overall, our simulations suggest that in efforts aiming for LF elimination as a public health problem, each round missed generally extends the programme by the same amount (Figure 3), provided programmes can resume activities achieving similar

Table 1. Estimated timeline to achieving 1% mf prevalence goal by baseline endemicity and estimated extension of the programmes required (i.e. delay to reaching 1% mf) for different delays in the deployment of the next MDA. Timeframes over 12 y from the baseline are beyond 2030 and thus are estimated to miss the goal.

Baseline prevalence (2018)	Africa-like population: <i>Anopheles</i> transmission, IA treatment			India-like population: <i>Culex</i> transmission, DA treatment		
	Low prevalence (5–10% mf)	Medium prevalence (15–20% mf)	High prevalence (25–30% mf)	Low prevalence (5–10% mf)	Medium prevalence (15–20% mf)	High prevalence (25–30% mf)
Time to goal from 2018 if no interruption (counterfactual)	5.89 (3–9)	9.51 (7–18)	11.8 (8–21)	5.57 (4–12)	8.54 (6–17)	10.13 (7–19)
6-month delay (1.5-y gap)	No extension (0–2)	No extension (0–4)	No extension (0–4)	No extension (0–2)	No extension (0–3)	No extension (0–3)
12-month delay (2-y gap)	+0.79 (0–2)	+0.81 (0–4)	+0.85 (0–5)	+0.96 (0–3)	+0.95 (0–4)	+0.92 (0–4)
18-month delay (2.5-y gap)	+0.7 (0–2)	+0.92 (0–4)	+1 (0–5)	+0.77 (0–3)	+0.97 (0–4)	+0.94 (0–4)
24-month delay (3-y gap)	+1.63 (0–3)	+1.72 (0–5)	+1.82 (0–5)	+1.92 (0–4)	+1.87 (0–5)	+1.85 (0–5)

Values presented as mean (95% confidence intervals) in years.

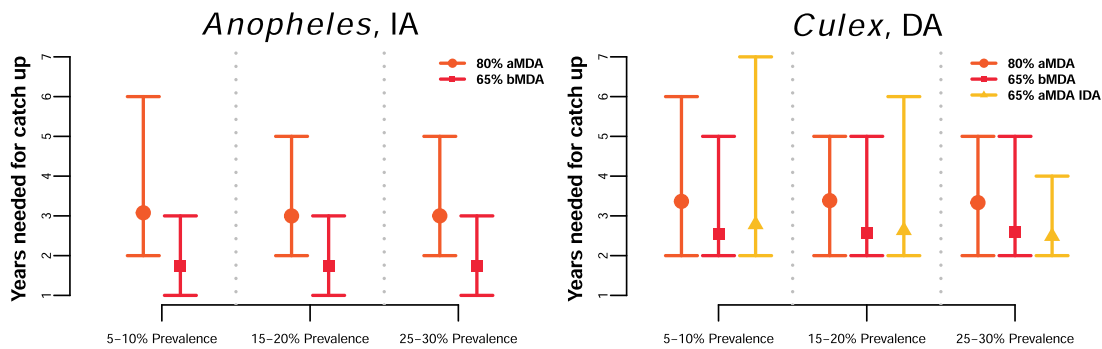


Figure 4. Estimated average number of years of the enhanced interventions needed after a 1-y delay in MDA and resuming activities to catch-up to the counterfactual no-disruption scenario for the two settings considered.

levels of coverage as before the disruption. As an example, a programme that would have reached elimination after five rounds of treatment and misses one round this year could resume their MDA campaigns the next year and would on average still need to do only five rounds in total. In this example the programme is likely to be only 1 y behind (i.e. delivering the round that it missed), although in some cases it could lead to longer delays (Figure 3 and Table 1). Moreover, baseline prevalence has a very limited effect on the delays, as seen in Figure 3, with the exception of very low-prevalence areas (<5% mf). However, the estimated time to reach 1% mf prevalence has a larger uncertainty in high-prevalence areas (Table 1). These results, which are specific for LF-endemic areas with *W. bancrofti*, are consistent across the two settings considered (*Anopheles*-dominated transmission with IA-based MDA and *Culex*-dominated transmission with DA-based MDA).

Medium- (15–20% mf) and high-prevalence (25–30% mf) areas are more at risk of missing the 2030 target should the delays not be mitigated. In low-prevalence areas (5–10% mf in 2018), a 2-y delay (3-y gap between treatment rounds) could lead in some extreme cases to missing the 2030 goal (Table 1). However, we expect that on average those areas, or those with even lower baseline prevalence, will reach the 2030 goals ahead of time, in spite of the COVID-19 disruption. In the supplementary materials we show that results for programmes that started their MDA earlier/later are qualitatively similar.

