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Heterogeneity in elimination efforts could increase the risk of resurgence of lymphatic filariasis in Madagascar

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ABSTRACT

Background: Progress in lymphatic filariasis (LF) elimination is spatially heterogeneous in many endemic countries, which may lead to resurgence in areas that have achieved elimination. Understanding the drivers and consequences of such heterogeneity could help inform strategies to reach global LF elimination goals by 2030. This study assesses whether differences in age-specific compliance with mass drug administration (MDA) could explain LF prevalence patterns in southeastern Madagascar and explores how spatial heterogeneity in prevalence and age-specific MDA compliance may affect the risk of LF resurgence after transmission interruption.

Methodology: We used LYMFASIM model with parameters in line with the context of southeastern Madagascar and explored a wide range of scenarios with different MDA compliance for adults and children (40–100%) to estimate the proportion of elimination, non-elimination and resurgence events associated with each scenario. Finally, we evaluated the risk of resurgence associated with different levels of migration (2–6%) from surrounding districts combined with varying levels of LF microfilaria (mf) prevalence (0–24%) during that same study period.

Results: Differences in MDA compliance between adults and children better explained the observed heterogeneity in LF prevalence for these age groups than differences in exposure alone. The risk of resurgence associated with differences in MDA compliance scenarios ranged from 0 to 19% and was highest when compliance was high for children (e.g. 90%) and low for adults (e.g. 50%). The risk of resurgence associated with migration was generally higher, exceeding 60% risk for all the migration levels explored (2–6% per year) when mf prevalence in the source districts was between 9% and 20%.

Conclusion: Gaps in the implementation of LF elimination programme can increase the risk of resurgence and undermine elimination efforts. In Madagascar, districts that have not attained elimination pose a significant risk for those that have achieved it. More research is needed to help guide LF elimination programme on the optimal strategies for surveillance and control that maximize the chances to sustain elimination and avoid resurgence.

1. Introduction

Lymphatic filariasis (LF) is a parasitic neglected tropical disease endemic to countries in Asia, South America, and Africa (Local Burden of Disease 2019 Neglected Tropical Diseases Collaborators, 2020). In 2018, around 51 million people were infected and 36 million suffered chronic disability (World Health Organization, 2022). The WHO established the Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000 to achieve elimination by 2020 (World Health Assembly WHA50.29, 1997). The GPELF strategy relies heavily on regular mass drug administration (MDA) of albendazole and diethylcarbamazine or albendazole and ivermectin, depending on onchocerciasis endemicity. In 2018, WHO suggested a triple drug combination to accelerate elimination (World Health Organization, 2019), but no effective vaccine is available against LF (Chavda et al., 2021). So far, 17 of the 73 endemic countries have achieved LF elimination, reducing the MDA-requiring population by 49% (World Health Organization, 2022). However, the 2020 objective was not met, leaving 863 million people still at risk of infection (World Health Organization, 2022). Consequently, WHO revised the goal to eliminate LF in at least 80% of endemic countries by 2030 (Abela-Ridder et al., 2020). Major challenges remain, such as ensuring high MDA compliance and coverage (Babu and Babu, 2014; Spetch et al., 2019; Stolk et al., 2015), setting cessation criteria for MDA to prevent resurgence (Harris and Wiegand, 2017; Sheel et al., 2018)

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and monitoring LF prevalence's spatial and individual heterogeneity (Stolk et al., 2015).

Mathematical modeling has been a useful tool to help guide LF elimination programs at both international and national levels. LF-specific models have been used to simulate transmission dynamics in multiple geographic settings (Asep and Anggriani, 2012; Kastner et al., 2015; Matapo et al., 2023; Moraga et al., 2015; Xu et al., 2019), to evaluate the effect of several treatment options (Jambulingam et al., 2016; Stolk et al., 2003, 2018) and vector control strategies (Davis et al., 2021), and to inform surveillance (Prada et al., 2020a). They have helped define appropriate thresholds under which treatment can be stopped (Collyer et al., 2020; Sharma et al., 2023), including the use of antigenaemia and microfilaraemia as stopping decision criteria (Stolk et al., 2022; Sunish et al., 2002). Recently, these models have quantified the effect of Covid-19 on LF elimination efforts (Borlase et al., 2022; Prada et al., 2020b). A particular focus of modeling studies has been on characterizing the impact of spatial and individual heterogeneities in LF prevalence on disease control efforts (Davis et al., 2019; Eneanya et al., 2019; Gambhir et al., 2010; Michael and Singh, 2016; Stolk et al., 2015; Xu et al., 2019), as these have implications for the threshold of LF elimination (Gambhir et al., 2010), the required duration of MDA, and vector control strategies (Singh and Michael, 2015). Spatial heterogeneity in prevalence is typically modeled as a result of ecological conditions driving vector dynamics (Gambhir et al., 2010; Irvine et al., 2018; Singh and Michael, 2015), leading to heterogeneity in nightly biting rates and individual heterogeneity in parasite density (Irvine et al., 2018). However, after more than two decades of implementation of national PEFLs in almost all endemic contries, only few studies have investigated how local heterogeneities in MDA implementation could influence the effectiveness of elimination initiatives and the possibility of LF resurgence (Babu and Babu, 2014; El-Setouhy et al., 2007a).

