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Modelling lymphatic filariasis elimination in American Samoa: GEOFIL predicts need for new targets and six rounds of mass drug administration

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ABSTRACT

Background: As part of the global effort to eliminate the debilitating mosquito-borne disease lymphatic filariasis (LF), seven rounds of two-drug (diethylcarbamazine and albendazole) mass drug administration (MDA) were conducted in American Samoa over 2000–2006. However subsequent surveys demonstrated ongoing transmission prompting further rounds of three-drug (diethylcarbamazine, albendazole, and ivermectin) MDA starting in 2018.

Methods: We extend GEOFIL, a spatially-explicit agent-based model of LF transmission to predict the probability and timing of the local elimination or resurgence of LF for different MDA scenarios starting in 2018: two-drug vs. three-drug MDA, two to seven annual rounds, and population coverage rates of 55–75%. We developed an interactive visualisation comparing the effect of MDA strategies on different outcomes.

Results: At least six annual rounds of three-drug MDA treating 75% of the population were required to achieve LF elimination in American Samoa by 2035 in $>$ 50% of simulations. In scenarios where MDA did not achieve elimination, prevalence doubled approximately every three years, even if MDA reduced antigen prevalence to $<$1% (the target recommended by the World Health Organisation). Prevalence in six- and seven-year-old children was approximately one quarter of the prevalence in the general population.

Conclusion: The three rounds of three-drug MDA conducted in 2018, 2019, and 2021 may have come close to WHO targets but are unlikely to interrupt LF transmission in American Samoa without further interventions. The recommended post-MDA surveillance strategy of testing primarily six and seven-year-old children will delay detection of resurgence compared to population representative surveys. The recommended elimination targets (reducing antigen prevalence below 0.5%, 1%, or 2%) may not be sufficient to interrupt transmission in countries with LF epidemiology like American Samoa. Alternative surveillance strategies and interventions designed to identify and eliminate spatially localized residual transmission may need to be considered. Interactive visualisations may assist decision-makers to choose locally appropriate strategies.

1. Introduction

Lymphatic filariasis (LF) is a mosquito-borne parasitic disease caused by three species of microscopic nematodes, *Wuchereria bancrofti, Brugia timori, and B. malayi*. Nearly 900 million people live in LF-endemic areas (World Health Organisation, 2013; 2021), which are primarily low- and middle-income countries with tropical and sub-tropical climates. Although LF is asymptomatic for many, 36 million people live with disfigurement and disability due to severe lymphoedema and swelling of the limbs (elephantiasis) or scrotum (hydrocele) (World Health Organisation, 2013; 2021). In 2000 the World Health Organization (WHO) began a global campaign to eliminate LF as a public health problem by using mass administration (MDA) of anthelminthic drugs (combinations of ivermectin, diethylcarbamazine citrate, and albendazole) to reduce LF prevalence below key thresholds and ensure a minimum package of treatment for all persons with lymphoedema and hydrocele (World Health Organisation, 2017a). Before the program, there were approximately 119 million infected people across more than 70 endemic countries. By 2020, 17 countries had reduced prevalence below the target thresholds, but 863 million people in 48 countries still needed MDA (World Health Organisation, 2021).

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In 1999, 16.5% of the population of American Samoa was positive for LF antigen (World Health Organisation Western Pacific Regional Office, 2006), down from 24% microfilaremia (Mf) prevalence around 1950 (Hairston and Jachowski, 1968). Seven rounds of two-drug MDA (diethylcarbamazine and albendazole) between 2000 and 2006 reduced antigen prevalence in all age groups to 2.3% (Coutts et al., 2017); and transmission assessment surveys (TAS) of six- and seven-year-olds in 2010 (TAS-1) and 2015 (TAS-2) passed WHO recommended thresholds (Won et al., 2018). However, research surveys from 2010 to 2016 (Lau et al., 2014, 2017; Sheel et al., 2018) demonstrated that transmission of LF had not been interrupted, and American Samoa failed TAS-3 in 2016 (Sheel et al., 2018). Following 2017 WHO guidelines for settings where effectiveness of MDA has been suboptimal and where onchocerciasis is not endemic (World Health Organisation, 2017b), American Samoa distributed an additional three rounds of three-drug MDA (ivermectin, diethylcarbamazine, and albendazole) in 2018, 2019, and 2021.

The parasites causing LF have a complex lifecycle spanning mammalian and mosquito hosts. For bancroftian filariasis, which accounts for most human infections, humans are the only mammalian host. Mature adult worms live in the lymphatic system of the mammalian host. A pair of mature adult male and female worms can produce millions of microfilariae (Mf) over the course of a four- to six-year lifespan. Microfilariae circulate in the blood and may then be ingested by *Culex, Anopheles, Mansonia, or Aedes* mosquitos where they progress through the next stages of maturity in two to four weeks. Parasites that reach the L3 larval stage can then be deposited once more into a human host where they reach sexual maturity after 6–12 months (Ottesen, 2006).

