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Les barrières à la lutte contre les maladies infectieuses dans les zones rurales à faibles revenus : cas de la filariose lymphatique et de la vaccination infantile dans le Sud-Est de Madagascar

Elinambinina Rajaonarifara

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Ecole doctorale Pierre Louis de Santé Publique

Epidémiologie et Sciences de l'information biomédicale

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Les barrières à la lutte contre les maladies infectieuses dans les zones rurales à faibles revenus : cas de la filariose lymphatique et de la vaccination infantile dans le Sud-Est de Madagascar

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Dédicace

Je dédie cette thèse à mon mari et mes enfants !

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Liste des abréviations

- BCG: Bacille Calmette-Guérin
- CSB: Centre de Santé de Base/ Health center
- DHS: Demographic and Health Surveys
- DTP: Diphteria, tetanus, pertussis
- DMM: Distribution Médicamenteuse de masse
- DTCoq: Diphtérie, Tétanos, Coqueluche
- DTC-HepB-Hib: Vaccin contre la Diphtérie, le Tétanos, la Coqueluche, L'Hépatite B et Méningites
- EPI: Expanded Program on Immunization
- FL: Filariose Lymphatique
- FTS: Filarial Test Strip
- GAVI: Global Alliance for Vaccine and Immunization
- GIS: Geographic Information Systems
- GLMM: Generalized Linear Mixed Model
- GPELF: Global Program to Eliminate Lymphatic Filariasis
- HSS: Health System Strengthening
- IHOPE: Ffanadiana Health Outcomes and Prosperity Evaluation
- INSTAT: Institut Nationale des STATistiques
- IBM: Individual-Based Model
- ICT: Immunochromatographic Test
- LF: Lymphatic Filariasis
- LMICs: Low and Middle Income Countries
- MDA: Mass Drug Administration
- MICS: Multiple Indicator Cluster Survey
- MoPH: Ministry of Public Health
- MTN: Maladie Tropicale Négligée
- OMS: Organisation Mondiale de la Santé
- ONG: Organisation Non Gouvernementale
- OR: Odds Ratio

- PELF: Programme d'Élimination de la Filariose Lymphatique
- PEV: Programme Élargi de Vaccination
- Polio: Poliomyélite, polyomyélie
- RI: Routine Immunization
- RSS: Renforcement du Système de Santé
- SIA: Supplementary Immunization Activities
- TAS: Transmission Assessment Survey
- VAR: Vaccin Anti- Rougeole
- VW: Vaccination Weeks
- WHO: World Health Organization

Introduction générale

Contexte générale

La lutte contre les maladies infectieuses est un combat continu dans le domaine de santé publique. Même si une diminution importante du fardeau des maladies infectieuses a été constatée au niveau global ces dernières décennies [1], certaines régions du monde et en particulier l'Afrique subsaharienne continuent à supporter un poids très important de ces maladies. Par exemple, cette région comprend 40% du fardeau des maladies tropicales négligées (MTN) [2] et plus de 90% des décès liés au paludisme [3]. Pour certaines maladies, les agents pathogènes ont des cycles de vie complexes ou il n'existe pas des moyens de lutte efficaces pour les prévenir, ce qui les rend difficiles à être contrôlées ou éliminées. Cependant, même pour des maladies où il existe des vaccins efficaces et qui sont donc évitables avec les moyens de lutte actuels, comme la rougeole ou la poliomyélite (polio), elles continuent à faire des ravages dans les pays à faible revenus [4]. Par exemple, une hausse de 400% des cas de rougeoles a été observée en Afrique entre 2021 et 2022 [5]. En plus de ces maladies endémiques, l'émergence de pathogènes d'origine zoonotique est en pleine accélération [6], ce qui pose des problèmes à l'échelle mondiale comme le montrent l'épidémie de COVID-19 touchant presque toute la planète depuis 2020, ou encore le virus Ebola en 2014-2016 qui a causé plus de 10 000 morts et des lourdes pertes économiques estimées à 25 milliards de dollars pour l'Afrique occidentale [7].

Cette distribution disproportionnée des maladies infectieuses dans les pays à faibles revenus peut être expliquée en partie par un lien étroit et bidirectionnel entre les maladies infectieuses et la pauvreté [8–10]. D'un côté, les personnes à faibles ressources sont plus à risque de transmission des maladies infectieuses à cause d'une exposition et vulnérabilité accrue (moins de moyens de prévention, comportements plus à risque, faible accès aux soins, etc.). D'un autre côté, l'invalidité et les dépenses causées par les maladies accentuent les problèmes économiques de ces populations. Ce cercle vicieux entre la maladie et la pauvreté entraîne, au niveau macro, un progrès inégal dans la prévention et la lutte contre les maladies infectieuses. Malgré le fait que l'Afrique subsaharienne soit la plus touchée par ces maladies infectieuses, cette zone compte parmi les investissements per capita en santé les plus faibles au monde [11], ce qui aide à expliquer le retard en termes de lutte contre les maladies infectieuses. Même au sein d'un même pays, on reconnaît une divergence en défaveur des zones rurales et à faible revenus [12].

Par ailleurs, certaines maladies affectant les communautés les plus pauvres des zones tropicales ou subtropicales ont été largement négligées pendant des décennies en termes de prise en compte dans l'action mondiale en faveur de la santé. Ces maladies, classées comme MTN, sont peu visibles par les services de santé des pays endémiques car elles ont souvent des manifestations chroniques à long terme [13]. Cependant, ces maladies sont fortement invalidantes et peuvent enfoncer encore plus la communauté concernée par la pauvreté [14]. Par exemple, la filariose lymphatique (FL) peut causer des lésions au niveau du système lymphatique des bras, des jambes ou des parties génitales, l'onchocercose et les trachomes peuvent conduire à la cécité des patients et l'ulcère de Buruli peut provoquer des lésions cutanées irréversibles extrêmement graves. Même si des progrès importants ont été faits dans le contrôle de nombreuses de ces maladies [15], le manque de vaccins efficaces contre les MTN complique leur prévention, contrôle et/ou élimination [16].

La vaccination est l'un des principaux moyens de prévention actuels pour de nombreuses maladies infectieuses, en particulier pour les maladies infantiles, et la couverture vaccinale a connu une progression remarquable ces dernières décennies au niveau mondial [17]. Depuis l'introduction de la vaccination en 1796, elle a permis l'éradication de la variole en 1978 [18] et l'effet de la vaccination contribue à une réduction considérable de la mortalité [19]: chaque année, la vaccination permet d'éviter entre 3.5 et 5 millions de décès dus à des maladies telles que la diphtérie, le tétanos, la coqueluche, la grippe ou la rougeole [19]. Selon l'Organisation mondiale de la santé (OMS), après l'eau potable, la vaccination est l'intervention médicale la plus efficace en termes de vies sauvées [17]. Malheureusement, les pays à faibles revenus ont du mal à atteindre des taux de vaccination suffisants pour obtenir une immunité de groupe au niveau de leur population, et souffrent donc encore considérablement de ces maladies évitables par des vaccins [20]. Des disparités liées à l'accès aux soins (financier, géographique, etc.), la fragilité des systèmes de santé de ces pays, et des défis persistants dans le financement de la santé parmi d'autres facteurs, constituent des barrières considérables à la lutte contre les maladies infectieuses.

Madagascar est un bon exemple des défis liés au contrôle et à l'élimination des maladies infectieuses dans des pays à faibles revenus. Cet état-île d'environ 29 millions d'habitants est fréquemment classé parmi les 10 pays les plus pauvres du monde, et il est le seul à l'être sans avoir vécu une guerre dans l'histoire récente. Environ 80% de la population vit dans des conditions d'extrême pauvreté (moins de 2.15 US dollars), et plus de 80% des gens habitent dans des zones rurales [11]. En 2020, Madagascar était le deuxième pays au monde avec les plus faibles investissements en santé par habitant, estimés à 18 dollars par habitant et par année [11]. Ces faibles investissements en santé se traduisent en un système de santé publique fragile et sous-performant, caractérisé par un très faible

nombre de professionnels de santé par habitant (moins de 5 médecins, infirmiers ou sages femmes par 10 000 habitants) [21] et supporté par un taux important de paiements directs par les patients dû à l'absence d'une assurance nationale. Ces défis entraînent un très faible accès aux soins chez la population. Par exemple, seuls 40-60% des enfants de moins de 5 ans malades ont accès aux soins au niveau national, et environ 40% des enfants de moins de 2 ans avaient reçu tous les vaccins recommandés; ces taux sont bien inférieurs dans les zones rurales du pays [22].

L'interaction entre ces différents défis à Madagascar (pauvreté, faiblesse du système de santé, manque d'accès aux soins, etc.) limite la capacité du système de santé à lutter contre des maladies endémiques et émergentes. Par exemple, le nombre de cas et de décès liés au paludisme ont presque doublé entre 2010 et 2019 [23]. Le pays a souffert récemment d'épidémies récurrentes, comme la plus grande épidémie de peste pulmonaire de l'histoire récente en 2017, ou encore la plus grande épidémie de rougeole à Madagascar en 2018-2019 (un quart des cas au niveau mondiale pendant cette période-là) [24]. Peu des progrès ont été constatés également pour le contrôle de nombreuses maladies tropicales négligées, qui dépendent des campagnes régulières de distribution médicamenteuse de masse (DMM), comme la schistosomiase, les géohelminthiases, ou la FL. Par exemple, 46 districts sur 114 sont encore hyperendémiques à la schistosomiase (prévalence supérieure à 50%), 52 districts sont hyperendémiques aux géohelminthiases, et 98 sur 111 districts sont encore endémiques à la FL [25]. Cette thèse se concentre sur les barrières à la mise en œuvre de deux stratégies majeures de lutte contre les maladies infectieuses à Madagascar: les campagnes de DMM, à travers l'exemple du programme d'élimination de la FL (PELF), et la vaccination, à travers l'exemple du programme élargie de vaccination (PEV) et la vaccination infantile de routine. Ces deux programmes sont décrits plus en détail ci-dessous.

La lutte contre la filariose lymphatique à Madagascar

La FL est une maladie tropicale négligée causée par les parasites *Wuchereria bancrofti*, *Brugia malayi* et *Brugia Timori*. Elle peut provoquer un handicap permanent dont l'éléphantiasis (gonflement des membres) ou l'hydrocèle (gonflement de scrotum). La transmission d'une personne à une autre se fait par l'intermédiaire des moustiques du genre *Anophèle*, *Culex* ou *Aedes* et les pays tropicaux d'Afrique, d'Asie et d'Amérique du Sud sont les plus touchés avec 882 millions des personnes habitant dans l'un des 44 pays endémiques en 2021 [26]. Un programme global d'élimination de la FL a été implémenté en 2000, ayant pour objectif fondamental de stopper la transmission en 2020. Les principaux piliers du programme consistaient à interrompre la transmission de la maladie et à atténuer la souffrance due à l'infection par une meilleure prise en charge de la morbidité. Le contrôle

de la transmission se fait par la réduction de la charge parasitaire dans le sang de personnes infectées (notamment des microfilaries), en utilisant la DMM de manière régulière. En fonction de la co-endémicité de la FL avec d'autres maladies parasitaires (loase et onchocercose) un, deux ou trois de ces médicaments est utilisée: albendazole, ivermectine, et citrate de diéthylcarbamazine. Dans chaque pays, la DMM est précédé par une cartographie pour déterminer les zones endémiques et le suivi de la mise en œuvre est fait par une surveillance dans des sites contrôle et sites sentinelle. Enfin, une enquête populationnelle de séroprévalence (dite « *transmission assessment survey* », ou TAS) se fait pour vérifier si la transmission a été arrêtée. Après 5 tours de DMM avec au moins 65% de couverture, une zone géographique est susceptible d'interrompre la transmission de FL, et éventuellement mener à son élimination. Cependant, les progrès de la mise en œuvre de la DMM dans les pays endémiques restent hétérogènes, avec peu de pays qui atteignent les objectifs fixés (Figure 0-1). Après 20 ans de mise en œuvre du programme, l'objectif d'élimination globale n'était pas atteint et un nouvel objectif est lancé en 2018 pour atteindre une élimination en 2030, avec des mesures de contrôle et surveillance sont renforcés pour l'atteindre.