Madagascar, like other African nations, faces ongoing challenges in eliminating LF (Local Burden of Disease 2019 Neglected Tropical Diseases Collaborators, 2020). The disease was first reported on the island in 1909 (Coulanges, 1983). The main vectors in Madagascar are *Anopheles funestus* and *Anopheles gambiae,* and the parasite responsible is *W. bancrofti* (Champetier De Ribes, 2000; Coulanges, 1983; Brunhes, 1969). The southeast coast has been historically most affected (Champetier De Ribes, 2000; Hawking, 1976; Ministère de la Santé Publique, 2016). A 2004–2005 mapping revealed that 98 of 114 districts were endemic (Ministère de la Santé Publique, 2016). The national PEFL started MDA in 2005 of albendazole and diethylcabamazine, administered door-to-door by community health workers for adults and children not enrolled in school, and at schools for enrolled children (Ministère de la Santé Publique, 2016). Since the implementation of MDA in Madagascar, 74 districts have enrolled in drug distribution with an average coverage of 75% (Appendix A), and 4 districts have successfully passed the TAS survey. The distribution is discontinuous due to various reasons such as lack of funding for campaign implementation, restrictive health measures during other outbreaks (plague in 2017 and Covid in 2020), or drug stockouts. After 10 rounds of MDA, the first transmission assessment survey (TAS) (World Health Organization., 2013) conducted in school-age children in three districts of southeastern Madagascar suggested transmission interruption and eligibility for MDA cessation (Garchitorena et al., 2018). However, parallel community surveys unveiled substantial heterogeneity in age-specific prevalence, with adults having higher circulating filarial antigeneamia (CFA) prevalence, and in spatial prevalence trends (Garchitorena et al., 2018). The main hypothesis was that age-specific differences in compliance between school-age children and adults could be behind these findings. The goal of this study was to assess whether differences in age-related compliance to MDA could explain observed prevalence patterns in southeastern Madagascar and to explore under which conditions these two sources of heterogeneity (spatial variation in prevalence and age-specific MDA compliance) could increase the risk of resurgence after interruption of LF transmission.

2. Methodology

2.1. Study setting and previous results

The districts of Manakara Atsimo, Vohipeno, Mananjary and Ifanadiana are located in the southeastern region of Madagascar. The estimated population in each district averages around 250,000 people (Statistique, 2019). In 2004, Immunochromatographic test (ICT) prevalence in these districts was very high (>30%) (Garchitorena et al., 2018). Each district received 10 rounds of MDA between 2005 and 2016 with a mean coverage of 75%. Surveillance at sentinel and spot check sites occurred every two years starting in 2007. After 10 rounds of MDA, 3 of the 4 districts where eligible for a TAS. In 2016, in addition to routine surveillance at sentinel and spot check sites, a school-based TAS was launched in schools of Manakara Atsimo, Mananjary and Vohipeno, and a community-based survey was conducted in Ifanadiana. Using CFA for all surveys, the study revealed important differences in CFA prevalence between adults and children, and between districts. No child had a positive CFA in the TAS surveys, and only one child (<15 years) from Mananjary tested positive at sentinel and spot check sites (Garchitorena et al., 2018). In contrast, 3.6% of individuals of 15–90 years age tested positive at sentinel and spot check sites in Mananjary, and 10.05% in Vohipeno. In Ifanadiana District, combined results from the community survey and sentinel and spot check sites found an CFA prevalence of 0.7% in children under 15 years, and 12.06% for individuals of 15–90 years (Garchitorena et al., 2018).

2.2. Model description

Our modeling study relies on the LYMFASIM model, one of the most commonly used and accepted models of LF. Here we present a brief description of the model, a more detailed description is given elsewhere (Jambulingam et al., 2016; Plaisier et al., 1998; Stolk et al., 2008). LYMFASIM is an individual-based, stochastic, micro-simulation that models the life events of an individual person and their filarial parasites. It simulates the transmission from person to person via mosquito vectors, dependent on the level of individual exposure.

In the model, the demographics of the human population are governed by birth and death rates, with women of reproductive age assigned an age-dependent fertility rate (Plaisier et al., 1998; Stolk et al., 2008). The human population size cannot exceed a fixed maximum each year. The expected number of births at a time t (using annual timesteps) is given by:

$$R_b(t) = \sum_{a=1}^{n_a} N_f(a,t).r_b(a) \tag{1}$$

Where $N_f(a,t)$ represents the number of women in age-group a at time t, $r_b(a)$, the annual fertility rate in age-group a and n_a the number of age-groups considered.

The dynamics of infection within human hosts are modeled by defining the reproductive capacity of female worms inside the human assuming the presence of a male worm. The density of mf for each individual person at time t is a function of the number of mf surviving from $t-1$ and the reproductive capacity of the total number of female worm present at time t (Eq. 2):

$$m_i(t) = s \times m_i(t-1) + F_i(t) \times r_i(t) \tag{2}$$

With s being the monthly survival rate of mf and r_i the number of mf produced by each female worm per month and per 20 μl blood smear of a person i. F_i quantifies the number of adult female worms in a host.

The transmission of mf from an infected individual to a susceptible mosquito is dependent on the density (per 20 μl) of mf (m_i) in the host. These mf then develop into infectious larvae within the mosquito vector. The relationship between the density (per 20μl) of mf (m_i) in a person i and the number of L_3 that will develop in feeding mosquitoes for the case of *Anopheles* is defined via Eq. (3):

$$L_{3_i} = a \times \left(1 - e^{-(bm_i)^c}\right) \tag{3}$$

In this expression, a is the maximum number of L_3 larvae that can develop in a mosquito, $b = \frac{1}{scale}$ and $c = power$ parameter. The force of infection (in terms of number of larvae received at time t) experienced by an individual person is then given by:

$$foi_i(t) = mbr(t) \times \overrightarrow{L_3}(t) \times E_i(t) \times sr \tag{4}$$

Where $mbr(t)$ is the monthly mosquito biting rate at time t, $\overrightarrow{L_3}(t)$ is the average number of infective larvae released per vector bite, $E_i(t)$ is the individual-level relative exposure to mosquito bites at time t and sr is the success ratio describing the chance that an inoculated L3 larva will survive and reach the stage of immature worm. The individual-level relative exposure is defined as the product of an age-sex dependent component $(E_{ai}(a_{i(t)}, s_i))$ and a random component E_{ii}.