The sexual reproduction of these parasites requires the presence of at least two mature adult worms in a single human host, allowing the possibility of a critical prevalence threshold below which local transmission is insufficient to maintain endemicity (May, 1977). Based on the experience of the successful elimination campaign in China, where reducing Mf prevalence below 1% was observed to be sufficient to interrupt transmission (Xiaodan et al., 2020; De-Jian et al., 2013), the WHO global elimination strategy adopted a threshold of 1% Mf or (later) antigen prevalence to classify countries or areas as endemic and needing MDA, and 1% antigen prevalence in *Aedes* areas and 2% in all other areas as the thresholds used for reaching elimination targets. For validation of interruption of transmission, at least three surveys in the six years after the last round of MDA must demonstrate that antigen prevalence in six and seven year-old children is less than 1% in *Aedes* areas (World Health Organisation, 2011, 2017c). Several mathematical models have been developed to estimate critical prevalence thresholds or otherwise estimate the effect of MDA coverage, compliance, drug combinations, number of rounds, and other factors on the likelihood of achieving elimination (e.g (Gambhir and Michael, 2008; Gambhir et al., 2010; Irvine et al., 2015, 2017, 2018; Stolk et al., 2008; Xu et al., 2019; Collyer et al., 2020).). Model-based estimates of the critical prevalence threshold depend on the choice of model and setting-specific factors such as vector species and biting rates, with some estimates as high as 3%, but others lower than the 1% threshold recommended by the WHO (Gambhir et al., 2010).

However, LF transmission can be focal or clustered (Joseph et al., 2011), so surveillance, elimination efforts, and assessments based on critical prevalence thresholds needs to be applied at the appropriate spatial scale. Heterogeneity and clustering of infection may be dependent on the spatial distribution of mosquito and human population, and other environmental, climatic, and behavioral factors that influence the local likelihood of transmission. Mosquito dispersal can be purposive (for host-seeking and oviposition) or wind-assisted, and the upper limit ranges from less than 200 m to over 30 km depending on the species, climate, vegetation, and availability of hosts and oviposition sites. *Aedes* mosquitos, which are the primary vectors of *W.bancrofti* in American Samoa, have typical flight ranges on the order of hundreds of meters (Silver, 2007).

We therefore applied GEOFIL, the first spatially explicit model of LF transmission, to assess elimination scenarios for American Samoa (Xu et al., 2019). We extended GEOFIL to investigate critical prevalence thresholds and estimate how MDA coverage, the number of MDA rounds, and the choice of two- or three-drug MDA determine key outcomes: the probability of elimination, the timing of resurgence, and the prevalence of LF in American Samoa until 2035.

2. Methods

Though a single Mf-positive person can potentially infect many mosquitoes over the course of their infection, the probability of developing an LF infection from a single bite from an infected mosquito is very low (Hairston and de Meillon, 1968). This implies that an infected person poses the highest risk of exposure to people with whom they spend months or years within a distance less than the typical flight range of the vector mosquito, i.e. family members, housemates, neighbors, colleagues and schoolmates. Therefore, to model the transmission of LF, we use GEOFIL, a spatially explicit, agent-based model which has been described in detail elsewhere (Xu et al., 2019). Briefly, GEOFIL uses a synthetic population model (Xu et al., 2017) that captures the demographics, family structure, and locations of residence, work, and education for the population. These characteristics are projected forward using forecasted death tables, age-structured birth rates, marriage rates, and divorce rates to simulate births, deaths, and formation and breakup of family units. Each family unit, workplace, and school is assigned to a location in space determining which human agents are within the geographic range where transmission may occur. GEOFIL explicitly models the acquisition, maturation, fertility, and death of each adult worm in each human agent. The vectors and the life stages of the filarial parasites in the vectors are modelled implicitly. In this paper, we build on GEOFIL to model the impact of MDA up to the year 2035 under different scenarios with two- or three-drug regimens, number of annual rounds, and population coverage.

2.1. Model of human agents

To model daily movement of people around the country, all human agents were assigned a night-time location (a home building in a home village) and a daytime location (a school if studying, a workplace if employed, and home if neither employed nor studying). Children of school age were assumed to attend the closest school to their household. In the absence of data specific to American Samoa, the employment rate by age-group was assumed to be equal to the labor force participation rate for the urban population of Samoa (Samoa Bureau of Statistics (SBS) and Ministry of Commerce, Industry, and Labour (MCIL), 2014). The working population includes a small proportion of children over 15 years old who participate in the workforce rather than attending school. To reflect known employment features of American Samoa, 17.6% of the population was assumed to work at a single workplace (a tuna cannery, the largest private employer in American Samoa) in the village of Atu'u, with the workforce drawn evenly from across the island (Xu et al., 2018). The place of work for the remaining employed individuals was modelled using a radiation model (Simini et al., 2012) in which the probability of an individual working in a given village depends on the road-distance from their home and the presence of closer population centers.