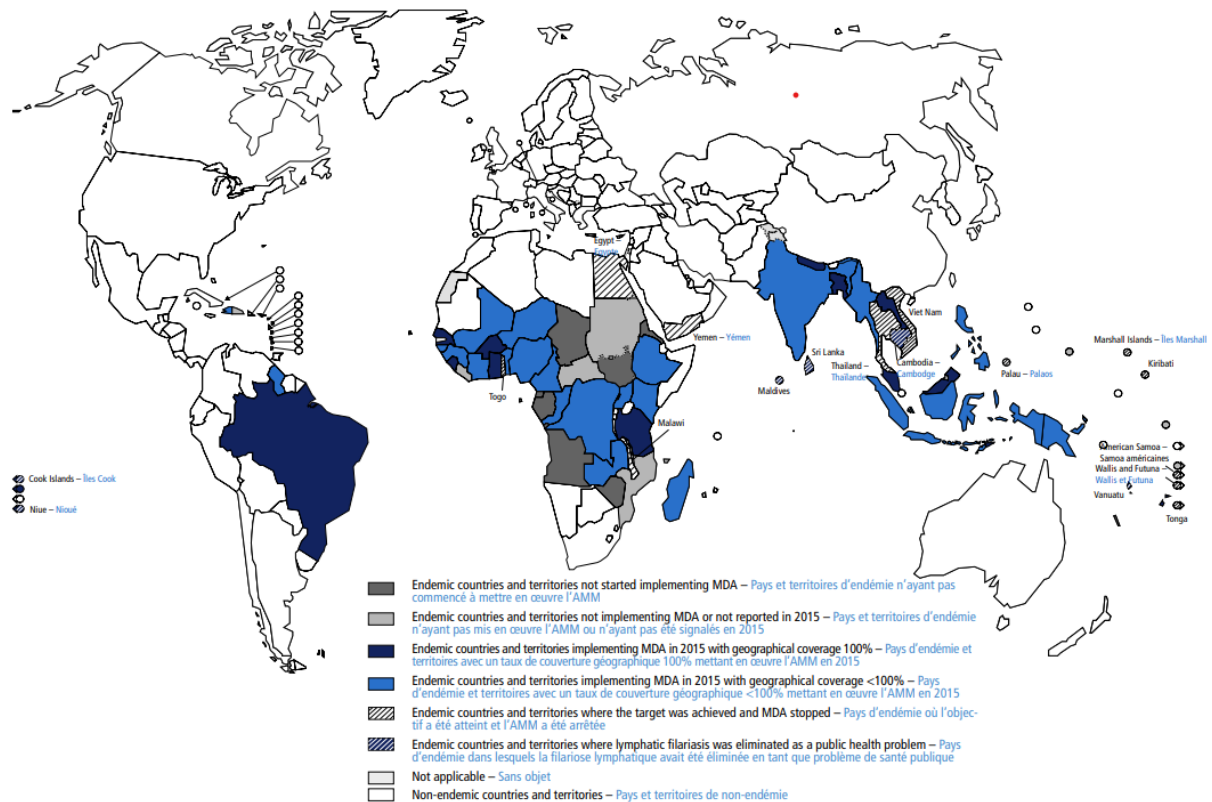


Figure 0-1: Répartition de la filariose lymphatique et status du DMM en 2015

Source: World Health Organization, 2016 [27]

Pour Madagascar, le PELF à Madagascar a débuté en 2002 et des cartographies de l'endémicité faites en 2004, 2015 et 2019 ont recensé 98 districts endémiques sur les 114 existants [25,28]. Les campagnes de DMM ont été mises en œuvre depuis 2005. 62 districts ont effectué entre 3 et 10 tours de DMM en 2016, mais seulement 4 districts (Manakara, Mananjary, Vohipeno et Nosy Boraha) étaient éligibles pour passer au premier TAS [28]. Perturbée par l'épidémie de la peste en 2017, les aléas climatiques quasi-annuels, des manques de financement, et la pandémie Covid-19, la DMM n'a pas eu lieu entre 2016 et 2021. Actuellement, seuls les districts de Manakara, Mananjary, Vohipeno et Nosy Boraha ont atteint l'arrêt de la transmission à Madagascar et n'ont plus besoin de DMM [25]. Même pour ces districts, la question se pose de savoir s'ils resteront éliminés ou bien une résurgence est possible: une étude en 2018 a trouvé que les adultes de Mananjary et Vohipeno avaient encore des taux importants de prévalence (antigenaemia) et que des districts environnants avaient une transmission encore très élevée, ce qui pourrait favoriser le risque de résurgence due à l'immigration.

Progrès dans la vaccination infantile à Madagascar

Des vaccins efficaces existent contre plusieurs maladies qui entraînent une morbidité et mortalité importante, et qui font l'objet des programmes nationaux et internationaux d'immunisation. C'est le cas notamment des vaccinations de la petite enfance qui sont administrés pendant la première année de vie contre le Bacille Calmette-Guérin (BCG), ou tuberculose, contre la polio, contre le tétanos, diphtérie et coqueluche (DTCoq), et contre la rougeole. Bien que la vaccination de la petite enfance existe depuis longtemps, les Objectifs du Développement du Millénaire ont entraîné une augmentation spectaculaire des taux globaux de vaccination, qui a augmenté de 72 à 86% entre 2000 et 2015, grâce à des efforts internationaux comme la création de l'Alliance Mondiale pour la Vaccination et l'Immunisation (GAVI par ses sigles en anglais).

Pour Madagascar, c'est par le moyen du programme élargi de vaccination (PEV) que la vaccination est effectuée depuis 1976. Le PEV distribue les vaccins de la petite enfance gratuitement, à travers deux modes de vaccination principaux: une "stratégie fixe", où les parents viennent au centre de santé pour faire vacciner les enfants à l'âge recommandée, et une "stratégie avancée" qui permet aux personnels de santé de distribuer les vaccins au sein de la communauté pendant une période restreinte, grâce à des équipes mobiles et des campagnes de vaccination. Cette stratégie avancée se fait de manière régulière pendant les « semaines mères-enfants » deux fois par an, généralement au mois de Juin et Décembre, et pendant des campagnes nationales extraordinaires lorsqu'un rattrapage des taux de couverture vaccinale est nécessaire. L'inégalité de la couverture vaccinale est fréquente dans le pays (Figure 0-2) et les zones rurales et enclavées sont souvent les plus défavorisées.

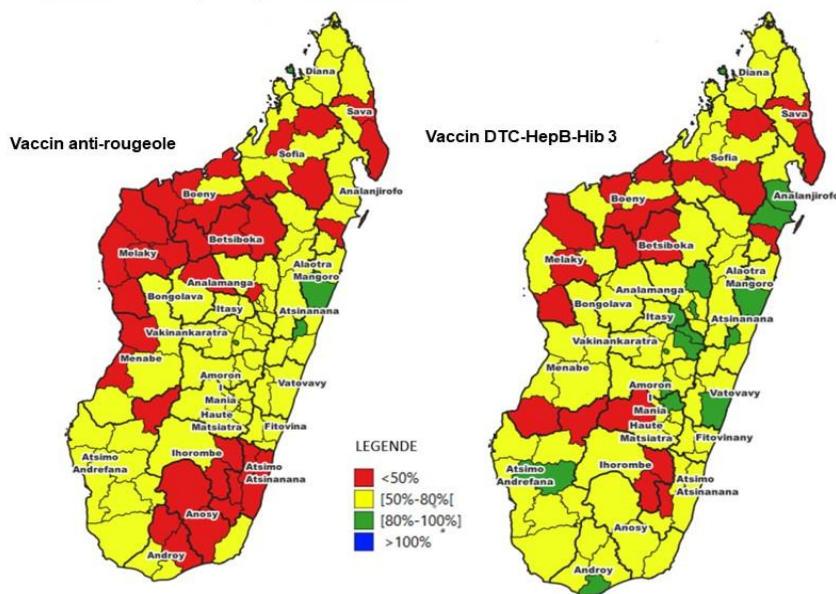


Figure 0-2: Distribution de la couverture vaccinale des vaccins VAR et DTC-HepB-Hib 3 en Janvier 2023

Source: Performance de la Vaccination de Routine Janvier 2023 [29].

Pour la vaccination infantile, Madagascar reste l'un des pays avec le plus grand nombre d'enfants n'ayant reçu aucune dose des vaccinations recommandées. Plus de 300 000 enfants de moins d'un an n'ont reçu aucun vaccin (Performance de La Vaccination de Routine Janvier 2023). Au niveau national, les taux de couverture vaccinale des vaccins recommandés sont compris entre 49% et 70% (Performance de La Vaccination de Routine Janvier 2023), loin du taux minimal de 90% recommandé par l'OMS. Au niveau district, une grande partie de districts ne dépassent pas le taux de couverture vaccinale de 50%, alors que la recommandation est que tout district ait une couverture supérieure à 80%. Par exemple pour le vaccin anti-rougeole (1^{ère} dose sur 3), 36 districts ont une couverture vaccinale inférieure à 50%, et des couvertures sous-optimales sont associées à des grandes épidémies comme celle de 2018-2019 qui a recensé plus de 200 000 cas, un phénomène connu en épidémiologie comme épidémie « post-honeymoon » [31]. La fragilité du système de santé et le faible accès aux soins entraîne un faible taux de vaccination de routine (stratégie fixe) et le non-respect du calendrier vaccinal alors que c'est lorsqu'ils sont administrés au bon moment que les vaccins donnent une protection optimale. La méthode de distribution par stratégie avancée telle que les campagnes de vaccination, même si elle améliore la couverture globale, peut augmenter le risque de non-respect du calendrier vaccinal, laissant des cohortes d'enfants non vaccinés entre campagnes qui peuvent donc mener à des épidémies. D'une manière alternative, le renforcement de systèmes de santé (RSS)

pourrait contribuer à une amélioration de la vaccination de routine (stratégie fixe), mais l'effet de ce genre d'intervention sur l'efficacité des programmes de vaccination est peu étudié dans la littérature.

Objectif de la thèse

L'objectif principal de cette thèse est d'étudier les barrières à la mise en œuvre de deux stratégies majeures de lutte contre les maladies infectieuses dans une zone rurale du Sud-Est de Madagascar, à travers des cas particuliers des campagnes de DMM au sein du Programme d'élimination de la filariose lymphatique (PEFL), et des stratégies de vaccination mises en place par le PEV, afin de guider l'amélioration de ce genre de stratégies.

Les objectifs spécifiques sont:

- (1) Faire une revue des différentes modélisations existantes sur la FL et leur apport aux programmes d'élimination.
- (2) Utiliser la modélisation mathématique pour étudier comment l'hétérogénéité dans la mise en œuvre du PEFL peut augmenter le risque de réémergence.
- (3) Étudier l'impact du RSS sur l'efficacité des stratégies de vaccination et identifier des inégalités persistantes dans la couverture vaccinale.

Ainsi, cette thèse mobilise des techniques de revue de littérature, de modélisation mathématique et de modélisation statistique, et est structurée en 3 chapitres. Le premier présente une revue de la littérature des modèles mathématiques existantes sur la FL: les modèles compartimentaux, les modèles stochastiques individus-centrés, et la combinaison de deux ou plusieurs modèles (« ensemble modeling ») ainsi que leur application pour guider les programmes d'élimination. Dans le deuxième chapitre, on utilise un modèle mathématique pour montrer comment l'hétérogénéité sur la mise en œuvre du PEFL dans le sud Est de Madagascar peut augmenter le risque de réémergence. On se focalise sur le problème d'hétérogénéité au sein des programmes de DMM, et en particulier l'hétérogénéité dans l'adhérence au traitement selon les groupes d'âge et l'hétérogénéité spatiale dans l'avancement de la DMM, étudiant le risque de résurgence que ceux-ci peuvent engendrer. Enfin dans le troisième chapitre, on étudie l'impact du RSS dans un district du sud Est de Madagascar sur l'efficacité des stratégies de vaccination et l'amélioration de la couverture vaccinale, grâce à des analyses d'enquête au sein d'une cohorte. On terminera avec une discussion générale sur comment les méthodes utilisées et les résultats obtenus contribuent à la littérature sur les défis de mise en œuvre des programmes de lutte.