$$E_{i(t)} = E_{ai}\left(a_{i(t)}, s_i\right) \times E_{ii} \tag{5}$$

The average number of infective larvae released per mosquito-bite $\overrightarrow{L_3}(t)$ is given by:

$$\overrightarrow{L_3}(t) = \nu \times \frac{\sum_{i=1}^{N(t)} E_{i(t)} \times L_{3i}(t)}{\sum_{i=1}^{N(t)} E_i(t)} \tag{6}$$

$N(t)$ is the total number of individuals in the human population. L_{3_i} is the average number of L_3-larvae resulting from a blood meal on person i defined via Eq. (3). The transmission probability of the mosquito vector to a host is defined by a constant ν which includes the probability that an L_3 will be released, the fraction of potentially infectious mosquitoes and survival of the mosquitoes in field conditions.

When the force of infection is constant, the number of mature worms in an individual at the equilibrium is given by the following equation:

$$M_i = foi(t) \times (\overline{Tl} - Ti) \tag{7}$$

Where $\overline{Tl}$ is the average lifespan of the parasite and Ti the duration of the immature stage. Female worms are assumed to be 50% of the total worm population in an individual.

2.3. Model simulations

Each simulation began in the year 1850 to allow for a 150-year warm-up and obtain the endemic equilibrium. An initial force of infection of 1 worm per 2 persons per year (0.5) was introduced for the first 10 years of simulations to establish infection. This force of infection was then removed, allowing only for local transmission dynamics. Although the model and simulations are theoretical, they were calibrated to reflect the overall conditions of Manakara Atsimo, Mananjary Vohipeno and Ifanadiana. For this, population size was set to 200,000 people. Additionally, the constant monthly biting rate and probability of transmission were adjusted to varying values, ensuring that mf prevalence at equilibrium fell between 20% and 30%, aligning with baseline mf prevalence observed in those districts before MDA implementation (Garchitorena et al., 2018) (Table 1). After simulations achieved equilibrium, we carried out the analysis from 2000 to 2030, the new WHO target year for LF elimination. In conformity to what occurred in the southeastern region of Madagascar, 10 rounds of MDA were modeled from 2005 to 2016 with an average coverage of 75% (Garchitorena et al., 2018). The impact of drug treatment on parasite population in an individual hosts in three ways: it immediately kills a proportion of adult worms, it immediately kills a proportion of mf, and it reduces the reproductive capacity of a female worm. We assumed that each treatment killed 50% of adult worms (Stolk et al., 2008) and it cleared 95% of mf (Truscott et al., 2020) (Table 1). We did not consider immunity in the model as suggested in (Stolk et al., 2008). Parameter values specific to

Table 1
Parameters used in each model for each scenario.

Model	Parameters	Value	Sources
For all simulations	Simulation start year	1850	To allow 150 years of warm up
	Simulation stop year	2030	New target year of elimination (World Health Organization, 2019)
	Maximum human population size	200,000	District setting (Garchitorena et al., 2018)
	Fertility rate per age category for women	Age Fertility rate 5 0.000 15 0.000 20 0.116 25 0.230 30 0.245 35 0.207 40 0.147 45 0.077 50 0.031 99 0.000	(Stolk et al., 2008)
	Number of mf produced per female parasite (per 20 μl blood smear)	0.58	(Subramanian et al., 2004)
	Parameters of mathematical function describing the uptake of infection by Anopheles mosquitoes	$a = 1.666$ $b = 0.027$ $c = 1.54$	(Stolk et al., 2008)
	Monthly bite rate (mbr)	550 bites per person per month	(Ravoahangimalala et al., 2008; Stolk et al., 2008)
	Success ratio (sr)	0.00088	(Stolk et al., 2008)
	Transmission probability (ν)	0.1	(Stolk et al., 2008)
	Duration of the immature stage (Ti)	8 months	(World Health Organization, 1992)
	Average lifespan of adult parasites (Tl)	10 years	(Subramanian et al., 2004)
	Exposure by age	0.1 at birth and increases linearly with age to reach a maximum 1 at age 20	(Stolk et al., 2008)
	Exposure variability	Gamma distribution with mean 1 and shape parameter 0.26	(Stolk et al., 2008)
	Proportion of mf killed by MDA	0.95	(Collyer et al., 2020; Truscott et al., 2020)
	MDA period	10 rounds between 2005 and 2016	District setting: (Garchitorena et al., 2018)
	MDA coverage (The percentage of the population receiving MDA)	75%	District setting: (Garchitorena et al., 2018)
For modeling age-specific MDA compliance	MDA compliance (the percentage of the covered population who correctly follows the treatment regime)	Adults: 60%, 65%, 70%, 75%, 80% Children: 100%,95%, 90%, 85%, 80%	
For modeling risk of resurgence due to age-specific compliance	MDA compliance	Adults: range from 40% to 100% Children: range from 40% to 100%	

(continued on next page)

Table 1 (*continued*)

Model	Parameters	Value	Sources
For modeling migration and risk or resurgence due to it	*MDA compliance*	*90%*	*Assumed*
	Average exposure of adult migrants	*0.7*	*Estimated via Exercise 1*
	Average number of mf (L3) per infected migrant	*10*	*Estimated via Exercise 1*
	Percentage of population that migrates	*Ranged from 2% to 6% (4000–12,000 migrants per year)*	(Poussou et al., 1988)
	Mf prevalence level at original district of migrants	*Ranged from 0 to 24%*	

southeastern Madagascar are shown in Table 1, with default values in the LYMFASIM program kept for all other parameters. Simulations were conducted using monthly timesteps.