2.2. Model of the lifecycle and transmission of filariasis worms

We modelled two transmission periods per day: day-time and night-time with different mosquito species active in each period. We assumed that the average numbers of bites each person receives in their day-time and night-time locations were the same. Mosquito population dynamics and the prevalence of larvae in mosquitoes were not modelled explicitly. Rather, for each location in the model, the proportion of mosquitoes

positive for L3 larvae and therefore capable of infecting a human was assumed to be proportional to the prevalence of Mf-positive humans within a 100-meter radius (the mean flight range of the *Aedes polynesiensis* mosquitoes (Hapairai et al., 2013), the main vector in American Samoa (Schmaedick et al., 2014)), where infection risk from each person is weighted by $100-d$ where d is the distance in meters between the location and the person.

In our previous work we only modelled the transmission, maturation, and death of mated pairs of adult worms. In this work we extended this to include individual male and female worms. A bite from an infected mosquito has probability $p_1$of passing on L3 larvae of one sex, and probability p_2 of passing on L3 larva of both sexes. For simplicity, these probabilities include only those larvae that survived to maturity and we assumed that larvae acquired in the same bite reached maturity simultaneously and died simultaneously. The estimation procedures for p_1 and p_2 are described below.

As in our previous work L3 larvae were assumed to have an immature period of 6–12 months (Ottesen, 2006) following which worms enter maturity lasting 4–6 years during which they can produce Mf. As the relationship between mature worm burden and Mf burden is unclear, we assumed that people carrying more than one pair of mated mature worms and people carrying only one pair of mated mature worms were equally infectious.

2.3. Model of test positivity and drug efficacy

We assumed that people were Mf-positive and infectious as soon as the worms they carried reached maturity and Mf-negative as soon as the worms died. We modelled antigen positivity by assuming that all people carrying at least one mature worm (whether mated or unmated, sterile or fertile) were antigen-positive. As antigen appears to linger after treatment and presumptive killing of mature worms, we assumed that the probability of returning a positive antigen test decayed exponentially after the death of the last mature worm, with a half-life of 90 days (McCarthy et al., 1995).

We considered two different combinations of drugs: diethylcarbamazine + albendazole (DA), and ivermectin + DA (IDA). For each drug combination we considered two sets of assumptions of their efficacy: an optimistic (high efficacy) set of assumptions and a more conservative (low efficacy) set of assumptions. The high efficacy assumptions for IDA and the low efficacy assumptions for DA were equivalent to those used by Irvine et al. (denoted as IDA1 and DA in (Irvine et al., 2017)). The low efficacy assumptions for IDA were informed by drug trials in Brazil, Fiji, and Papua New Guinea (Kimura and Mataika, 1996; King et al., 2018; Norões et al., 1997). The high efficacy assumptions for DA were chosen as an optimistic comparison to Irvine's conservative assumptions. All sets of assumptions are summarised in Table 1, and further details are provided in the supplementary materials.

2.4. Model initialization

For our analysis of MDA scenarios, the model was initiated in 2010 with Mf prevalence assumed to be 0.47% amongst adults across American Samoa, but 4.76% in the village of Fagali'i which was identified as a hotspot in the 2010 survey (Lau et al., 2014) and confirmed as a hotspot in 2014 and 2016 (Lau et al., 2017, 2020a). For all analyses, the initial Mf prevalence in 0–7-year-olds was assumed to be zero while the initial Mf prevalence in 8–14-year-olds was assumed to be half the prevalence in adults. In addition to those infected with a pair of Mf-producing mature worms at initialization, a fraction of the population was infected with a pair of immature adult worms of each sex, or a single mature adult worm of either sex (Table S2). We did not include any clustering below the village level at model initialization, i.e. the probability of infection at initialization depended only on age and village but not on the prevalence in those living or working in close proximity. Further details of these assumptions are provided in the supplementary material.

2.5. Model parameters and parameter estimation

Our model retains the majority of the parameters from our previous work (Xu et al., 2019) but introduces two new parameters: the probability that a bite from an infective mosquito will pass on L3 larvae of a single sex (p_1) or L3 larvae with one of both sexes (p_2) that survive to maturity in the human host (Table S1). We estimated p_1 and p_2 using approximate Bayesian computation with software ABCtoolbox (Wegmann et al., 2010) with semi-informative uniform priors, fitting to the results of antigen and mf surveys in 2014 and 2016. Using both antigen and mf prevalence data allowed the model to reproduce the declining Ag:mf prevalence ratio over the period (see supplementary materials in (Xu et al., 2019)).