**Chapitre 1: Revue de littérature sur les
différentes modélisations existantes sur la
filariose lymphatique et leur contribution
aux programmes d'élimination.**

Résumé du chapitre 1

L'utilisation des modèles statistiques et mathématiques est une approche essentielle dans un large éventail de secteurs, en particulier dans le domaine de santé publique. Ces modèles sont des outils puissants pour analyser, comprendre et prédire des phénomènes complexes en se basant sur des données empiriques et des principes mathématiques. La complexité du mode de transmission de la FL rend essentiel le recours à ces approches pour le contrôle de la FL. Nous avons réalisé une revue de littérature en consultant les articles publiés sur PubMed concernant la modélisation de la FL, et ajoutant des références citées dans certaines revues antérieures. Cette démarche nous a permis d'identifier un total de 60 articles pertinents, correspondant à notre profil de recherche. Au cours de cette revue, nous avons examiné l'évolution temporelle de l'utilisation de la modélisation mathématique et statistique dans le contexte de la FL. De plus, nous avons identifié les principaux types de modèles fréquemment employés et nous avons évalué les différentes applications de ces modèles dans l'étude de la FL.

Nous avons constaté que la modélisation de la FL a débuté dans les années 1960. Vers 1990, elle a commencé à devenir de plus en plus complète, mais c'est à partir des années 2000, avec la mise en œuvre de PEFL, que son utilisation a explosé. Les modèles utilisés englobent les approches statistiques et/ou spatiales, déterministes, individu-centrées, ainsi que des combinaisons de plusieurs modèles. Ils sont employés pour comprendre la dynamique de la transmission de la FL, évaluer l'impact des interventions, déterminer la surveillance appropriée et faire des prédictions sur les tendances futures. L'utilisation des modèles existants a grandement contribué aux progrès réalisés vers l'élimination de la maladie, cependant, d'importants défis subsistent, notamment sur la nécessité de comprendre les hétérogénéités qui subsistent dans la prévalence.

The use of mathematical and statistical modeling to inform lymphatic filariasis elimination: a review.

1.1- Introduction

Mathematical modeling is a commonly used tool in epidemiology and disease ecology that allows to understand and simulate the dynamics of transmission of infectious and parasitic diseases, as well as the impact of different disease control and surveillance strategies. Mathematical models are constructed using sets of equations that describe the dynamics of different populations through time (humans, animal hosts, vectors, etc.), their interactions, and how pathogens are transmitted among these populations. The application of mathematical modeling to the study of infectious diseases gained traction in the early 20th century with work by Hamer on measles [32] and Ross on malaria [33], among others, and has since been applied to dozens of disease systems.

One of such disease systems is lymphatic filariasis (LF), a debilitating disease caused by filarial worms and transmitted to humans through the bites of infected mosquitoes. The parasites responsible for the LF infection are *Wuchereria bancrofti* [34], *Brugia malayi* [35] and *Brugia timori* [36]. LF affects millions of people in tropical and subtropical regions [26]. The disease primarily affects the lymphatic system, leading to painful swelling of body parts, such as limbs and scrotum, and causes long-term disability and social stigma. The use of mathematical models has been critical to understand the complex interactions between human, mosquito and LF parasite populations. The parasites have two stages in their life cycles, one in the human host and one in mosquito (Figure 1-1). Early models were developed in the 1960s to better understand observed patterns of infection [37–39], and have since evolved to address several practical questions related to the control and elimination of LF. Indeed, LF is one of several diseases targeted for elimination as a public health problem, because there exist drugs that are cheap, safe, and effective in reducing the number of microfilariae in the bloodstream of the human host. Therefore, mass drug administration (MDA) of antifilarial drugs to entire endemic communities, regardless of their infectious status, has been a key pillar of elimination efforts over the past decades, the design of which has been heavily informed by mathematical model simulations.

Given the key role played by mathematical modeling over the last 50 years, this article presents a review of LF mathematical models. We have reviewed 60 papers from PubMed [40] and from reviews of other papers [41,42] about LF modeling. We start with a brief history of modeling of LF, followed

by a description of the different types of models developed over the years (including statistical/spatial, deterministic, stochastic and ensemble models), and end with the different applications of these mathematical models to inform the control and elimination of LF.

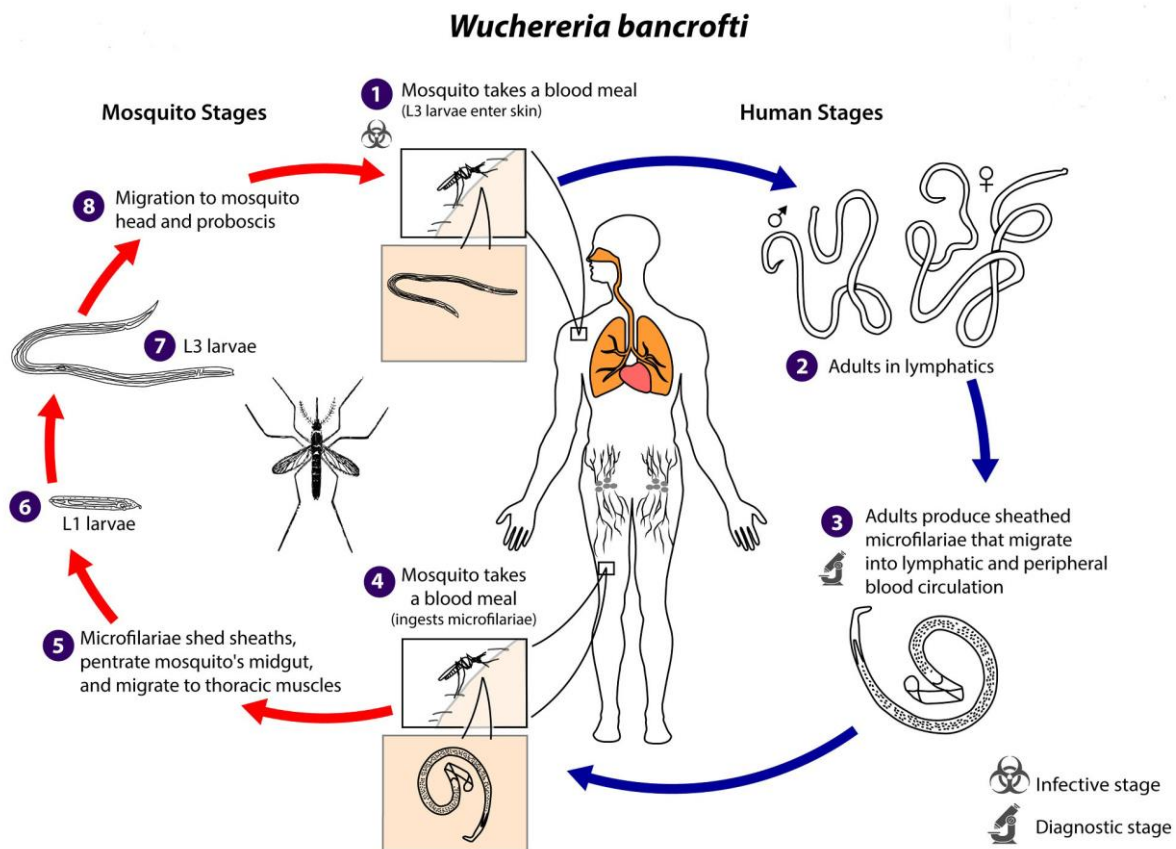


Figure 1- 1: The life cycle of *Wuchereria bancrofti* in human and mosquito

Source: <https://www.cdc.gov/dpdx/lymphaticfilariasis/index.html>

1.2- History of lymphatic filariasis modeling

The mathematical/statistical modeling of LF has a history that dates back several decades [43]. It has been developed and refined over the years to better understand the transmission dynamics of LF, evaluate control strategies and guide policy decisions [37–39,44–46]. Figure 1-2 shows the repartition of papers talking about mathematical and statistical models for LF study throughout successive years. The first mathematical models of LF dynamics emerged during the 1960s to explain age-prevalence patterns of infection [38,47]. These early models captured the dynamics of infection in humans only. As a better understanding of the relationship between parasite loads in mosquito populations and the density of microfilaria in humans was gained during the 1970s and 1980s [48,49], researchers began to develop in the 1990s more sophisticated LF models that considered the complex interconnection between the LF parasite, mosquito vectors and human hosts [50]. This model considered factors like

age-dependent susceptibility, intensity of worm load and mf-load, and vector biology. In 1998, the first LF IBM called LYMFASIM was developed. In this model, the interactions between individual humans and mosquitoes are explicitly simulated, allowing to capture finer scale details of LF transmission dynamics [51].

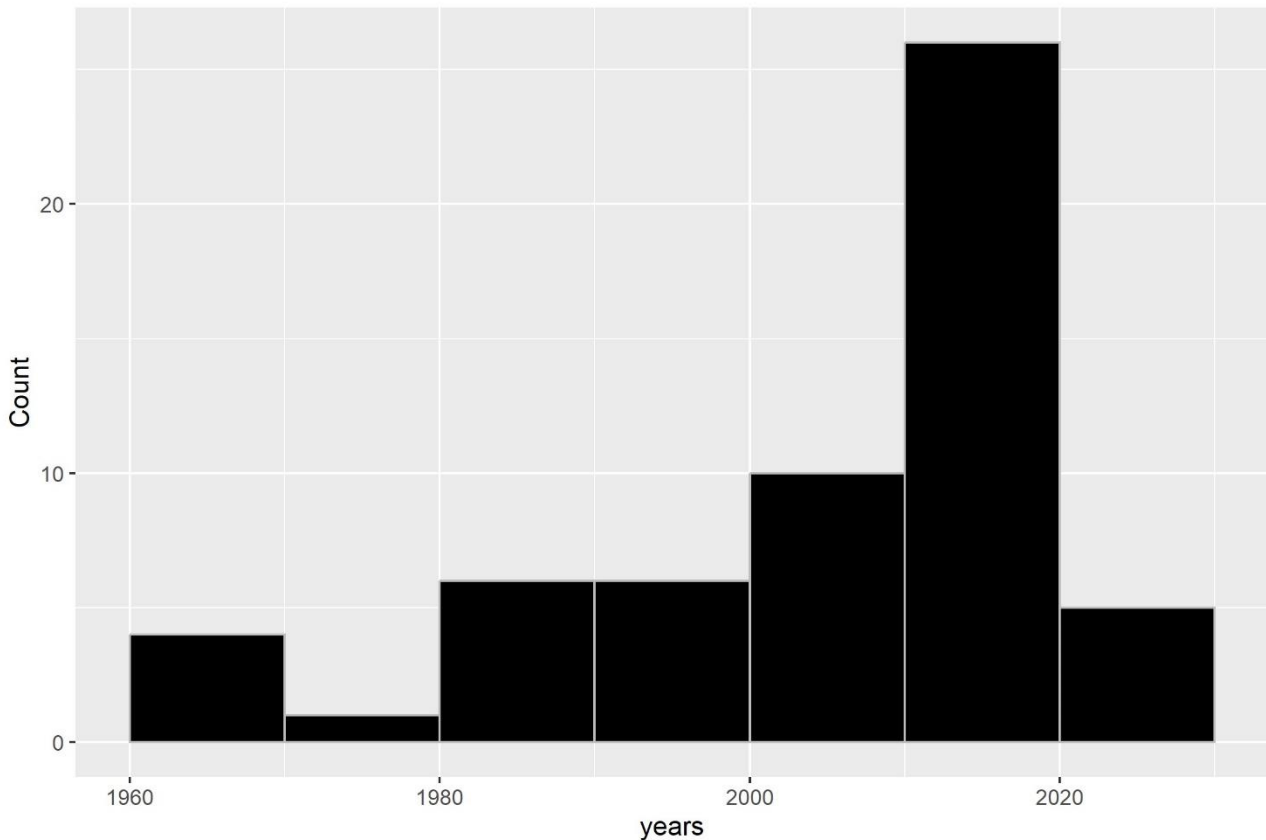


Figure 1- 2: Distribution of the number of mathematical and statistical models published across different periods.

The launch of the Global Program to Eliminate Lymphatic Filariasis (GPELF) by the World Health Organization (WHO) in 2000 raised further interest in LF modeling. Researchers developed models to assess feasibility and impact of MDA campaigns, which are the cornerstone of LF control efforts [52,53]. Since then, the use of mathematical modeling has exploded, 35 of 60 papers included in this study were published between 2000 and 2020 (Figure 1-2). Modeling efforts expanded to consider integration of vector control measures, such as bed net distribution and insecticide-treated materials, into LF elimination strategies [54–56]. These models aimed to optimize the combination of MDA and vector control to obtain the most effective results. With advances in geographic information systems (GIS) and spatial modeling techniques, researchers have recently developed models that can capture the spatial heterogeneity of LF transmission [57–59].