2.4. *Exercise 1: Modeling the impact of age-specific compliance on LF CFA prevalence*

The goal of our first modeling exercise was to assess whether age-specific MDA compliance better explained the observed age-specific patterns in LF CFA prevalence rates than age-specific differences in exposure alone. Differences in LF prevalence between adults and children are common because contracting the disease depends strongly on the exposure of the person to mosquito biting, and adults are believed to be more exposed than children due to behavioral differences (Harris and Wiegand, 2017; Singh and Michael, 2015). This is modeled in LYMFASIM by setting exposure as a linearly increasing function of age starting from 0.1 for newborn babies, increasing until the age of 20 to reach a maximum of 1 and remaining constant after that. We first simulated the model with difference in exposure alone and compared the resulting CFA prevalence by age group with data observed in Manakara Atsimo, Mananjary, Vohipeno and Ifanadiana, assuming that MDA compliance is 90% for everyone.

Second, we simulated differences in MDA compliance between children (under 15 years old) and adults (15 years and older), assuming that children have higher MDA compliance than adults. This assumption is because children receive drugs in a more controlled environment such as their school, where the presence of their teachers and other adults ensures adherence. In contrast, adults may not always be present when community health workers distribute the drugs and may also decide not to take them. MDA compliance is defined as the proportion of people who ingest drugs among those who have received them. Thus, in every MDA round, the probability for an individual to be effectively treated is the product of MDA population coverage and age-specific compliance. Values of MDA compliance in adults and children ranged from 60% to 100%, with difference in compliance between the two age groups ranging from 0.1 to 0.4, at 0.1 intervals. The average compliance in both adults and children was maintained constant to capture only the variation of the difference in compliance. The age-specific difference in CFA prevalence in 2016 was estimated as the difference between CFA prevalence in adults and CFA prevalence in children during that year. 100 simulations were conducted for each set of MDA compliance values, and the observed difference in prevalence in 2016 between age groups for each district was compared to simulated results.

2.5. *Exercise 2: Modeling the risk of resurgence due to age-specific difference in MDA compliance*

To explore the risk of resurgence caused by age-specific differences in MDA compliance, we set MDA coverage at 75% and varied compliance in adults and children ranging from 40% to 100%, at 10% intervals, totaling 49 scenarios. We classified each simulation into one of the following outcomes: 1) True elimination, when prevalence of mf measured at one-year post-MDA was lower than 1% (threshold recommended by the WHO) and it did not increase above that for >2 years until the end of the study period. If it increased above the threshold for 2 years or less, it was assumed to have occurred by chance as a result of the stochasticity in the model. 2) Non-elimination: when prevalence never decreased under 1% for >2 years, and 3) Resurgence, when prevalence fell below 1% one year after MDA cessation but it returned above the threshold for >2 years before the end of the study period. For each theoretical scenario, the proportion of each of these three outcomes is estimated as the percentage of simulations with a particular outcome (Fig. 1). Finally, the proportion of resurgence for the districts of Mananjary, Vohipeno and Manakara Atsimo were assessed according to the age-specific difference in compliance estimated in the previous section.

2.6. *Exercise 3: Modeling the risk of resurgence due to migration from neighboring districts with varying levels of LF mf prevalence*

Heterogeneity in MDA implementation and ecological conditions can lead to districts achieving interruption of transmission at different times, resulting in spatial heterogeneity in LF prevalence. Human migration from districts with high mf prevalence towards those that have achieved elimination could increase the risk of resurgence (Dorkenoo et al., 2021). We explored under what levels of migration from and LF mf prevalence in neighboring districts the risk of resurgence might increase in a focal district. We modeled the effect of migration by assuming both uninfected and infected migrants migrated to the focal district at the same rate. Uninfected migrants contributed only to the relative exposure of individuals by also attracting mosquito bites, while infected migrants also introduced a constant number of L_3 per individual to the mosquito vector population. Then, the equation representing the average number of larvae released per mosquito bite from Eq. 6 is rewritten as Eq. 8:

$$\overrightarrow{L_3}(t) = \nu \times \frac{\sum_{i=1}^{N(t)+M(t)} E_{i(t)} \times L_{3i}(t)}{\sum_{i=1}^{N(t)+M(t)} E_i(t)} \tag{8}$$

Where $M(t)$ is number of migrant populations at time t. We assumed that migrants are adults with constant exposure E_M and that number of larvae introduced by each infected migrant is also constant (L_{3M}). These two constant rates were estimated as the mean of these values in the adult populations from simulations in Exercise 1. Eq. 8 can then be rewritten as Eq. 9:

$$\overrightarrow{L_3}(t) = \nu \times \frac{\sum_{i=1}^{N(t)} E_{i(t)} \times L_{3i}(t) + \sum_{i=N(t)+1}^{N(t)+M(t)} E_M \times L_{3M}}{\sum_{i=1}^{N(t)} E_i(t) + \sum_{i=N(t)+1}^{N(t)+M(t)} E_M} \tag{9}$$

Because we assume constant rates E_M and L_{3M} across individuals and time, the total contribution of the migrant population to exposure and the force of infection can be simplified into a constant increase to the force of infection at each timestep, rather than a summation.

$$\text{Therefore, } \overrightarrow{L_3}(t) = \nu \times \frac{\sum_{i=1}^{N(t)} E_{i(t)} \times L_{3i}(t) + M(t) \times Pr \times E_M \times L_{3M}}{\sum_{i=1}^{N(t)} E_i(t) + M(t) \times E_M} \tag{10}$$