2.6. Critical threshold behavior

In our previous work the transmission sub-model in GEOFIL was unable to exhibit critical prevalence threshold behavior because only pairs of male and female worms were modelled. To identify possible critical prevalence thresholds in the updated model, we ran simulations for the fitted and counterfactual values of p_1 and p_2, initialised with Mf-prevalence ranging from 0.005% (i.e. approximately three Mf-positive people) to 30%, with 100 model runs per combination of initial prevalence and parameter values. The simulations covered 2010–2035 and assumed (counterfactually) that no MDA or other interventions occurred over this period. The prevalence in 2035 was compared to the initialised prevalence in 2010. Sets of parameters were considered to demonstrate critical threshold behavior if the prevalence decreased over time in >75% of simulations when initialised at a low prevalence but increased over time in >75% of simulations when initialised at a higher prevalence.

Table 1
Assumptions on the effect of drugs on adult worms, with the probability of three mutually exclusive outcomes. Our primary analyses used the high efficacy assumptions, with the low efficacy assumptions considered as sensitivity analysis. The low efficacy assumptions for DA and the high efficacy assumptions for IDA are similar to the assumptions by Irvine et al (Irvine et al., 2017). Drug effects were random and independent across hosts but had the same outcome for all adult (mature or immature) worms in a host.

	High efficacy		Low efficacy	
	IDA	DA	IDA	DA
Probability of immediate adult worm death	55%	50%	50%	55%
Probability of complete adult worm sterilisation (no Mf production and no transmission potential)	45%	33%	46%	0%
Probability of partial adult worm sterilisation (reduced Mf production and reduced transmission potential)	0%	17%	4%	0%
Duration of sterilisation in months	Permanent	12	36	NA

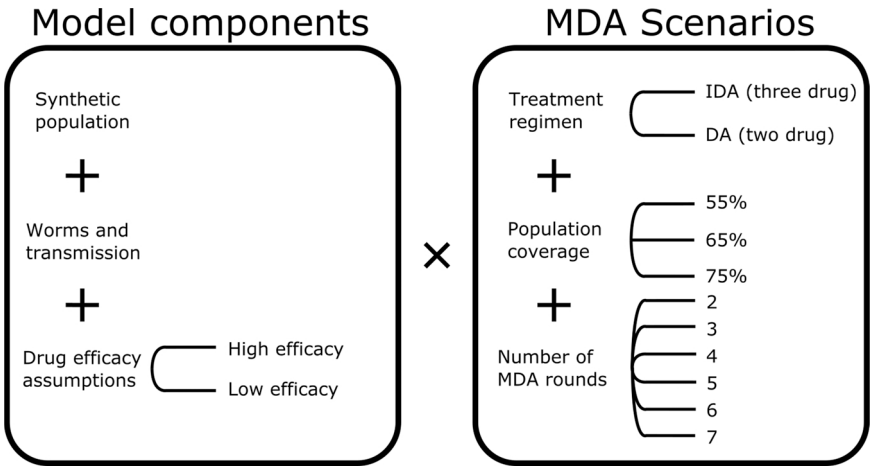

Fig. 1. Overview of all the combinations of model assumptions and mass drug administration (MDA) scenarios considered.

2.7. Scenario analysis

We considered many combinations of MDA scenarios and model assumptions, running 200 simulations per combination (Fig. 1). The different modelling assumptions compared two sets of drug efficacy assumptions (high vs low). MDA scenarios were defined by the combination of the drug regimen (DA or IDA), treatment coverage proportion (55%, 65%, or 75%), and the number of annual rounds (2–7). The coverage proportion was calculated across the total simulated population at the time of each MDA; however, drugs were only given to those who were eligible. Pregnant women and children less than two years of age were not eligible to receive any drugs. In MDA rounds with IDA, we assumed children aged two, three, or four were ineligible to receive ivermectin but could receive the other two drugs. The receipt of drugs was independent across the population and MDA rounds, i.e. we did not consider systematic non-treatment over time, or clustering of non-treatment by geographical area, household, school, or workplace. For each simulation we recorded the prevalence at yearly intervals to measure progress towards elimination or resurgence. The median time below target threshold was defined as the median number years after the first round of MDA in which Ag prevalence remained <1% in the general population.

3. Results

3.1. Critical threshold behavior

We estimated the probability that a single bite from an infected mosquito transmits L3 larvae of a single sex surviving to maturity (p_1) or both sexes surviving to maturity (p_2) as 7.1×10^{-4} and 2.3×10^{-4} respectively. GEOFIL did not exhibit a critical prevalence threshold for the fitted parameter values; however critical threshold behavior was observed with counterfactual parameter values $p_1 < 0.003$ and $p_2 = 0$. For the fitted parameter values, even when the initial mf prevalence was as low as 0.003%, transmission led to rising prevalence in the absence of interventions in the majority of simulations (Fig. S1). The counterfactual parameters $p_1 = 0$ and $p_2 = 2.3 \times 10^{-4}$ were also sufficient for maintaining LF endemicity i.e. for the fitted value parameter values, mosquito bites that passed only L3 larvae of a single sex (p_1) contributed to transmission, but were not essential for the maintenance of ongoing transmission (Fig. S1).