These models have helped identify high-risk areas and target interventions more efficiently. As some countries and regions have achieved significant reductions in LF prevalence, models are being used to guide post-elimination surveillance strategies [60,61], helping to determine how to monitor for potential LF resurgence and when to transition from MDA to surveillance-only activities. Since all LF models are based on a set of assumptions as for any other pathogens, and then no particular LF model is bias-free, the use of ensemble modeling, which involves using multiple mathematical models into a common analytic framework, has emerged to address the uncertainty in the predictions of one single model and make more robust recommendations [62,63].

1.3- Main types of LF mathematical models

Several types of mathematical modeling have been used to study LF. The choice of modeling type depends on the specific research questions, the data available and the status of LF transmission in a particular setting. Figure 1-3 shows the distribution of the types of models that are commonly used, that are: statistical/spatial, deterministic, probabilistic models, or combination of multiple models.

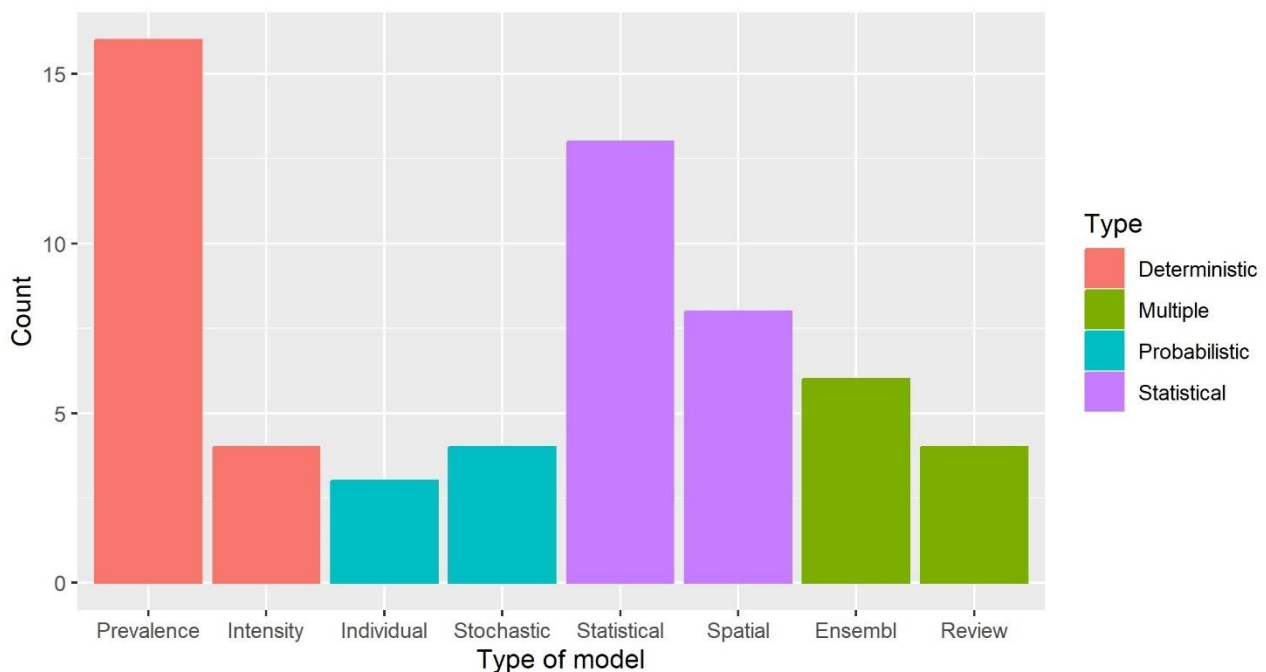


Figure 1- 3: Repartition of the use of each type of models

1.3.1 Statistical and spatial modeling

Statistical and spatial modeling can provide useful information to understand the transmission and future trend of infectious disease when there is reliable and up-to-date data. It can help design

effective control measures. Developing a statistical and spatial modeling framework for studying disease like LF involves a systematic approach that integrates various components and methods. The general framework of statistical and spatial modeling is shown in Figure 1-4, showing the difference and linkage of these two approaches. The first step for both analyses is data collection, including epidemiological data, demographic data, environmental data, and any other dataset required for the analysis. The second step involves spatial data integration for spatial models. This consists of combining different datasets, incorporating spatial information such as coordinates to create a comprehensive dataset. Then, in the following step, statistical analysis or spatial analysis is performed. It is about using appropriate statistical techniques to examine the relationship between prevalence and potential factors. In the case of spatial models, it is about employing spatial statistical techniques to assess patterns of disease clustering or dispersion. It considers hotspot analysis, spatial regression and spatial interpolation and then create thematic maps and use GIS to visualize the distribution of LF cases, risk factors and other relevant spatial information.

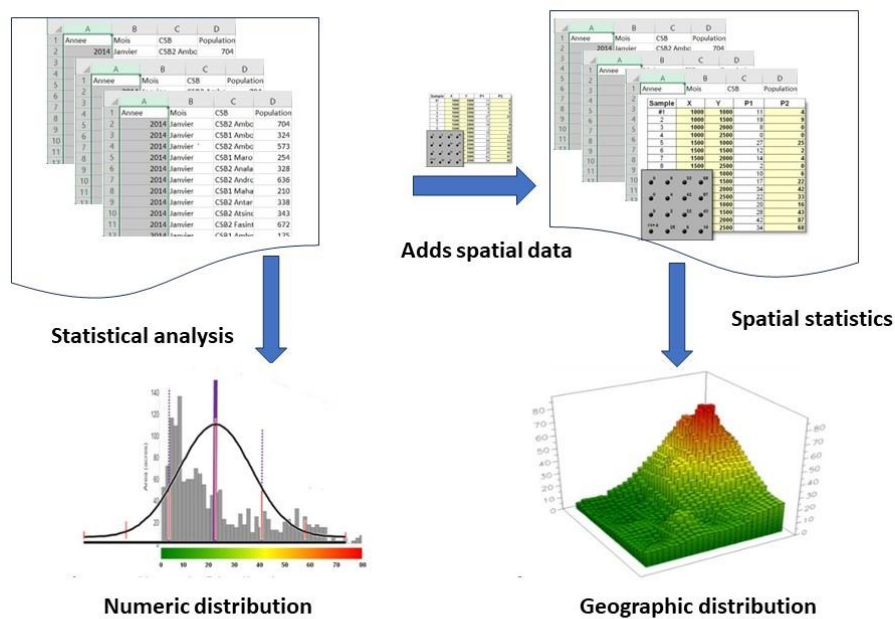


Figure 1- 4: Comparison and linkage between simple statistical model and spatial models

For LF, data from surveys are analyzed and combined with environmental and demographic factors to estimate LF prevalence in areas where data may be sparse [64]. Statistical models help identify risk factors associated with transmission [57,65,66]. This includes factors like climate, density of population, age or gender. They are applied for surveillance and monitoring of LF and can help predict trends and identify areas where LF transmission is increasing or decreasing which is essential for program planning [67,68]. Statistical modeling is used to analyze the results of epidemiological

studies that investigate the impact of control programs such as MDA and assess the effectiveness of intervention [64,67].

Spatial modeling uses spatial statistics to analyze the spatial distribution of LF. It helps in identifying hotspots of LF transmission and prioritizing control efforts [61,69]. This information guides interventions like MDA and the targeting of high-risk populations. Environmental data such as temperature, rainfall and land use are incorporated into spatial models to understand their impact on LF transmission [69,70]. These models can predict changes in transmission risk based on environmental factors. Spatial models assess the accessibility of healthcare services including the distribution of treatment centers and the availability of healthcare resources in endemic areas of LF or other diseases [71,72].

While statistical and spatial modeling are valuable tools in studying (LF) and other diseases, they come with certain challenges and limitations. Specific techniques and methods used in statistical or spatial modeling vary depending on the available data, the research questions, and the geographical context of the study. The use of statistical and spatial modeling requires high quality data. An up-to-date data on LF prevalence, environmental factors and healthcare resources are required. However, in many LF-endemic areas, data may be limited, of varying quality or outdated, making it challenging to construct accurate statistical or spatial models.

1.3.2 Population-based, deterministic models

Deterministic models of LF are mathematical representations of how the disease is transmitted across populations and where processes do not occur in a probabilistic way. The model calculates the average behavior of LF transmission over time, assuming that all parameters and variables are fixed and known precisely. Deterministic models are often expressed as sets of differential equations that describe how different populations (humans, mosquito vectors) in different states of infection change over time. For LF, there are two main types of deterministic models, those that consider LF as a microparasite (and then consider only the infection status of individuals as either infected or not infected) [73–77], or as a macroparasite (which consider parasite load within the vector and the human host) [78–83]. For the sake of readiness and to stay coherent with the terminology present in the literature, we will refer to this model as “prevalence” and “intensity” models respectively [41,84].

Prevalence models use the standard notation of disease states such as susceptible (S_h), Latent (L), infected (I_h) in human population and (S_v), (I_v) in mosquito population where $S_h + L + I_h = N_h$

and $S_v + I_v = N_v$. An example of a prevalence model framework is shown in Figure 1-5.A [76]. These models are among the most simplified versions of LF models and omit many details on the LF transmission cycle, such as infection intensity, but can provide some basic understanding of the set of conditions leading to an endemic or disease-free equilibrium in a population among other things. A diagram for a typical intensity model (EPIFIL) is shown in Figure 1-5.B, where W represents the mean worm burden in the human population, M the mean microfilarial intensity, L the mean intensity of infective stage L3 filarial larvae in the mosquito population, and I the mean level of immunity in the human population to the filarial worms [80].

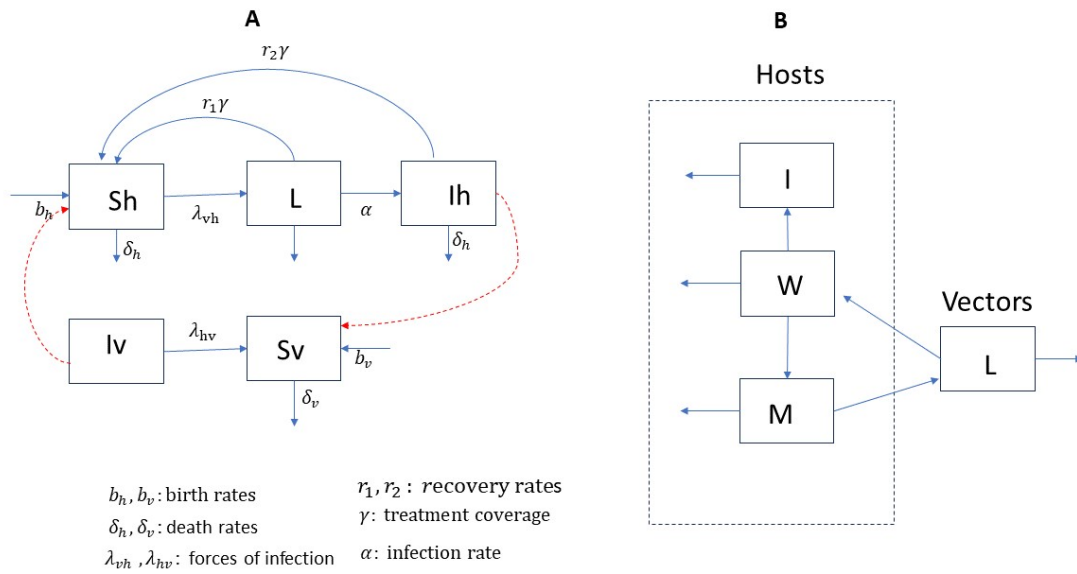


Figure 1- 5: Framework of typical models of Lymphatic filariasis.