This simplification allowed us to implement migration from neighboring districts into the existing LYMFASIM architecture without needing to rewrite the underlying Java script on which the microsimulations are based. Migrants were assumed to follow a commuting pattern of mobility, where they returned to their initial district at the end of each timestep and therefore did not contribute to overall

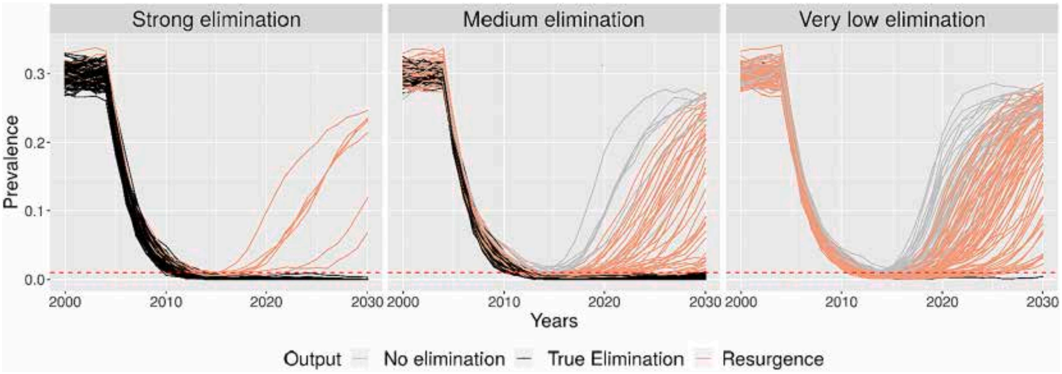

Fig. 1. Illustration of possible outputs for each simulation: true elimination, resurgence or non-elimination. True elimination occurs when prevalence measured at one-year post-MDA was lower than 1% and did not increase above that till the end of the study analysis. Non-elimination occurs when prevalence never decreased under 1%. Resurgence occurs when prevalence fell below 1% one year after MDA cessation but returned above the threshold before the end of the study period. Strong elimination: Case of 7% of resurgence and 93% of elimination and no case of non-elimination. Medium elimination: Case of 52% of elimination, 37% of resurgence and 11% of non-elimination. Very low elimination: Case of 1% of elimination, 61% of resurgence and 38% of non-elimination.

prevalence levels within the focal population. We did not model LF transmission dynamics in neighboring districts and prevalence rates in the origin districts of migrants were assumed to be constant.

We simulated a range of scenarios where 2% to 6% (in 0.5% increments) of the population migrate from surrounding districts (equivalent to 4000–12,000 migrants) ref., with mf prevalence in the source districts ranging from 0% to 24%. We simulated each of the 81 scenarios 100 times, and we estimated the proportion of simulations with each of the three outcomes (true elimination, resurgence, non-elimination).

3. Results

3.1. *Exercise 1: The impact of age-specific MDA compliance on LF CFA prevalence*

Using the LYMFASIM model, we found that allowing for age-specific differences in mosquito exposure, but not age-specific MDA compliance rates only explained observed CFA prevalence rates in Manakara Atsimo, where both age groups had a 0% CFA prevalence. For the other 3 districts, the observed difference in CFA prevalence between adults and children were 3.2%, 10.05% and 11.3% in Mananjary, Vohipeno and Ifanadiana, respectively, which were not explained by age-specific differences in exposure alone (Table 2). The magnitude of difference in age-specific MDA compliance needed to match observed CFA prevalence rates differed by district. Observed CFA prevalence in the district of Mananjary was consistent with a difference in compliance between age groups of 20% or 30%, where children had a 90–95% compliance and adults a 65–70% compliance rate. In turn, observed CFA prevalence in Vohipeno and Ifanadiana were consistent with an age-specific MDA compliance difference of 40%, where children had a 100% compliance rate and adults a compliance rate of 60%.

Table 2
Observed and simulated difference in CFA prevalence due to differences in age-related compliance.

Difference in compliance between age groups (%)	Compliance in adults vs. children (%)	Difference in CFA prevalence, % (95% interval)	Corresponding district
0	80–80	0.54 (−1.22–2.3)	Manakara Atsimo (0%)
10	75–85	1.09 (−0.47-2.65)	
20	70–90	2.9 (1.13–4.66)	Mananjary (3.4%)
30	65–95	3.9 (1.9–5.87)	Mananjary (3.4%)
40	60–100	9.27 (6.99–11.55)	Vohipeno (10.05%) Ifanadiana (11.3%)

3.2. *Exercise 2: The risk of resurgence due to age-specific MDA compliance*

By simulating a range of MDA compliance rates in both adults and children from 40% to 100%, we found that the proportion of scenario reaching true elimination was very low (under 2%) when compliance in both adults and children was 60% or below, or when compliance in one of the age groups was as low as 40% (Fig. 2). In contrast, the proportion of scenarios attaining true elimination exceeded 80% when compliance in both adults and children was above 70% and the average compliance was over 80%. For example, if the compliance rate of adults was 70%, the compliance rate in children had to be 90% to achieve true elimination. The proportion of resurgence in our scenarios ranged from 0 to 19% and occurred mostly in cases of intermediate levels compliance (Fig. 2). Out of the 49 scenarios, 14 of them (28%) presented a risk of resurgence of >10% and the majority of those (9 out of 14) were cases where MDA compliance rates in adults were lower than in children (Appendix A). When the MDA compliance rates were 90% in children and 50% in adults, nearly one in five simulations resulted in resurgence after initial elimination. These results suggest that particular attention should be paid to those cases where mf prevalence is below the threshold of 1%, at the population level (meaning it would pass the sentinel and spot-check site evaluations, leading to a TAS) and in the child population (meaning it would also pass the TAS evaluation), but not in the adult population. While only a small proportion (4–8%) of simulations resulted in this combination of mf prevalence levels, over half of these simulations eventually ended in resurgence (Table 3).