Unless specified otherwise, all the following results are for the fitted parameterisation of the updated model. Selected results are presented in Tables 2 and 3 and Fig. 2, with additional sensitivity analyses and MDA scenarios presented in the supplementary materials and in an interactive online figure (https://angusmclure.shinyapps.io/GEOFILAmSamMDA).

Table 2
Probability that Mf-prevalence reaches 0% by 2035 for different mass drug administration (MDA) scenarios and drug efficacy assumptions. The scenarios compared coverage proportions 55–75%, and two to seven rounds with a three drug (IDA) treatment regimen. Mf-prevalence did not reach 0% in simulations with two drug regimens (DA). The different drug efficacy assumptions are summarised in Table 1.

Population	Number of rounds of mass drug administration					
Coverage	2	3	4	5	6	7
Probability that Mf prevalence reaches 0% by 2035						
IDA – High efficacy assumptions						
55%	<1%	<1%	<1%	<1%	<1%	<1%
65%	<1%	<1%	<1%	<1%	31%	10%
75%	<1%	<1%	4%	39%	75%	92%
IDA – Low efficacy assumptions						
55%	<1%	<1%	<1%	<1%	<1%	<1%
65%	<1%	<1%	<1%	<1%	<1%	1%
75%	<1%	<1%	<1%	2%	13%	37%

Table 3
The median number of years after 2018 where Ag prevalence remained <1%. Where Ag prevalence was still <1% in more than half of simulations by 2035, the proportion of simulations with prevalence <1% is given in parentheses. The scenarios compared two to seven annual rounds of MDA, coverage proportions 55–75%, and two-drug treatment of diethylcarbamazine citrate and albendazole (DA) to a three-drug treatment of ivermectin and DA (IDA). All scenarios in this table used our high drug efficacy assumptions (see Table 1).

Population coverage	Number of rounds of mass drug administration					
	2	3	4	5	6	7
Median number of years with Ag prevalence <1%						
IDA- High efficacy assumptions						
55%	0	0	0	3	8	>12 (53%)
65%	0	0	6	12	>13 (87%)	>13 (98%)
75%	0	7	>14 (55%)	>14 (94%)	>14 (>99%)	>14 (>99%)
DA- High efficacy assumptions						
55%	0	0	0	0	0	0
65%	0	0	0	0	0	3
75%	0	0	0	3	6	10

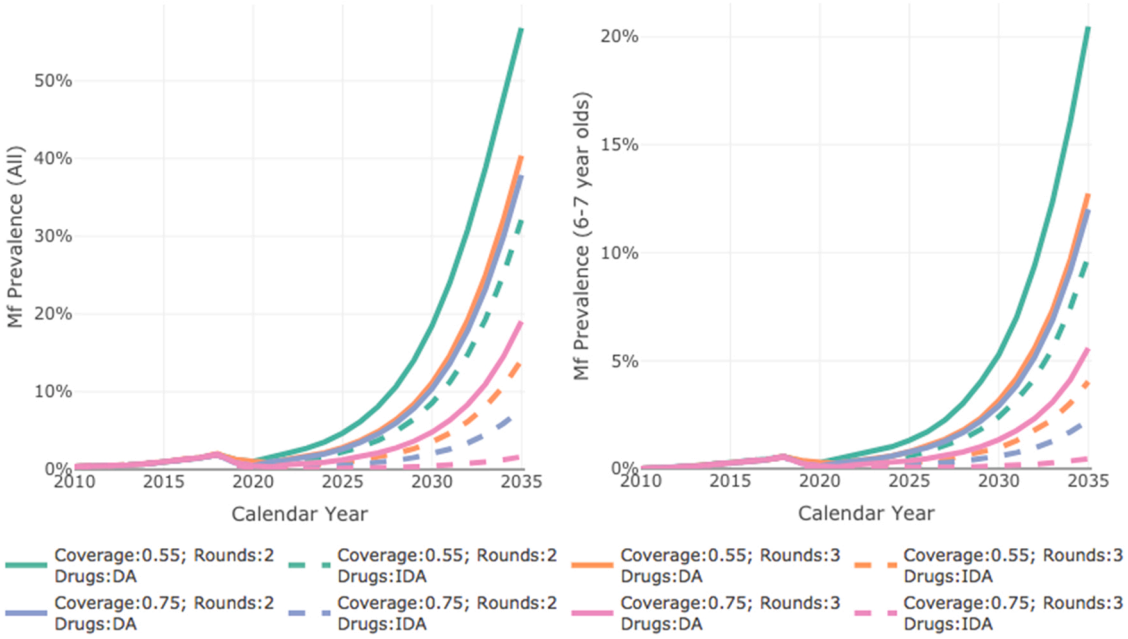

Fig. 2. Simulated mean prevalence of Ag for different MDA strategies – drugs: diethylcarbamazine citrate and albendazole (DA) vs ivermectin + DA (IDA); number of rounds 2 vs 3; coverage 55% vs 75%). Left panel: prevalence for the whole population in each year. Right panel: prevalence among children aged six and seven. A wide range of other model outputs and scenario comparisons can be explored using an online interactive figure.