A) Prevalence model, where populations are either in the susceptible class, latent class, or infected class. B) Intensity model, which considers intensity of worm-load and mf-load

For all deterministic models of LF, differential equations are used to capture the change per unit of time from one state to another, using different parameters that present the rate of change. The set of differential equations corresponding to the prevalence model on the diagram in Figure 1-5.A is:

$$\begin{aligned}
 \frac{dS_h}{dt} &= b_h N_h + (r_1 L + r_2 I_h) \gamma - (\lambda_{vh} + \delta_h) S_h \\
 \frac{dL}{dt} &= \lambda_{vh} S_h - (\alpha + r_1 \gamma + \delta_h) L \\
 \frac{dI_h}{dt} &= \alpha L_h - (r_2 \gamma + \delta_h) I_h \\
 \frac{dS_v}{dt} &= b_v N_v - (\lambda_{hv} + \delta_v) S_v
 \end{aligned} \tag{1.1}$$

$$\frac{dI_v}{dt} = \lambda_{hv}S_v - \delta_v I_v$$

Where $\lambda_{vh} = \beta\theta_{vh}\frac{I_v}{N_h}$ and $\lambda_{hv} = \beta\theta_{hv}\frac{I_h}{N_h}$

The basic reproduction number for this model is:

$$R_0 = \sqrt{\frac{\alpha\beta^2\theta_{vh}\theta_{hv}(1-p\gamma)b_h b_v N_v}{\delta_v^2 \delta_h N_h (\alpha + r_1\gamma + \delta_h)(r_2\gamma + \delta_h)}} \quad (1.2)$$

Where, β is the average number of bites per mosquito per unit of time, and θ_{vh}, θ_{hv} are probabilities of successful transmission from mosquito to human and from human to mosquito respectively. For the intensity model in Figure 1-5.B, the equation is given by 3 partial differential equations for the worm, microfilaria and immunity and one ordinary differential equation for the larvae in mosquito:

$$\begin{aligned} \frac{\partial W}{\partial t} + \frac{\partial W}{\partial a} &= \lambda \frac{V}{H} \psi_1 \psi_2 s_2 L * e^{-\beta I} - \mu W \\ \frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} &= \alpha \phi(W, k) W - \gamma M \end{aligned} \quad (1.3)$$

$$\begin{aligned} \frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} &= W - \delta I \\ \frac{dL}{dt} &= \lambda k g \int_a \pi(a) (1 - f(M)) da - (\sigma + \lambda \psi_1) L \end{aligned} \quad (1.4)$$

$\lambda(\frac{V}{H})$ is the number of bites a host receives per unit time, where λ is the number of bite, V is the number of vectors and H is the number of hosts; μ is the death rate of adult worms; ψ_1 is the proportion of $L3$ which leave the mosquito when it bites; ψ_2 is the proportion of those $L3$ leaving the mosquito which enter the host and s_2 is the proportion of those $L3$ entering the host which survive to become adult worms. $M(a, t)$ is the mean intensity at age a at time t , k is inversely related to aggregation of the parasite within the host, g is the proportion of bites which are made on infected people and which result in the mosquito in the mosquito becoming infected; $\pi(a)$ is the age distribution of the population and σ is the death rate of $L3$. L^* is the equilibrium density of $L3$ larvae. The equilibrium level L^* is given by:

$$L^* = \frac{\lambda k g \int_a \pi(a) (1 - f(M)) da}{\sigma + \lambda \psi_1} \quad (1.5)$$

For an individual mosquito $L = k(1 - e^{-\frac{rM}{k}})$

$$\begin{aligned} f(M(a, t)) &= \frac{2}{1 + \frac{M(a, t)}{k} \left(1 - e^{-\frac{r}{k}}\right)^k} - \frac{1}{1 + \frac{M(a, t)}{k} \left(1 - e^{-\frac{2r}{k}}\right)^k} \\ f(M(a, t)) &= 1 + \frac{M(a, t)}{k} \left(1 - e^{-\frac{r}{k}}\right)^{-k} \end{aligned}$$

The basic reproduction number is derived using next-generation matrix approach.

$$R_0 = \frac{e^{-\frac{r}{k}} \left(e^{-\frac{r}{k}} - 1 \right) k g h \frac{V}{H} \alpha \lambda^2 s_2 \psi_1 \psi_2}{\gamma \mu (\sigma + \lambda \psi_1)} \quad (1.6)$$

Vector control is simulated by assuming a certain reduction in biting rate for a specified period and treatment is assumed to cause reduction in the microfilaria level by killing a proportion of adult worms, killing a proportion of microfilariae and temporary interrupting mf production of female worm.

All of these models inform that the disease is endemic when $R_0 > 1$ and that the disease dies out when $R_0 < 1$. Deterministic models rely on simplifying assumptions that events occur always at the same rate, which may not fully capture the complexities and heterogeneities present in LF transmission. They do not account for random variation, which is particularly relevant for disease with low transmission rates. In that case, stochastic models may be better suited to capture this variability.

1.3.3 Individual-based, stochastic models

As opposed to deterministic model, which simulate dynamics at the level of the whole population, individual-based models (IBM) of LF simulates the disease at the level of individual human hosts. Unlike deterministic models, IBM tracks in a probabilistic framework, the interactions, and characteristics of individual agents, allowing for more detailed realistic representation of LF transmission dynamics than population-based models. For LF IBM, each individual in the simulated population is represented as a distinct agent with specific attributes and behaviors. This includes information about their age, sex, infection status, immune response, mobility, and other relevant factors.

The model simulates the interactions between infected individuals, susceptible individuals, and mosquitoes. It tracks the progression of LF infection within individual hosts, including the development of microfilariae and clinical symptoms. Human behavior such as movement patterns, treatment adherence and the use of preventive measures can be incorporated into the model. This adds a layer of realism to the simulation. Stochasticity is introduced to capture randomness in event to reflects the probabilistic nature of the reality. LF IBM can be computationally intensive due to their complexity, especially when considering large populations and detailed spatial representations, but it offers a flexible and detailed approach to studying the disease's dynamics and evaluating control strategies.

There are two major IBM that are widely used: the LYMFASIM model [46,51] and the TRANSFIL model [85]. The framework of the LYMFASIM model is shown in Figure 1-6. TRANSFIL has a similar framework, excepting that it does not consider immunity. Table 1-1 presents the similarity and differences between these two models in their equations and their use. In TRANSFIL model, everyone initially starts with zero infection, and their exposure to infectious bite risk is determined by Gamma distribution with mean 1 and shape parameter denoted by k . As for the LYMFASIM model, it also initiates with a population entirely free of infection, introducing the force of infection at defined time points to initiate infections. Both models specify the dynamics of worm development leading to the derivation of mf-density in each individual (Table 1-1). This process is followed by the calculation of the L3 larval density for each person, then the computation of the average L3 density across the entire population. Finally, the rate at which individual becomes infected (force of infection) is derived. In LYMFASIM, the inclusion of immunity against microfilaria and worm is possible, while it is not available for TRANSFIL. Anti-L3 immunity in LYMFASIM is acquired by prolonged exposure to L3-antigens, resulting in a reduction of the success of inoculated L3-larvae to mature and settle in the human body, and anti-worm immunity is caused by the cumulative presence of adult parasites, modelled as a reduction in the fecundity of female worms.

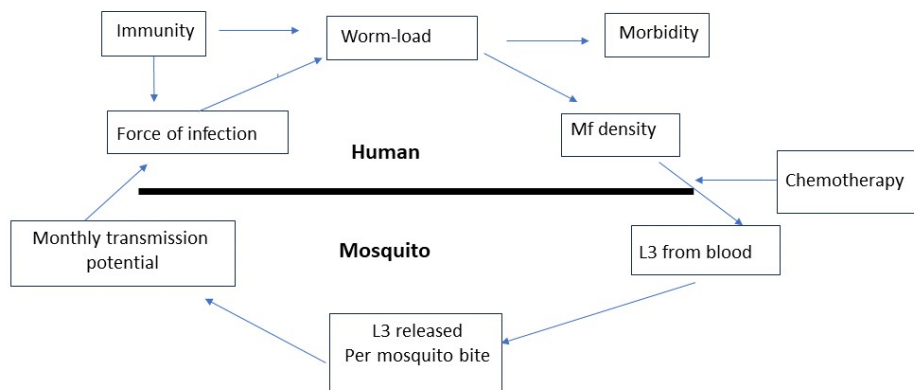


Figure 1- 6: Framework of individual-based model LYMFASIM

Table 1- 1: Similarities and differences between LYMFASIM and TRANSFIL

Model	LYMFASIM	TRANSFIL

Parameters	<p> W_i: number of mature worms F_i: number of female worm ($W_i/2$) foi: force of infection Tl, T_i: life span, immature stage m_i: density of microfilariae s: mf monthly survival rate r_i: number of mf produced by F_i a, b, c: describe uptake of infection by mosquito E_i: Exposure of individual i $L3$: Number of L3 $N(t)$: Total population size at time t $E_{a_i}(a_{i(t)}, s_i)$: exposure according to age and sex E_{ii}: individual random component R_l: anti-L3 immunity H_l: experience of L3 infection β_l: decreasing factor of H_l γ_l: translates experience to immunity ρ_{li}: Variation of experience </p>	<p> W_i^m: Number of male worms W_i^f: Number of female worms foi: force of infection μ: Worm death rate M_i: mf number γ: mf death rate α: production rate of mf per worm $I(W_i^m)$: equal to 1 if there are male worms L: larva developed from mf b_i: bite risk m: concentration of mf per 20μl blood r_1, k: describe the uptake of infection s_1: proportion of L3 developed to worm λ: number of bites per mosquito g: proportion of mosquito that take infection after biting infected person σ_1: death rate of mosquito $V:H$: ratio of vector to host ψ_1, ψ_2: Probabilities that L3 leave/enter the host during biting event N: total number of population </p>
Models equations		
Worms dynamic	$W_i = foi(t) \times (\overline{Tl} - T_i)$	$W_i^m = W_i^m + 1 \text{ at rate } foi \times L^*$ $W_i^m = W_i^m - 1 \text{ at rate } \mu W_i^m$ $W_i^f = W_i^f + 1 \text{ at rate } foi \times L^*$ $W_i^f = W_i^f - 1 \text{ at rate } \mu W_i^f$
Mf dynamic	$m_i(t) = s \times m_i(t - 1) + F_i(t) \times r_i(t)$	$\frac{dM_i}{dt} = \alpha W_i^f I(W_i^m > 0) - \gamma M_i$
L3	$L3_i = a \times (1 - e^{-(bm_i)^c})$	$L(m) = ks_1(1 - e^{-r_1 m / ks_1})$
Average number of L3 (equilibrium)	$\overline{L3} = \frac{\sum_0^{N(t)} E_i(t) \times L3_i(t)}{\sum_0^{N(t)} E_i(t)}$ $E_i(t) = E_{a_i}(a_{i(t)}, s_i) \times E_{ii}$	$\overline{L} = \frac{L(m_i)b_i}{\sum_0^N b_i}$ $\frac{dL}{dt} = \lambda g \overline{L} - (\sigma_1 - +\lambda \psi_1 L)$ $L^* = \frac{\lambda g \overline{L}}{\sigma_1 + \lambda \psi_1}$
Force of infection	$foi_i(t) = mbr(t) \times \overline{L3}(t) \times E_i(t) \times sr$	$foi = \frac{1}{2} \lambda (V:H) \psi_1 \psi_2 h(a)$
Immunity	$R_l(t) = 1 - e^{-\gamma_l \rho_{li} H_l(t)}$ $H_l(t) = \beta_l + H_l(t - 1) + mtp_i(t)$	None

Use of the models		
Effect of MDA	- A fraction of mf is killed - a fraction of female worm is permanently or temporarily sterilized - a fraction of worms is killed	- mf concentration and number of worms are reduced - production of mf is diminished
Compliance	Semi-systematic: a compliance factor indicates a person's tendency to participate. Random number define whether an individual is treated or not.	Systematic: each person is assigned a random value defining the likelihood of their participation
Vector control	Reduction of the average monthly biting rate in a given period, the number of such periods can be chosen	Reduce biting rate of mosquito
Immunity	Allow for immunity against L3 and adult worms	No immunity considered

The outputs of any type of LF model, whether population-based or individual-based, need to be validated using empirical data to ensure that they accurately represent real-world LF transmission dynamics. In addition, sensitivity analyses can be conducted to understand how variations in model parameters and assumptions affect model outcomes. This helps identify key parameters that play a key role in LF transmission and include uncertainty in the model predictions. However, it is important to acknowledge that there exist uncertainties inherent to the modeling framework itself, so the use of multiple models simultaneously in conjunction with empirical data can provide a more realistic range of outcomes.