3.3. *Exercise 3: The risk of resurgence due to migration from neighboring districts*

When accounting for migration of individuals from neighboring districts, we found that the proportion of simulations that ended in resurgence ranged from 0 to 75%. This suggests that the mf prevalence in neighboring districts can considerably impact the risk of resurgence in districts that have already achieved elimination, even at migration rates of only 2–6% per year. Beginning at prevalence rates in neighboring districts of 9%, the proportion of scenarios reaching elimination declines rapidly, with an increasing proportion of scenarios ending in resurgence as prevalence increases (Fig. 3). For example, at mf prevalence levels between 9% and 20% in surrounding districts, the associated risk of resurgence is higher than 60% even at relatively low migration levels of

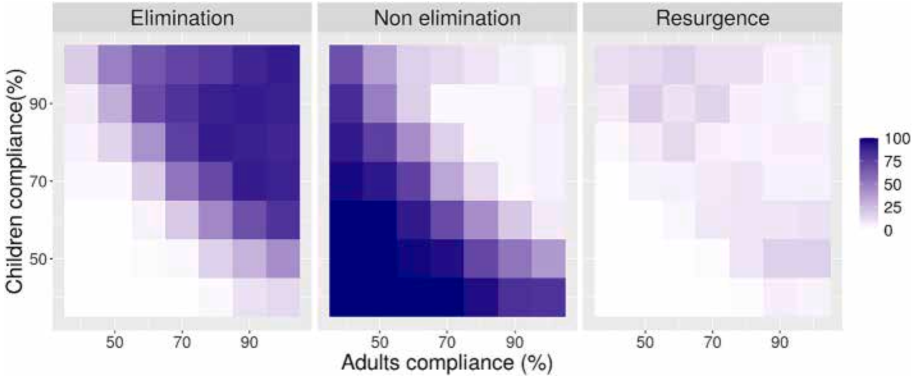

Fig. 2. Proportion of scenarios resulting in elimination, non-elimination and resurgence associated with different compliance scenarios for adults and children. Elimination: The proportion of scenario ending in elimination is estimated as the percentage scenarios where mf prevalence fall below 1% one year after MDA cessation and remain under that threshold until the end of the study period. Non elimination: The proportion of scenario ending in non-elimination is the percentage of scenarios where mf prevalence does not fall below 1% for >1 year during the study period Resurgence: The proportion of scenarios ending in resurgence is the percentage of scenarios where mf prevalence falls below 1% one year after MDA stop and returns above that threshold before the end of the study period.

Table 3
Associated resurgence in simulations where mf prevalence under the 1% threshold is achieved at the population level and in children (but not in adults) leading to MDA stop.

Compliance in adults (%)	Compliance in children (%)	# of simulation reaching MDA stoppage criteria	# of simulation with MDA stoppage criteria but adults over 1% threshold (adults' reservoir)	# of simulations of adult's source that result resurgence
40	100	31	7	4 (57%)
50	90	50	4	2 (50%)
50	100	63	4	3 (75%)
60	100	83	8	5 (62%)

2.5% of the population per year. When prevalence in the districts of origin is above 20%, most scenarios result in non-elimination exceeding 60% when migration rate is above 2.5%. In contrast, a high proportion of elimination (>78%) is observed when mf prevalence in original district is under 7% for all migration rates considered (Fig. 3).

4. Discussion

The objective of this study was to evaluate, through mathematical modeling whether differences in age-related compliance with MDA could help elucidate observed prevalence patterns in southeastern Madagascar. Additionally, we aimed to investigate the circumstances under which two sources of heterogeneity, namely spatial heterogeneity, and age-specific heterogeneity in MDA compliance, may amplify the risk of resurgence following the interruption of LF transmission. Despite ambitious global targets for LF elimination by 2020, progress has been slower than initially intended and the revised goals currently aim at elimination in 80% of endemic countries by 2030 (Abela-Ridder et al., 2020). A major challenge for elimination efforts is the individual and spatial heterogeneity in LF transmission (Gambhir et al., 2010; Irvine et al., 2018; Michael and Singh, 2016). Heterogeneity at the level of the individual and in prevalence across space are often modeled as the result of preventative behaviors that cause heterogeneity in exposure to mosquito vectors, for the former, or due to spatial heterogeneity in ecological conditions, for the latter (Gambhir et al., 2010; Michael and Singh, 2016). Using the case of southeastern Madagascar, where significant spatial and age-specific prevalence heterogeneity has been observed, we used theoretical models to explore how differences in MDA compliance among age groups and migration from neighboring districts could affect the risk of resurgence in districts having attained elimination.

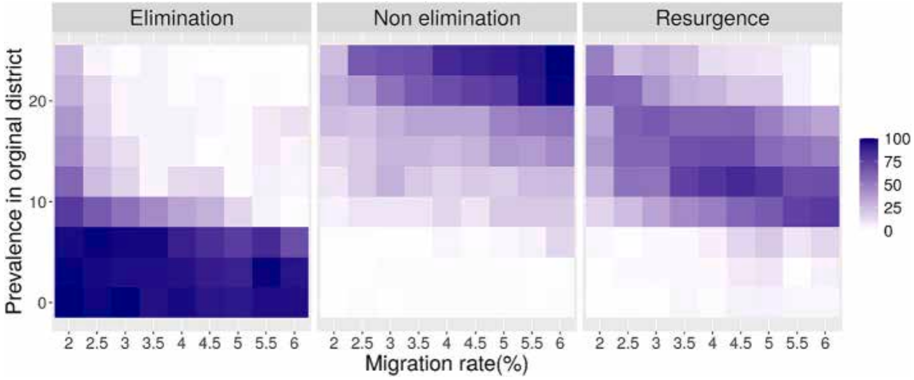

Fig. 3. Proportion of scenarios resulting in elimination, non-elimination and resurgence associated with different levels of migration and mf prevalence in surrounding districts. Elimination: The proportion of scenario ending in elimination is estimated as the percentage scenarios where mf prevalence fall below 1% one year after MDA cessation and remain under that threshold until the end of the study period. Non elimination: The proportion of scenario ending in non-elimination is the percentage of scenarios where mf prevalence does not fall below 1% for >1 year during the study period. Resurgence: The proportion of scenarios ending in resurgence is the percentage of scenarios where mf prevalence falls below 1% one year after MDA stop and returns above that threshold before the end of the study period.