3.2. Probability of achieving local elimination targets

All MDA scenarios with three or more rounds of MDA at 75% coverage reduced prevalence of Ag to $< 1\%$ in more than 75% of simulations, regardless of drug combination (either DA or IDA), or drug efficacy assumptions (Interactive Figure). However, no scenario with two or three rounds of MDA (either DA or IDA) achieved 0% Mf prevalence in the general population by 2035 in any simulations (Interactive Figure). If coverage was only 55%, even seven rounds of two-drug or three-drug MDA could not reduce Mf prevalence to 0% by 2035 (Table 2). However, the probability of reducing Mf prevalence to 0% by 2035 using four, five, six, or seven rounds of IDA at 75% coverage was 4%, 39%, 75% and 92% for the default (optimistic) assumptions, and $< 1\%$, 2%, 13% and 37% under conservative drug efficacy assumptions (Table 3).

3.3. Speed of resurgence after MDA

The sterilising effects of drugs resulted in some transient effects in years directly following MDA (see supplementary material section 8). However, under all assumptions, after any possible transient effects, the mean predicted Mf prevalence grew exponentially until 2035 (the last year of simulations), with the rate of growth independent of the MDA strategy employed or drug efficacy assumptions (Interactive Figure).

The mean predicted prevalence of Ag or Mf in six and seven-year-olds after MDA was less than one third of the prevalence Ag or Mf in the general population (Fig. 2, Interactive Figure). Even with only two rounds of three-drug MDA at 75% coverage, the antigen prevalence in six and seven year-olds did not exceed 1% until 2028, by which point the mean Ag prevalence in the general population was 3.6% (Fig. 2).

3.4. Effect of MDA strategy on outcomes

The number of MDA rounds, coverage, and choice of drugs determined the lowest prevalence achieved and the probability and timing of resurgence. Resurgence to $> 1\%$ Ag prevalence occurred earlier in strategies that used DA, fewer rounds, or lower coverage. For a given number of rounds, switching from DA to IDA was somewhat more effective at reducing prevalence and delaying (or preventing) the resurgence of Ag prevalence to $> 1\%$ than improving coverage from 55% to 75%. However the combination of high coverage and three-drug treatment was the most effective (Table 3, Interactive Figure).

For a given drug treatment regime, increasing the coverage from 55% to 75% was more effective than conducting an additional round. For instance, two rounds of IDA at 75% coverage was more effective at reducing projected mean prevalence than three rounds of IDA at 55% coverage (Fig. 2, Interactive Figure), while three rounds at 75% coverage was more effective than 5 rounds at 55% coverage (Interactive Figure).

For a given level of coverage, switching from DA to IDA was more effective at reducing mean Ag prevalence than conducting two or three additional rounds. For instance, at 75% coverage two rounds of IDA was more effective than four rounds of DA, while four rounds of IDA was more effective than seven rounds of DA (Interactive Figure).

4. Discussion

We estimate that at least six annual rounds of three-drug MDA with 75% coverage would be required for a 50% probability of interrupting the transmission of LF in American Samoa. Similarly, at least four annual rounds of three-drug MDA with 75% coverage would be required for a 50% probability of maintaining antigen prevalence below 1% until 2035. In contrast to other modelling studies (May, 1977; Gambhir and Michael, 2008; Gambhir et al., 2010; Irvine et al., 2015; Collyer et al., 2020), our model fitted to American Samoa does not predict a critical prevalence threshold (e.g. 1% Ag prevalence or 0.5% Mf prevalence) below which prevalence will decline in the absence of ongoing interventions.

Two rounds of three-drug MDA were distributed in American Samoa in 2018 and 2019. The first of these rounds had an estimated coverage of 73% (Brant et al., 2019). Our model suggests that the second round of three-drug MDA is very likely to have reduced Mf prevalence to between 0.1% and 1% but is unlikely to have reduce antigen prevalence below 1% and is very unlikely to lead to the long-term elimination of LF without further intervention. In fact, we estimate that if only two rounds of interventions were implemented then by 2028 Ag prevalence will be

4% (90% simulations 2–6%) and there would be a 60% chance that Mf prevalence exceeds 1%.