1.3.4 Ensemble modeling

Ensemble modeling involves using a variety of LF models that may differ in terms of structure, assumptions, and parametrization. These models may include population-based models, IBM, or hybrid models that combine elements of both. Each model represents a different perspective on LF dynamic. Steps taken in ensemble modeling involve calibration, uncertainty analysis and weighting, and validation [60,62], framework is shown in Figure 1-7. Each single model within the ensemble is calibrated to observed data from LF-endemic regions. Calibration adjusts model parameters to match historical disease trends, prevalence data, and other relevant epidemiological information. This step helps ensure that each model accurately reflects LF transmission in specific contexts. Then, the performance of each model is weighted. Ensemble modeling allows for the exploration of uncertainty in LF prediction. Models within the ensemble may produce different results due to parameter uncertainty or structural differences. By analyzing these variations, researchers can quantify

uncertainty in their predictions and assess how robust they are in order to inform policy recommendations. The final step is the model validation to assess prediction from the multi-model generated.

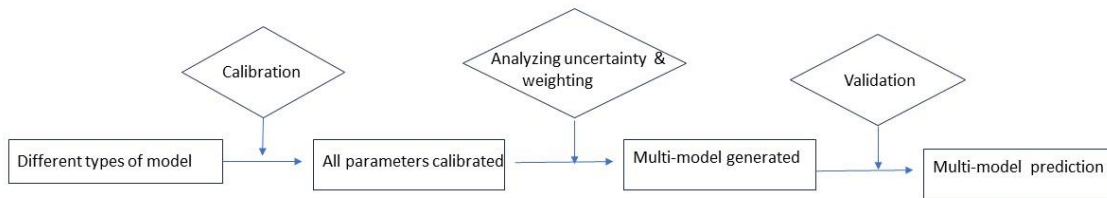


Figure 1- 7: Framework of Ensemble modeling of lymphatic filariasis

Ensemble modeling helps identify strategies that are consistently effective across different modeling approaches. Instead of relying on a best single model, ensemble modeling often involves model averaging, where predictions from multiple models are combined to produce a more robust estimate of LF dynamics or the likely outcomes of interventions. Model averaging can reduce the influence of a single model’s biases.

1.4- Application of mathematical models to guide LF elimination

Mathematical models of LF have been used in numerous settings to explore a wide range of research questions, with applications for elimination programs aimed at better understanding, managing, and ultimately eliminating the disease. Mathematical modeling can provide policymakers with evidence-based recommendations for LF control and elimination, helping inform decisions about funding priorities, intervention strategies, and program monitoring. Models can be used to explore hypotheses about LF transmission and control, allowing researchers to simulate scenarios that may be challenging to test in the field. The Figure 1-8 illustrates the application of modeling in the study of LF and the quantity of research papers that have employed mathematical or statistical model for each specific purpose.

Almost all of 60 papers reviewed here have used modeling for transmission dynamic (Figure 1-8). For instance, models have been used to better understand the role of particular factors in the transmission dynamics of LF, such as the role of human [86,87], mosquito vectors [88] and environmental conditions in disease spread [69,74]. In human, the role of immunity in (LF) infection varies across different regions. For example, in India, it has been demonstrated that adults develop

immunity against L3 larvae, as observed in the study by [51]. In contrast, this phenomenon has not been substantiated in Africa, as indicated by the research conducted by [46]. Regarding the mosquito population, spatial variations in mosquito biting patterns have been confirmed to be a consequence of environmental conditions [88]. By explicitly simulating spatial patterns in LF transmission over time, researchers have provided insights into how LF spreads across different populations and geographic areas [59,76,79,89,90].

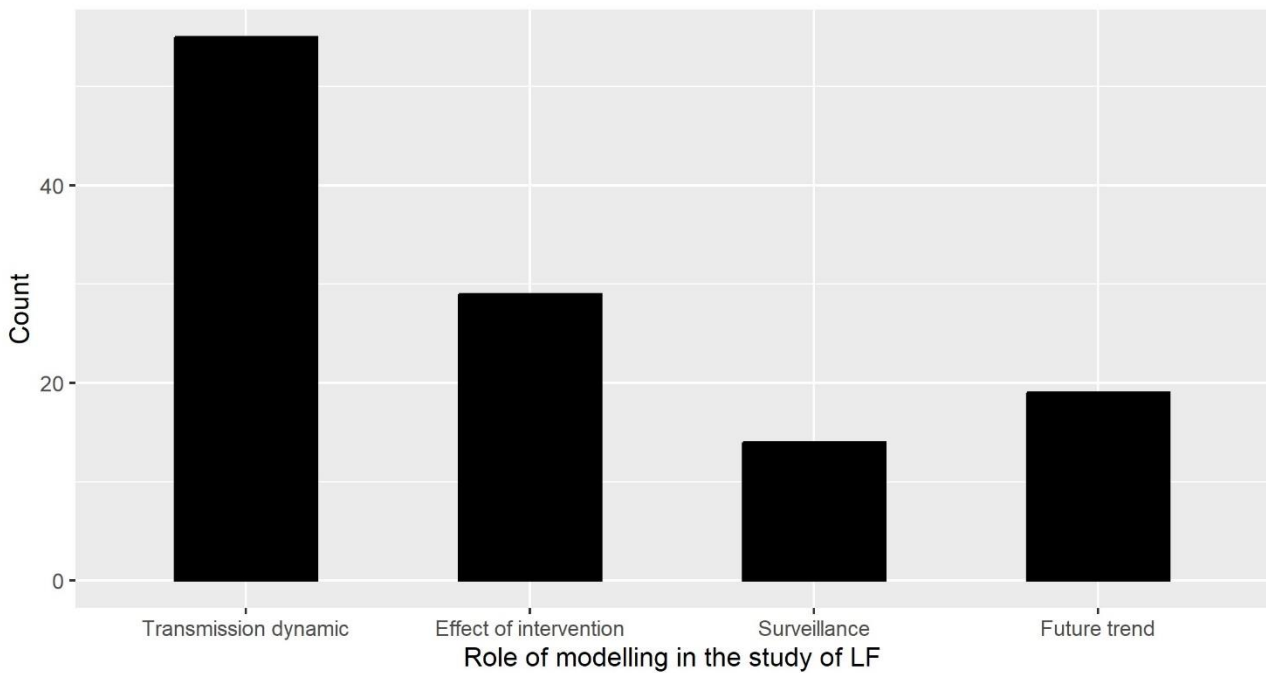


Figure 1- 8: Application of mathematical and statistical modeling in the study of lymphatic filariasis

Beyond a better understanding of disease transmission, mathematical modeling can be used to predict future trends in LF including the expected number of new infections, the prevalence of the disease at particular points in time, and its geographic distribution [57,59,62,89]. Because the effect of different drugs on the filarial worms is well known from experimental studies, the impact of different mass drug regimens can be incorporated in these predictions, helping guide intervention planning. Moreover, by including in the different LF control scenarios their cost-effectiveness [91–94], models help allocate limited resources more efficiently. Models are also used to assess the impact of various combinations of control strategies, such as combining MDA with vector control measures [54], and with other interventions such as quarantine treatment in reducing LF prevalence and transmission [75]. Given how such strategies have been deployed in practice in particular settings and the progress achieved by the corresponding elimination programs, models are used to estimate when LF elimination goals can be achieved in specific regions or countries [63,95], considering factors such as current disease prevalence, intervention coverage and program effectiveness.

A key component of LF elimination programs is the design of surveillance and monitoring systems to allow for decisions of when and where to stop the interventions deployed [68,96] In that sense, several modeling efforts have aimed at comparing the antigeneamia and microfilaria as criteria to stop intervention [97–100]. Such modeling exercises can help determine where and how to collect data to detect cases and assess the success of control efforts, help to identify areas with higher risk of LF transmission, and guide post-elimination surveillance [101,102]. This information is valuable for targeting surveillance and monitoring to the populations and geographic regions most at risk.

Despite the multiple applications of mathematical modeling to LF elimination, there remain significant gaps in our understanding of how elimination efforts that are simulated theoretically are implemented in practice, and what the consequences different sources of heterogeneity in real-world implementation can have on the prospects of elimination in particular geographic settings. For instance, in the next chapter we use an IBM to better understand how heterogeneities in MDA compliance in different age groups and spatial heterogeneities in the progress of LF elimination across different regions within Madagascar can impact the risk of resurgence in areas where LF has been officially eliminated.

1.5- Conclusion

Mathematical models are powerful tools that have helped guide the fight against LF around the world over the last decades. Multiple modeling frameworks have been developed and refined over the years, with the goal to improve the predictions they generate and to acknowledge the uncertainty in their estimates. By allowing to simulate a wide range of future scenarios and strategies, they enable researchers, public health officials, and policymakers to make informed decisions, allocate resources effectively, and work toward the ultimate goal of LF elimination. However, data inference for LF can be challenging due to various factors, including the latency period between infection and heterogeneity in parasite load. LF has a long latency period which can make it challenging to track cases as infected individuals may not exhibit symptoms for an extended period. Moreover, many LF infections are subclinical, and they do not result in overt clinical symptoms. These subclinical infections can go unnoticed and may not be captured by routine surveillance, affecting the quality of available data. Because LF control and elimination efforts can span several years or even decades, long-term monitoring data collection are essential which can be leading to a logistical challenge.

Achieving the global elimination target continues to pose a significant challenge in many endemic countries, including Madagascar. Furthermore, even in areas where elimination has been successfully realized, there remains a potential risk of resurgence. The issue of migration and spatial heterogeneity presents significant challenges in the elimination process, which are not comprehensively addressed in current modeling approaches. Conducting scenario analyses that consider impact of immigration on LF elimination efforts and explore strategies to mitigate its effects is essential to ensure sustainable elimination of LF.

**Chapitre 2: Utilisation de la modélisation
mathématique pour étudier comment
l'hétérogénéité dans la mise en œuvre du
programme d'élimination de la filariose
lymphatique peut augmenter la
réémergence.**

Résumé du chapitre 2

Les avancées vers l'élimination de la FL sont spatialement hétérogènes dans de nombreux pays endémiques, ce qui peut entraîner des résurgences dans les zones qui ont atteint l'élimination. Comprendre les moteurs et les conséquences d'une telle hétérogénéité pourrait aider à informer les stratégies pour atteindre les objectifs mondiaux d'élimination de la FL d'ici 2030. Cette étude a pour objectif d'est d'évaluer, du point de vue de la modélisation mathématique, si les différences de compliance au traitement en fonction de l'âge peuvent expliquer les schémas de prévalence observés dans le Sud-Est de Madagascar et d'explorer dans quelles conditions deux sources d'hétérogénéité (variation spatiale de la prévalence et différences de compliance au traitement en fonction de l'âge) pourraient augmenter le risque de résurgence après l'interruption de la transmission de la filariose lymphatique.

En utilisant le modèle LYMFASIM et des paramètres conformes au contexte du sud-est de Madagascar, nous avons évalué si les différences de compliance au traitement pour les adultes et les enfants de moins de 15 ans pouvaient mieux expliquer l'hétérogénéité de la prévalence de la FL observée entre ces groupes d'âge dans 4 districts de Madagascar que la seule exposition aux piqûres de moustiques en fonction de l'âge. Nous avons ensuite exploré un large éventail de scénarios avec différents taux de compliance au traitement pour les adultes et les enfants (40-100%) et estimé la proportion d'événements d'élimination, de non-élimination et de résurgence associés à chaque scénario. Enfin, nous avons évalué le risque de résurgence associé à différents niveaux de migration (2-6%) des districts voisins, combinés à différents niveaux de prévalence des microfilaires de la FL (0-24%) au cours de la même période d'étude. Les différences de compliance au traitement entre les adultes et les enfants expliquent mieux l'hétérogénéité observée dans la prévalence de la FL pour ces groupes d'âge que les différences d'exposition seules.

Le risque de résurgence associé aux différences de compliance au traitement allait de 0 à 19%, et était le plus élevé lorsque la compliance était faible chez les adultes (-50%). Le risque de résurgence associé à la migration était généralement plus élevé, dépassant 60% de risque pour tous les niveaux de migration étudiés (2-6% par an) lorsque la prévalence dans les districts sources était comprise entre 9% et 20%. Les lacunes dans la mise en œuvre du programme d'élimination de la FL peuvent augmenter le risque de résurgence et saper les efforts d'élimination. Des recherches supplémentaires sont nécessaires pour guider les programmes d'élimination de la FL sur les stratégies optimales de surveillance et de contrôle qui maximisent les chances de maintenir l'élimination et d'éviter la résurgence.