Encouragingly, interventions that are commonly considered to accelerate progress towards the goals, such as increased coverage or frequency of the interventions,⁷ can also be used to mitigate the impact of the missed rounds. With a 6-month delay in the MDA programme, effectively deploying two MDA rounds 6 months apart (see Figure 1) is similar to resuming activities

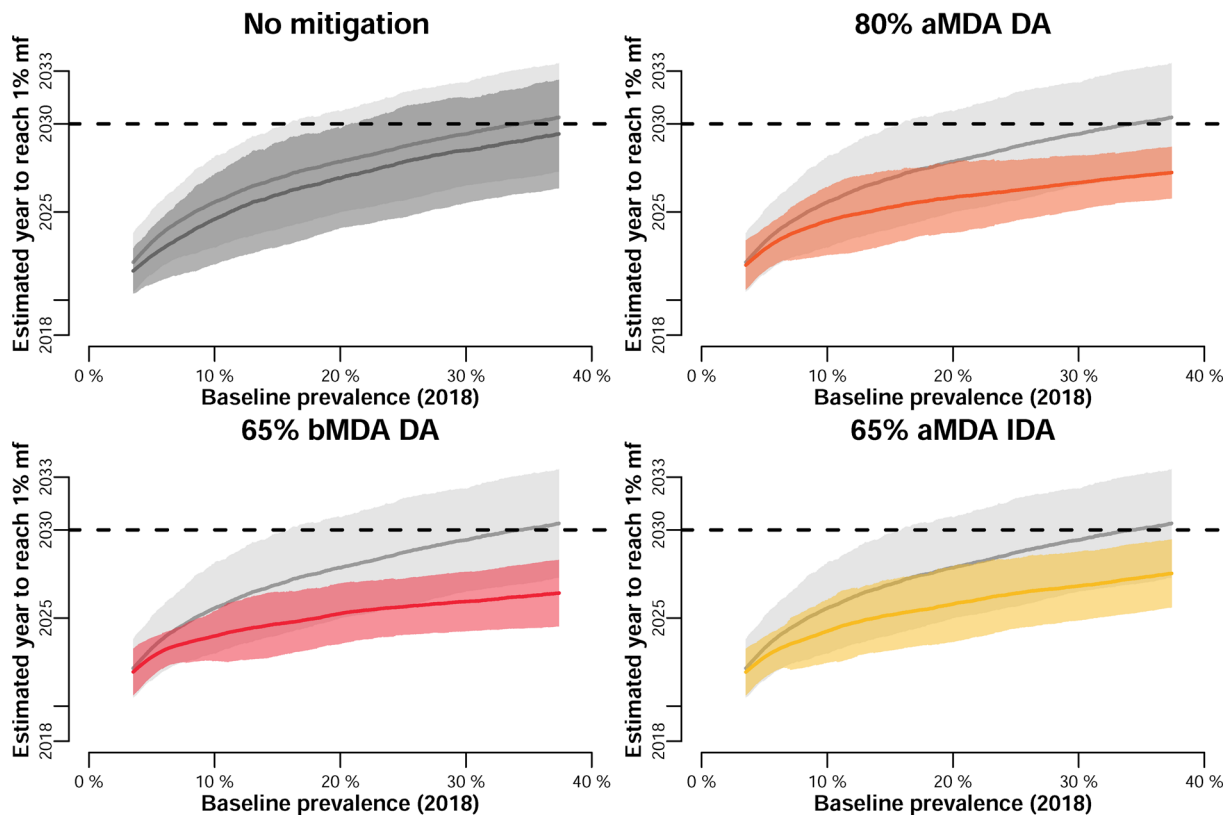


Figure 5. Estimated year of achieving the 1% mf threshold relative to the prevalence at baseline (assumed here in 2018) for the setting with *Culex* transmission treated with DA. Top-left plot compares the counterfactual to the no-mitigation scenario (after a 12-month delay). The rest of the plots show the different acceleration strategies (in colour) against the no-mitigation situation (in grey). The horizontal dashed line indicates the year 2030; areas beyond 2030 are unlikely to reach the goal. The solid line shows the moving average (window size of 4000) and the shaded area is the standard deviation (volatility).

with a biannual strategy, where 1 y is sufficient to catch up to the expected progress of the programme in the absence of any delays (Figure 4). In these simulations, mitigating with IDA has the largest variation (and thus uncertainty) (Figure 4), possibly because the drug pressure with biannual rounds or 80% coverage is higher. Nevertheless, these results highlight the importance of implementing the missed round as soon as possible when it is safe to do so, which would also prevent the expiry of medication already stocked. Should these enhanced strategies be maintained once the programmes resume activities until the 1% mf threshold is reached, as much as 3 y could be gained (Figure 5). Our models predict that the extended use of these enhanced strategies will ensure that even high-prevalence areas will be able to reach the 2030 targets.