We found that age-specific differences in exposure alone were not sufficient to explain the observed difference in prevalence between adults and children in this area. However, age-specific differences in MDA compliance of 20–40% were able to reproduce age-dependent prevalence rates similar to those seen in southeastern Madagascar. We also found that age-specific compliance could impede elimination efforts, leading to a non-negligible 10–20% risk of resurgence in certain scenarios. The LYMFASIM model does not consider on spatial heterogeneity. However, when considering spatial heterogeneity via human migration, we found that spillover from neighboring districts led to a 60% risk of resurgence when prevalence in the district of origin was over 15%. The risk of non-elimination approached 60% only at high levels of prevalence in the district of origin (>20%) and migration (6%), suggesting spatial heterogeneity is more likely to interrupt elimination than block elimination completely. As countries approach elimination targets over the next decade, these sources of heterogeneity in transmission must be considered to prevent resurgence and ensure local elimination is maintained.

Under appropriate treatment coverage levels, elimination success and the risk of resurgence in our study depended strongly on individual compliance to MDA regimes. At the levels of age-specific differences in compliance estimated in our initial modeling exercise, we estimate the risk of resurgence due to this individual-level heterogeneity to be between 50 and 60% in our study area of southeastern Madagascar. This is in line with previous studies, which have shown that low compliance had negative impacts on achieving elimination (Babu and Babu, 2014; Kumar et al., 2023; Lahariya and Mishra, 2008). Several studies have already discussed the importance of MDA compliance in achieving elimination of LF (Babu and Mishra, 2008; El-Setouhy et al., 2007b; Remme et al., 2006), with lower compliance rates increasing the number of rounds of MDA needed to achieve elimination. Several factors can affect compliance, such as the drug delivery mechanism and whether the recipient knows the distributor personally (Krentel et al., 2013; Maddren et al., 2023). In Madagascar, where drugs are distributed at schools for children and door-to-door by community health workers for adults, it is reasonable to believe that children would have higher compliance than adults. Teachers, who are authority figures, typically assist with distribution of MDA at school, and children receiving treatments from adults have little agency to refuse a treatment. For adults, community health workers are not their typical health provider (they typically diagnose and treat only common illnesses of children under 5 years), and adults may hesitate to comply with the treatment while feeling healthy or may be absent at the time of the distribution campaign. While distribution coverage is routinely reported during MDA campaigns, there is no simple way to report compliance which could undermine LF control and surveillance strategies. Improving the monitoring of MDA compliance, especially in adults, could therefore be crucial for the success of elimination programs.

Our simulations show that certain age-specific MDA compliance scenarios can lead to a reduction in prevalence under the 1% threshold at the total population level and in children, but not in the adult population. WHO guidelines would suggest a cessation of MDA interventions in these instances due to the population passing both routine monitoring and TAS evaluation. However, in those particular cases, the risk of resurgence can be high, as transmission is maintained by a pool of infected adults who are omitted under the current evaluation methods. This is in line with other studies demonstrating the limitations of TAS evaluations at detecting certain underlying transmission trends (Harris and Wiegand, 2017). A second TAS conducted post-cessation of MDA can help assess whether transmission has increased after several years, but financial and logistic constraints for national programme may prevent the implementation of second TAS in an appropriate timeframe to inform timely action. Similarly, a second TAS may be deprioritized versus other key activities (MDA in endemic districts, first TAS in candidate districts).

In cases where there are important geographic differences in MDA progress between neighboring districts, such as those observed in Madagascar, human migration may increase the risk of resurgence in districts that have achieved LF elimination. Human migration has been long recognized as a potential source of introduction of new LF infections (Plaisier et al., 2000; Ramaiah, 2013). For instance, phylogeographic analyses of *W. bancrofti* in India suggested that the introduction of LF into the country was strongly driven by migration from the Southeast Asian archipelago (Thangadurai et al., 2006). Yet, the impact of local migration patterns on population-level transmission dynamics in areas under elimination is under-investigated and differs across contexts (de Souza et al., 2014). In Sierra Leone and Liberia, mass migration from LF endemic rural areas towards cities due to war did not result in LF resurgence in these urban areas (de Souza et al., 2014), while a spatially explicit model of LF in American Samoa predicted that migration could explain observed transmission patterns in the island (Xu et al., 2019). Our results imply that to successfully reach LF elimination and to avoid resurgence, MDA campaigns should be continued until all neighboring districts reach the elimination criteria.