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. The goal of this study is to assess, from a mathematical modeling perspective, whether differences in age-related compliance to MDA could explain observed prevalence patterns in southeastern Madagascar and to explore under which conditions two sources of heterogeneity (spatial variation in prevalence and age-specific differences in MDA compliance) could increase the risk of resurgence after interruption of LF transmission.

Methodology: Using the LYMFASIM model and parameters in line with the context of southeastern Madagascar, we assessed whether differences in compliance for adults and children under 15 years could better explain the heterogeneity in LF prevalence observed between these age groups in 4 districts of Madagascar than age-specific exposure to mosquito bites alone. We then explored a wide range of scenarios with different MDA compliance for adults and children (40-100%) and estimated 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 of 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. More research is needed to help guide LF elimination programmes on the optimal strategies for surveillance and control that maximize the chances to sustain elimination and avoid resurgence.

2.1. Introduction

LF is a parasitic neglected tropical disease caused by the filarial parasites *Wuchereria bancrofti* [34], *Brugia malayi* [35] and *Brugia timori* [36]. LF is endemic to tropical areas in Asia, South America and Africa [103], with an estimated 51 million people infected in 2018 and 36 million suffering disability such as chronic swelling of the limbs or scrotum [104]. LF is also associated with mental health problems, social marginalization, or impaired productivity [105]; therefore, its elimination could contribute to important economic benefits and poverty reduction [106]. The fact that humans are the only known reservoir host, along with the existence of safe and inexpensive drugs has made LF a candidate target for elimination by the WHO since 1997 [107].

The WHO established the GPELF in 2000 with the objective to achieve elimination by 2020 [107]. The GPELF strategy relies heavily on regular MDA of albendazole and diethylcarbamazine in countries where onchocerciasis is endemic, and a combination of albendazole and ivermectin otherwise. In 2018, WHO proposed a new guideline and recommended a combination of those three drugs to accelerate elimination [94,108,109]. Since the launch of the GPELF, 17 of the 73 endemic countries have achieved elimination of LF and the number of people requiring MDA has been reduced by 49% [104]. Despite progress, the GPELF initial objective was not achieved by 2020 and 863 million of people remain threatened by LF [104]. Consequently, a revised target was set by WHO to achieve elimination in at least 80% of endemic countries by 2030 [15]. Major challenges to reach global elimination include achieving high compliance and coverage of MDA [42,110,111], establishing appropriate measures for criteria to stop MDA to avoid resurgence [61,112] and monitoring spatial and individual heterogeneity in LF prevalence [42].

Mathematical modeling has been a useful tool to help guide LF elimination programs at both international and national levels since the beginning of the GPELF. LF-specific models have been used to simulate the dynamics of transmission in multiple geographic settings [59,113–115], to evaluate the effect of several treatment options [63,116,117] and vector control strategies [54], and to inform surveillance [101]. They have helped to define appropriate thresholds under which treatment can be stopped [100,118], including the use of antigenaemia and microfilaraemia as stopping decision criteria [97,99]. More recently, these models have quantified the effect of Covid-19 on LF elimination efforts [119,120]. A particular focus of modeling studies in the past ten years has been on characterizing the impact of spatial and individual heterogeneities in LF prevalence on disease control efforts [42,59,83,96,121,122]. Heterogeneity in spatial prevalence has implications for the threshold of LF elimination [96], the required duration of MDA, and vector control strategies

[55]. Most of these studies consider spatial heterogeneity in prevalence as a result of ecological conditions driving mosquito dynamics [55,88,96], which leads to spatial heterogeneity in nightly biting rates and individual heterogeneity in parasite loads [88]. However, after more than two decades of implementation of national PEFs, few studies have explored the impact that local heterogeneities in MDA implementation could have on the success of elimination efforts and the risk of LF resurgence [110,123].

Madagascar is one of several remaining countries in Africa still facing high prevalence of LF and major challenges to achieve its elimination [103]. The disease was first reported on the island in 1909 [124]. The main vectors in Madagascar are *Anophele funestus* and *Anophele gambiae*, and the parasite responsible is *W. bancrofti* [124–126]. The southeast coast of the Island has been historically the most affected region [28,126,127] but a mapping conducted in 2004-2005 revealed that 98 out of the 114 districts of Madagascar were endemic for LF [28]. The national elimination program started MDA in 2005 using combination 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 [28]. After 10 rounds of MDA, the first TAS [128] conducted in school-age children in three districts of southeastern Madagascar suggested that transmission had been interrupted and that this area was eligible for cessation of MDA [129]. However, community surveys conducted in parallel to the TAS revealed that there was substantial heterogeneity in age-specific prevalence within these districts, with adults having higher Filarial test strip (FTS) prevalence than children [129]. In addition, surveys found spatial heterogeneity in FTS prevalence rates, with prevalence in surrounding districts ranging from 3.85 to 27.78% [129]. 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, therefore, is to assess from a mathematical modeling perspective, 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.

2.2. Methodology

2.2.1 Study setting and previous results

The districts of Manakara Atsimo, Vohipeno, Mananjary and Ifanadiana are located in the southeastern region of Madagascar. The population of each district ranges between 150 000- 400 000 people [130]. In 2004, Immunochromatographic test (ICT) prevalence in these districts was very high (>30%) [129]. 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 were 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 FTS for all surveys, the study revealed important differences in LF FTS prevalence between adults and children, and between districts. No child had a positive FTS in the TAS surveys, and only one child (< 15 years) from Mananjary tested positive at sentinel and spot check sites [129]. In contrast, 3.6% of individuals 15-90 years 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 FTS prevalence of 0.7% in children under 15 years, and 12.06% for individuals 15-90 years [129].

2.2.2 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 [46,51,117]. 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 individual-level exposure rates.

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. 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:

$$R_b(t) = \sum_{a=1}^{n_a} N_f(a, t) \cdot r_b(a) \quad (2.1)$$

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):

$$m_i(t) = s \times m_i(t - 1) + F_i(t) \times r_i(t) \quad (2.2)$$

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 μ l 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 μ l) of mf (m_i) in the host. These mf then develop into infectious larvae within the mosquito vector. The relationship between the density (per 20 μ l) 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:

$$L_{3_i} = a \times (1 - e^{-(bm_i)^c}) \quad (2.3)$$

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:

$$foi_i(t) = mbr(t) \times \vec{L}_3(t) \times E_i(t) \times sr \quad (2.4)$$

Where $mbr(t)$ is the monthly mosquito biting rate at time t , $\vec{L}_3(t)$ 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 L_3 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 ($E_{a_i}(a_{i(t)}, s_i)$) and a random component E_{i_i} .

$$E_{i(t)} = E_{a_i}(a_{i(t)}, s_i) \times E_{i_i} \quad (2.5)$$

The average number of infective larvae released per mosquito-bite $\vec{L}_3(t)$ is given by:

$$\vec{L}_3(t) = \nu \times \frac{\sum_{i=1}^{N(t)} E_{i(t)} \times L_{3_i}(t)}{\sum_{i=1}^{N(t)} E_{i(t)}} \quad (2.6)$$

$N(t)$ 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:

$$M_i = foi(t) \times (\overline{Tl} - Ti) \quad (2.7)$$

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.

2.2.3 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, while the constant monthly biting rate and probability of transmission were manually calibrated so that mf prevalence at equilibrium fell between 20% and 30%, aligning with baseline mf prevalence observed in those districts before MDA implementation [129] (Table 2-1). After simulations achieved equilibrium, we carried out the analysis from 2000 to 2030, the new WHO target year for LF elimination. As occurred in the southeastern region of Madagascar, 10 rounds of MDA were modeled from 2005 to 2016 with an average coverage of 75%. The effect of drug treatment impacts the 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 [46] and it cleared 95% of mf [131] (Table 2-1). We did not consider immunity in the model such as in [46]. Parameter values specific to southeastern Madagascar are shown in Table 2-1, with default values in the LYMFASIM program kept for all other parameters. Simulations were conducted using monthly timesteps.

Table 2- 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 [108]	
	Maximum human population size	200,000	District setting [129]	
	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		[46]
	Number of mf produced per female parasite (per 20 μ l blood smear)	0.58	[132]	
	Parameters of mathematical function describing the uptake of infection by Anopheles mosquitoes	a=1.666 b=0.027 c=1.54	[46]	
	Monthly bite rate (mbr)	550 bites per person per month	[46,133]	
	Success ratio (sr)	0.00088	[46]	
	Transmission probability (ν)	0.1	[46]	
	Duration of the immature stage (Ti)	8 months	[134]	
	Average lifespan of adult parasites (Tl)	10 years	[132]	
	Exposure by age	0.1 at birth and increases linearly with age to reach a maximum 1 at age 20	[46]	
	Exposure variability	Gamma distribution with mean 1 and shape parameter 0.26	[46]	
	Proportion of mf killed by MDA	0.95	[118,131]	
	MDA period	10 rounds between 2005 and 2016	District setting: [129]	
	MDA coverage (The percentage of the population receiving MDA)	75%	District setting: [129]	

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%	
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% (4000-12000 migrants per year)	[135]
	Mf prevalence level at original district of migrants	Ranged from 0 to 24%	

2.2.4 *Exercise 1: Modeling the impact of age-specific compliance on LF FTS prevalence*

The goal of our first modeling exercise was to assess whether age-specific MDA compliance better explained observed age-specific patterns in LF FTS 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 [55,61]. 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 FTS 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 (their school,

with the presence of their teachers and other adults) and typically have less agency than adults (who may not be at home 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 were 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 FTS prevalence in 2016 was estimated as the difference between FTS prevalence in adults and FTS 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.

2.2.5 *Exercice 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 more than 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 because of the stochasticity in the model. 2) Non-elimination: when prevalence never decreased under 1% for more than 2 years, and 3) Resurgence, when prevalence fell below 1% one year after MDA cessation but it returned above the threshold for more than 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 (Figure 2-1). 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.

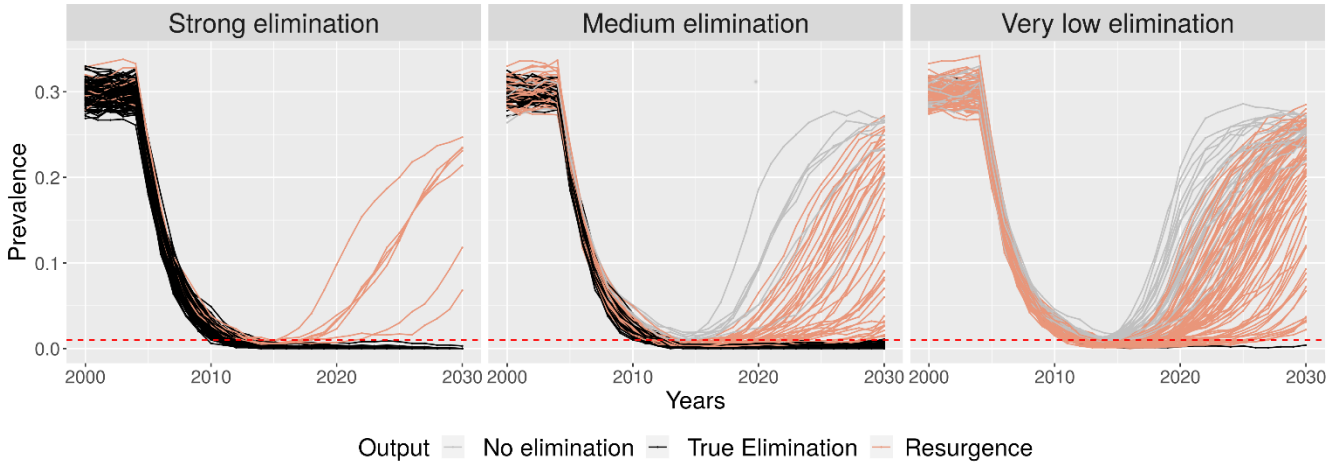


Figure 2- 1: Illustration of possible output of true elimination, resurgence or non-elimination.

(A) Case of 7% of resurgence and 93% of elimination and no case of non-elimination. (B) Case of 52% of elimination, 37% of resurgence and 11% of non-elimination. (C) Case of 1% of elimination, 61% of resurgence and 38% of non elimination.