An additional round of MDA was conducted in 2021, having been delayed by the COVID-19 pandemic. However, we estimate that a third round of MDA in 2020 would also not have been sufficient to interrupt transmission. Moreover, the delay may have allowed further resurgence. Nevertheless, our model suggests that interruption of transmission may be possible with further rounds of MDA, but that resurgence is possible even if a small number of infectious individuals remain following MDA or if a small number of travellers were to reintroduce the infection into the population. Given the large number of rounds required, and the risk of reintroduction, complementary or alternative control strategies may be necessary to achieve and maintain elimination status.

WHO guidelines suggest that ongoing transmission after MDA should be assessed by measuring antigen prevalence in six and seven-year-olds, with prevalence below 1% to be considered indicative of elimination (World Health Organisation, 2017c). Our models highlight two issues with following these recommendations in American Samoa. First, any number of infectious individuals remaining after MDA can lead to resurgence in our model. Consequently, the detection of even one Mf-positive person demonstrates the need for ongoing intervention. Second, we predict that, after MDA, antigen prevalence in six and seven-year-olds will be less than one third of the prevalence in the general population. Surveillance strategies that focus only on this age group will therefore be far less sensitive than surveillance of the general population and may consequently delay the detection of resurgence and prevent timely interventions. This conclusion is consistent with findings from our field studies in American Samoa and neighboring Samoa (Sheel et al., 2018; Lau et al., 2020a, 2020b).

Other LF models have predicted the existence of critical biting rate thresholds or critical prevalence thresholds, below which transmission is too diffuse to maintain endemicity (May, 1977; Gambhir and Michael, 2008; Gambhir et al., 2010; Irvine et al., 2015; Collyer et al., 2020). The primary mechanism leading to critical prevalence thresholds in these models is related to sexual reproduction of the filarial parasites. These models assume that the proportion of a mature worm's offspring that end up in a host with another mature parasite with which they can mate increases with the prevalence of the parasites amongst the host population. It is therefore theoretically possible for transmission intensity to be sufficient to maintain endemicity if prevalence is above a threshold value, but insufficient to maintain endemicity if below that threshold. However, if a single bite from an infective vector is sufficiently likely to deposit *both* a male and a female parasite that survive to maturity, or if the transmission intensity is very high, or if infective vector bites are concentrated on only a smaller subset of the population, then the chance that a mature parasite finds a mate may be sufficient to sustain ongoing transmission even if overall population prevalence is very low.

Though our model captured the sexual reproduction of mature worms, it did not exhibit a critical prevalence threshold when parameterised for the population of American Samoa. GEOFIL is the first spatially explicit modelling framework for LF transmission. The inclusion of spatial effects may partially account for the lack of a critical prevalence threshold behavior in our model, as they allow for clustering of exposures in populations with otherwise very low overall prevalence. Furthermore, in our model a small fraction of infective mosquito bites transmitted both male and female L3 larvae. Other agent-based models, though also not explicitly modelling the LF burden in mosquitos, have assumed that the number of LF larvae acquired in a given period of time is Poisson distributed (or otherwise not aggregated in time) (Irvine et al., 2015; Stolk et al., 2008). This assumption is mathematically equivalent to assuming that infective bites are uniformly distributed in time and that a single infective bite can pass at most one L3 larvae that survives to maturity (analogous to $p_2 = 0$ in our model), enabling critical prevalence threshold behavior. Counterfactual parameterisations of our model where the intensity of transmission is sufficiently low and nearly all infective mosquito bites deposit at most a single sex of L3 larvae (i.e. $p_2 \ll p_1$) do exhibit critical prevalence thresholds. Though this indicates that critical threshold behavior could theoretically be a feature in some populations even after accounting for spatial clustering, the assumptions required to produce these effects are not consistent with ratio of antigen to Mf prevalence observed in American Samoa between the rounds of MDA ending in 2006 and the rounds beginning in 2018.