Our study had several limitations. First, data to inform the simulations in this study were collected from 2004 to 2016 and we therefore lacked recent prevalence data. The predictions from our models should be validated with recent field data, but no recent data is available yet for southeastern Madagascar. While WHO protocols post-MDA cessation suggest conducting a second TAS after 2 or 3 years of the initial TAS to confirm the elimination status and the absence of resurgence (World Health Organization., 2013), the COVID-19 epidemic and lack of financial resources prevented the national GPEFL from carrying out such an evaluation in a timely manner. Second, our implementation of human migration was necessarily simplified due to constraints on computational resources, and we did not explicitly follow transmission dynamics in neighboring districts, assuming instead a constant source of infections. Given the importance of human migration observed in this study, spatially explicit models such as the recently developed GEOFIL (Xu et al., 2019) should be implemented for a more realistic investigation of the impact of human migration considering the current spatial heterogeneities in LF prevalence in Madagascar and other settings, as well as of the impact of the spatial distribution of larval habitat of LF vectors This model does not directly simulate vector dynamics, and we assumed equilibrium vector populations to be identical across the districts. In addition, it only includes two age classes, neglecting potential differences in prevalence patterns among adolescents. Adopting these assumptions allowed us to focus on our primary issues of MDA compliance and migration and explore the ability of these factors alone to impact prevalence rates. It is likely a combination of multiple sources of heterogeneity, some of which were not included in this study. Third, we considered only the widely used LYMFASIM model in this study (Plaisier et al., 1998; Stolk et al., 2008). However, other models exist such as EPIFIL (Chan et al., 1998; Norman et al., 2000), a deterministic population-level model, and TRANSFIL (Irvine et al., 2015), another stochastic microsimulation model of parasite loads at the individual level similar to LYMFASIM. More recently, ensemble modeling framework have been used to combine two or more of these models to explore consistency and variability among model predictions (Michael et al., 2018; Smith et al., 2017; Stolk et al., 2018) and future work in this area should adopt more comprehensive modeling framework such as ensemble modeling.

5. Conclusion

In conclusion, this study reveals that gaps in implementation of LF elimination programme, such as those caused by differences in age-specific MDA compliance or by a different pace of progress in LF elimination in neighboring districts, can increase the risk of resurgence and undermine elimination efforts. In Madagascar, districts that have not attained elimination pose a significant risk for those that have achieved it. More research is needed to help guide LF elimination programme on which optimal strategies for surveillance and control can maximize the chances to sustain elimination and avoid resurgence given these sources of heterogeneity. As countries near elimination, this research could inform adapted surveillance guidelines to better monitor for these sources of heterogeneity and prevent resurgence of disease.

CRediT authorship contribution statement

Elinambinina Rajaonarifara: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Benjamin Roche:** Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Cedric B. Chesnais:** Writing – review & editing, Validation, Supervision, Formal analysis, Conceptualization. **Holivololona Rabenantoandro:** Writing – review & editing, Visualization, Data curation. **Michelle Evans:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis. **Andres Garchitorena:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

No competing interest is declared.

Data availability

Data used in this study are available from the corresponding author on request.

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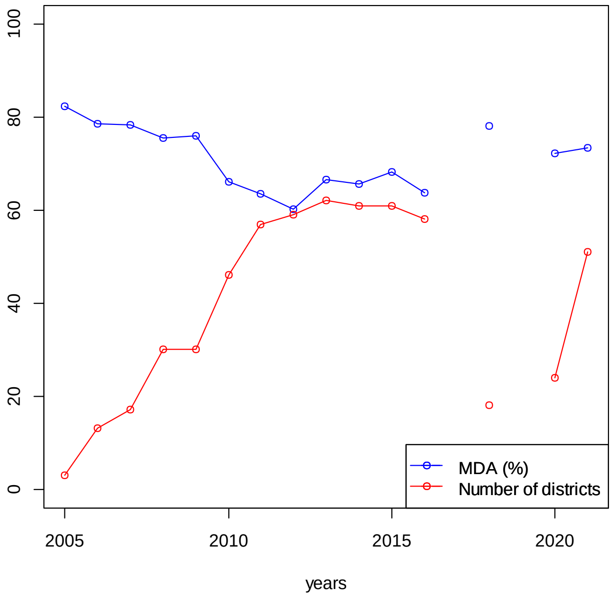
Appendix A. Evolution of the mass drug administration in Madagascar



Appendix B. Compliance in adults and children that correspond to proportion of resurgence >10%

Compliance in adults	Compliance in children	Proportion of true elimination	Proportion of non-elimination	Proportion of resurgence
0.4	1	0.19	0.69	0.12
0.5	1	0.49	0.37	0.14
0.6	1	0.66	0.17	0.17
0.7	1	0.74	0.14	0.12
0.8	1	0.78	0.1	0.12
0.5	0.9	0.31	0.5	0.19
0.6	0.9	0.71	0.18	0.11

(*continued on next page*)

(*continued*)

Compliance in adults	Compliance in children	Proportion of true elimination	Proportion of non-elimination	Proportion of resurgence
0.7	0.9	0.82	0.03	0.15
0.6	0.8	0.42	0.44	0.14
0.7	0.7	0.54	0.34	0.12
0.8	0.7	0.72	0.14	0.14
1	0.6	0.81	0.08	0.11
0.9	0.5	0.3	0.54	0.16
1	0.5	0.44	0.39	0.17

Source code

The code for the version of LYMFASIM used in this paper is part of the WORMSIM framework version2.58Ap59, freely available at [https://gitlab.com/erasmusmc-public-health/wormsim.previous.versions/-/blob/master/wormsim2.58Ap59_src.zip?ref_type=heads].

Author statement

Concieved and designed the experiment: ER, AG, CBC and BR.
Performed the analysis: ER and ME.
Wrote the initial draft of the manuscript: ER and AG.
Revised the manuscript and accepted it in its final form: ER, AG, ME, CBC, BR and HR.
Act as guarantor of the study: ER, AG and ME.

Ethical statement

This study was approved by the Madagascar National Ethics committee (041/MSANP/SG/AGMED/CERBM) and the Harvard Medical School Institutional Review Board (IRB16-0347).

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