Our analysis has a number of assumptions and simplifications that need to be considered. While we allow parameter uncertainty in the inputs (see supplementary material), and stochastic effects for LYMFASIM and TRANSFIL, we do not account for sampling of the human population, and thus the mf is the true value in the population >5 y of age (minimum age to be included in a survey). Similarly, the deployment of the drug and its effect takes place within one time step of the model (2 weeks/1 month depending on the model). This, combined with the assumption that compliance (the proportion of individuals treated in two

consecutive rounds) is the same between biannual rounds as between annual rounds, means that our results for biannual treatment might be slightly optimistic. Predicted timelines to achieve the 1% mf prevalence threshold depend on assumptions surrounding systematic non-compliance (the two stochastic models LYMFASIM and TRANSFIL account for a moderate amount on non-compliance, in line with recent work^{7,8} [see supplementary materials]). We conducted a sensitivity analysis for other simplifications, such as the effect of vector control and disruption occurring at a different point in the programme (see supplementary materials).

It is important to consider the timelines and flexibility of the evaluations carried out to assess progress, such as the transmission assessment survey (TAS). These generally take place 6–9 months after the last scheduled round of MDA, which means that resuming treatment, if needed, could lead to a 1- to 2-y gap. In our simulations we considered continuous treatment until the 1% mf prevalence threshold is met, which in medium- and high-prevalence settings is estimated to be 9–12 y on average (Table 1). Therefore, missing the third round as modelled here means there are 7–10 MDA rounds remaining. Thus a 1-y delay might not be too problematic in terms of programme duration, but it can still lead to missing the 2030 goals.

For our analysis we assumed that the programmes can resume MDA activities with a similar coverage as before the disruption. On previous occasions when MDA has been interrupted, programmes have reported good coverage the following years after resuming activities. In Haiti, following the 2010 earthquake, there was a reported coverage of MDA of 92% for LF in 2011, which was calculated from the doses administered and estimated population sizes; a household survey in Port-au-Prince the same year reported coverage of 71%.²² Similarly, the Sierra Leone and Liberia LF programmes missed MDAs in 2014 due to the West Africa Ebola epidemic,²³ but both managed to resume in 2015 and reported >70% coverage.^{24,25} However, while Guinea reported 16% coverage achieved during the outbreak, this only increased to 21% in 2015, but by 2016 coverage was reported up to 73%.²⁶ Unfortunately there is little information available on how these interruptions affected program outcomes, as the majority are still undertaking MDA, but by 2019, 9 of 14 districts in Sierra Leone had stopped MDA.²⁷ Some programmes are resuming activities with all the precautions necessary due to COVID, which combined with community weariness, can complicate achieving a high effective coverage.

One important aspect to consider, which we currently do not capture in our models, is that a delay in meeting the 1% mf elimination as a public health threshold could cause higher morbidity levels while transmission is ongoing. This may lead to new incident cases of morbidity, especially in areas that have not started MDA yet or with a relatively recent start. Even when implementing catch-up strategies, the time spent with a higher prevalence than originally planned will undoubtedly lead to higher morbidity in the affected communities. Moreover, morbidity management measures to relieve the suffering of those affected by hydrocele or lymphoedema may also be disrupted. Hydrocele surgeries will likely be delayed. Management of lymphoedema could potentially continue, as it is commonly managed at home, although disruptions might make this more difficult. Therefore it is not only important to mitigate the disruption, but to do it quickly.

In summary, progress towards the LF 2030 goals is not going to be greatly affected by the COVID-19 disruption if the interruption remains restricted to 6–24 months, especially if mitigation strategies are put in place. These enhanced strategies that will allow catching up are not particularly novel and have been discussed and considered recently for accelerating progress towards the 2030 goals. An opportunity could be present for programmes that resume MDA using one of these mitigation strategies, particularly those that recently started, as it will lead to a faster reduction in mf prevalence, and lower morbidity, should the strategies be maintained until the 1% mf threshold is met.

Supplementary data

Supplementary data are available at *Transactions* online.

Authors' contributions: JMP, WAS, ELD, PT and TDH conceived the study. JMP designed the study, carried out the analysis and drafted the manuscript. Model simulations were performed by SS and RMC

(EPIFIL), WAS and JM (LYMFASIM) and PT and ELD (TRANSFIL). All authors contributed to the interpretation of results and critically reviewed the manuscript.

Acknowledgements None.

Funding: This work was supported by the Bill and Melinda Gates Foundation through the NTD Modelling Consortium (grant OPP1184344). The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing interests: None declared.

Ethical approval: Not required.

Data availability: All data sources are described in detail and referenced in the supplementary data.

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