Our study has several limitations. There were relatively few data points available for fitting the transmission parameters in our model (surveys in 2010, 2014, and 2016); our model could be improved by verifying or fitting against surveys conducted since the start of triple-drug MDA. The initial conditions in our model simulations did not assume any clustering at the household or neighbourhood level and, except for a single village of high prevalence, assumed no clustering of cases at the village level. However, suboptimal coverage (incomplete reach of the MDA programme or non-adherence with MDA) during 2000–2006 may have been spatially correlated, as seen in neighboring Samoa (Willis et al., 2020), resulting in clusters of infectious persons in households, neighbourhoods, or workplaces which would have been amplified in subsequent transmission. As transmission is expected to be more efficient in a high prevalence cluster, failing to account for the clustering that may have existed in 2010 (the start year of our simulations) may have led us to overestimate transmission parameters to compensate, which would lead us to overestimate the probability and speed of resurgence. On the other hand, we also assumed no systematic non-participation and no spatial clustering of programme reach or non-participation in the MDA rounds starting in 2018. If these were present, we are likely to have overestimated the effectiveness of these subsequent rounds of MDA and therefore we may be underestimating the probability and speed of resurgence (Irvine et al., 2015; Stolk et al., 2008). We also assumed that mosquito population density and biting rates were spatially uniform. Failing to account for spatial heterogeneity in these factors and the potential intensification of spatial clustering they would produce, may (as above) have led us to either over- or underestimate the probability of elimination. In our model, the resurgence of prevalence since the cessation of MDA in 2006 implies a high intensity of transmission and predicts that, in the absence of further intervention, the eventual endemic Mf prevalence would be above 80% (simulations not shown). Though such high prevalence is not unprecedented (e.g. Papua New Guinea (Prybylski et al., 1994)) and prevalence has been high in American Samoa in the past (Hairston and Jachowski, 1968), 80% is higher than one may expect and difficult to verify empirically. However, our model should be more reliable for modelling transmission when prevalence is low, as it was for surveys used to fit the model. Other models have reconciled high transmission intensity and low/moderate endemic prevalence by assuming that biting rates are heterogenous across the population (Irvine et al., 2015; Stolk et al., 2008). Accounting for heterogenous biting rates in our model would likely have a similar result. However, we have used our model to consider strategies in the elimination setting, where the prevalence is far lower than the long-term endemic level. We also did not account for the potential introduction of parasites from other LF endemic countries. However, a post-MDA survey from 2014 in American Samoa (Graves et al., 2020) found no association between travel and seropositivity for antigen and antibodies. Therefore, accounting for travel is unlikely to substantially affect our predictions, provided elimination efforts in the broader region continue concurrently. However, if American Samoa achieves elimination before countries with which it has close travel connections, reintroduction will remain a risk. When emulating antigen-based surveillance we assumed that probability of testing positive for circulating filarial antigen would decay exponentially with a half-life of three months after the death of mature worms, in line with observations of antigen positive persons in the Cook Islands treated with DEC (McCarthy et al., 1995). However, one study in Papua New Guinea found that three quarters of Mf-positive patients treated with a three-drug regimen (including DEC) were still antigen-positive five years after treatment (King et al., 2020), suggesting that filarial antigen may sometimes linger for much longer than we have

assumed. However, the latter study was performed in a setting which (unlike American Samoa) had a very high burden of infection and no previous history of MDA, so the long-term antigen positivity could perhaps be explained by a high initial antigen load, residual infection with non-reproductive worms, or reinfection.

The absence of a critical prevalence threshold in our model has profound consequences for the elimination of LF in American Samoa. Unlike interventions to reduce biting rates or a hypothetical prophylactic treatment (e.g. vaccination), mass administration of anthelminthic drugs does not reduce the effective reproduction number for any parasites born after MDA. In the absence of a critical prevalence threshold, even a single infected person can lead to a resurgence in transmission. Consequently, in settings without critical prevalence thresholds, elimination strategies relying on treatment alone cannot reasonably use thresholds of 1%, 0.5%, or even 0.1% prevalence (Mf or Ag) to demonstrate elimination. Rather, interventions or surveillance should continue until there is enough evidence to demonstrate the total absence of transmission. However, identifying residual infections and foci of transmission becomes increasingly resource intensive as a population approaches local elimination (Lau et al., 2020a). Though school-based TAS offer logistical advantages (a large number of participants in a single place and time) compared with community-based population representative surveys that require visiting many different households when people are home (Sheel et al., 2018), testing only six- and seven-year-old children is likely to delay the detection of resurgence. School-based surveillance of older students or workplace-based surveillance of working adults may retain the logistical advantages of place-based surveys while improving detection rates by monitoring people with a higher risk of infection (Lau et al., 2017; Graves et al., 2020). Whatever the primary surveillance population, testing and/or treating the household members or neighbors of identified infected persons may provide an effective method of identifying and treating residual foci (Lau et al., 2014, 2020a; Drexler et al., 2012). Molecular xenomonitoring (i.e. trapping and testing vector mosquitos for evidence of filarial DNA) may be an appropriate complementary measure to human-based surveillance (Schmaedick et al., 2014; Lau et al., 2016; Rao et al., 2016; Pilotte et al., 2017; Subramanian et al., 2017).

While MDA has proven very effective at reducing prevalence in many settings including American Samoa, stopping MDA too soon is very likely to result in resurgence. Strategies other than MDA may be required in the final stages of elimination and post-elimination surveillance. Further modelling using a spatially explicit, agent-based framework like GEOFIL could help identify combinations of surveillance and transmission reduction strategies that are best able to achieve and maintain elimination.

CRediT authorship contribution statement

Angus McLure: Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Patricia M. Graves:** Conceptualization, Writing – review & editing. **Colleen Lau:** Conceptualization, Funding acquisition, Writing – review & editing. **Callum Shaw:** Formal analysis, Software, Writing – review & editing. **Kathryn Glass:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.epidem.2022.100591.

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