2.2.6 **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 [136]. 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 Equation 2.6 is rewritten as Equation 2.8:

$$\vec{L}_3(t) = \nu \times \frac{\sum_{i=1}^{N(t)+M(t)} E_{i(t)} \times L_{3i}(t)}{\sum_{i=1}^{N(t)+M(t)} E_i(t)} \quad (2.8)$$

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. Equation 2.8 can then be rewritten as Equation 2.9:

$$\vec{L}_3(t) = \nu \times \frac{\sum_{i=1}^{N(t)} E_{i(t)} \times L_{3i}(t) + \sum_{i=N(t)+1}^{N(t)+M(t)} E_M \times L_{3M}}{\sum_{i=1}^{N(t)} E_i(t) + \sum_{i=N(t)+1}^{N(t)+M(t)} E_M} \quad (2.9)$$

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.

Therefore,
$$\bar{L}_3(t) = \nu \times \frac{\sum_{i=1}^{N(t)} E_i(t) \times L_{3i}(t) + M(t) \times Pr \times E_M \times L_{3M}}{\sum_{i=1}^{N(t)} E_i(t) + M(t) \times E_M} \quad (2.10)$$

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 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 4,000-12,000 migrants), 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).

2.3.1 Exercise 1: The impact of age-specific MDA compliance on LF FTS 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 FTS prevalence rates in Manakara Atsimo, where both age groups had a 0% FTS prevalence. For the other 3 districts, the observed difference in FTS 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 2-2). The magnitude of difference in age-specific MDA compliance needed to match observed FTS prevalence rates differed by district. Observed FTS 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 FTS 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- 2: Observed and simulated differences in FTS prevalence due to differences in compliance.

Difference in compliance between age groups (%)	Compliance in adults vs. children (%)	Difference in FTS 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%)

Exercice 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% (Figure 2-2). 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 (Figure 2-2). Out of the 49 scenarios, 14 of them (28%) presented a risk of resurgence of more than 10% and the majority of those (9 out of 14) were cases where MDA compliance rates in adults were lower than in children (Table A-1). 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 2-3).

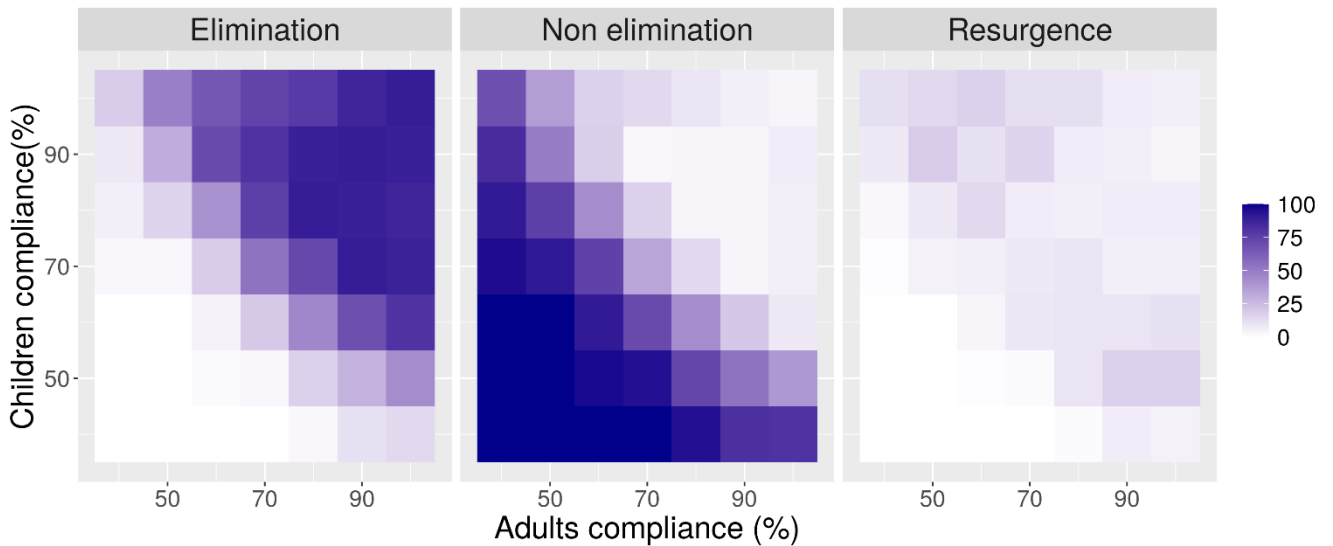


Figure 2- 2: Proportion of scenario resulting in elimination, non-elimination and resurgence associated with different compliance scenarios for adults and children.

(A) 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. (B) The proportion of scenario ending in non-elimination is the percentage of scenarios where mf prevalence does not fall below 1% for more than 1 year during the study period (C) 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 2- 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 adults' 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%)

2.3. Results

2.3.2 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 (Figure 2-3). 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 2.5% of the population per year. When prevalence in the districts of origin is above 20%, the majority of 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 (Figure 2-3).

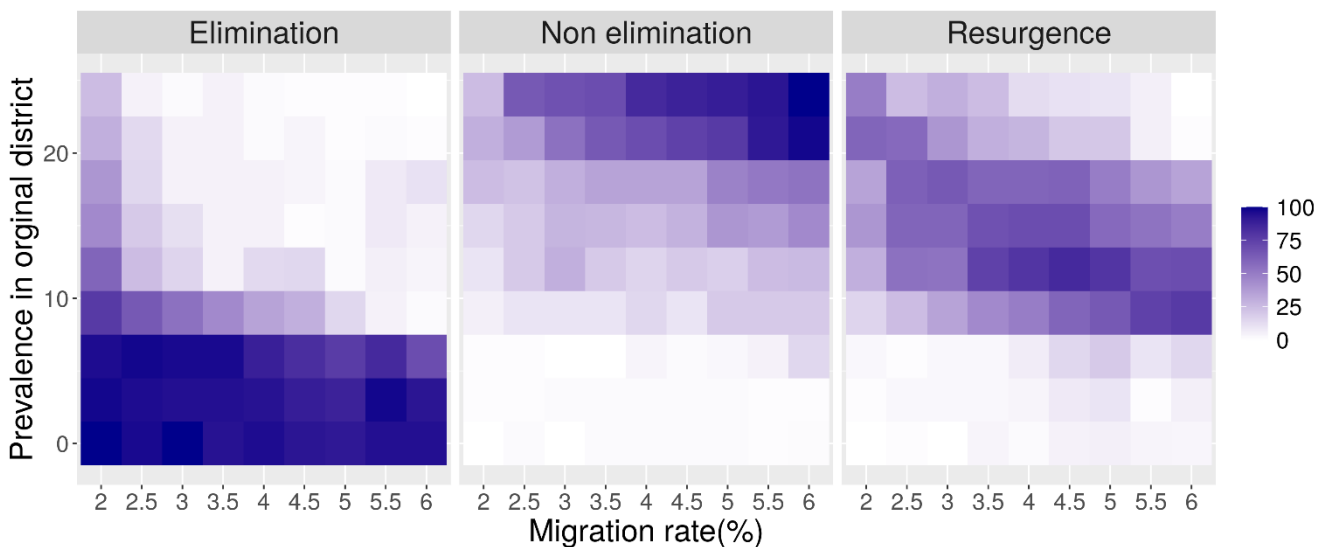


Figure 2- 3 The proportion of scenarios resulting in elimination, non-elimination and resurgence associated with different levels of migration and mf prevalence in surrounding districts.

2.4. Discussion

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 [15]. A major challenge for elimination efforts is the individual and spatial-heterogeneity in LF transmission [83,88,96]. 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 [83,96]. 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. 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. 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%. However, 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 50-60% 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 [110,137]. Several studies have already discussed the importance of MDA compliance in achieving elimination of LF [123,138,139], with lower compliance rates increasing the number of rounds of MDA needed to achieve elimination. A number of factors can affect compliance, such as the drug delivery mechanism and whether the recipient knows the distributor personally [140]. 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 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 [61]. 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 programmes 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 [93,141]. 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 [142]. Yet, the impact of local migration patterns on population-level transmission dynamics in areas under elimination is under-investigated and differs across contexts [143]. 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 [143], while a spatially explicit model of LF in American Samoa predicted that migration could explain observed transmission patterns in the island [59]. Our results imply that in order 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 [128], the COVID-19 epidemic and lack of financial resources prevented the national PEFL 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 [59] should be implemented for a more realistic investigation of the impact of human migration given current spatial heterogeneities in LF prevalence in Madagascar and other settings. Third, we considered only the widely used LYMFASIM model in this study [46,51]. However, other models exist such as EPIFIL [78,80], a deterministic population-level model, and TRANSFIL [85], 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 [60,62,63] and future work in this area should adopt more comprehensive modeling framework such as ensemble modeling.

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. 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.

**Chapitre 3: Etude de l'impact du
renforcement du système de santé sur
l'efficacité des stratégies de vaccination et
identification des inégalités persistantes
dans la couverture vaccinale.**

Résumé du chapitre 3

Afin d'atteindre les objectifs mondiaux en matière de vaccination, les programmes nationaux doivent trouver un équilibre entre la stratégie routine de vaccination dans les établissements de santé, les campagnes de vaccination et d'autres stratégies mobiles. Ces dernières renforcent la couverture à des moments spécifiques et contribuent à réduire les disparités géographiques. Cependant, lorsque la vaccination de routine est faible, un recours excessif aux stratégies avancées peut conduire aux non-respects du calendrier vaccinal. Dans cette étude, nous avons évalué comment une intervention de renforcement du système de santé (RSS) a modifié la contribution relative de la vaccination de routine et les autres stratégies de vaccinations dans les zones rurales de Madagascar.

Nous avons obtenu des données des centres de santé du district d'Ifanadiana sur le nombre mensuel de vaccins recommandés (BCG, rougeole, DTP et Polio) délivrés aux enfants entre 2014 et 2018. Nous avons également analysé les données d'une cohorte représentative du district réalisée tous les deux ans dans plus de 1500 ménages pendant ce même période. Nous avons comparé les changements à l'intérieur et à l'extérieur de la zone de couverture du RSS en ce qui concerne l'administration des vaccins recommandés, la couverture vaccinale au niveau de la population, les inégalités géographiques et économiques en matière de couverture, et le respect du calendrier vaccinal. L'impact du RSS a été quantifié à l'aide de régressions logistiques à effets mixtes.

L'intervention du RSS a été associée à une augmentation significative des taux de vaccination (Odds ratio entre 1,22 pour la rougeole et 1,49 pour le DTC), qui a diminué avec le temps. Les activités de sensibilisation ont été associées à un doublement des taux de vaccination, mais leur effet était plus faible dans la zone d'intervention du RSS. L'analyse des données de cohorte a révélé que le RSS était associé à une couverture vaccinale plus élevée (Odds ratio de 1,18 par année de RSS pour la rougeole et de 1,43 pour le BCG), à une réduction des inégalités économiques et à une proportion plus élevée de respect de calendrier vaccinal. Cependant, on observe des inégalités persistantes dans la couverture géographique au sein de la zone d'intervention du RSS, ce qui a empêché d'atteindre les objectifs internationaux de couverture. L'investissement dans des systèmes de soins primaires plus solides peut améliorer la couverture vaccinale, réduire les inégalités et améliorer le respect du calendrier vaccinal grâce à l'augmentation des vaccinations de routine. Toutefois, des efforts supplémentaires sont nécessaires pour atteindre les zones reculées et réduire les disparités géographiques.

Impact of health system strengthening on delivery strategies to improve child immunization coverage and inequalities in rural Madagascar

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Abstract

Background: To reach global immunization goals, national programs need to balance routine immunization (RI) at health facilities with vaccination campaigns and other outreach activities (e.g. vaccination weeks), which boost coverage at particular times and help reduce geographic inequalities. However, where RI is weak, an overreliance on vaccination campaigns may lead to heterogeneous coverage. Here, we assessed the impact of a health system strengthening (HSS) intervention on the relative contribution of RI and outreach activities to reach immunization goals in rural Madagascar.

Methods: We obtained data from health centers in Ifanadiana district on the monthly number of recommended vaccines (BCG, measles, DTP and Polio) delivered to children, during 2014-2018. We also analyzed data from a district-representative cohort carried out every two years in over 1500 households in 2014-2018. We compared changes inside and outside the HSS catchment in the delivery of recommended vaccines, population-level vaccination coverage, geographic and economic inequalities in coverage, and timeliness of vaccination. The impact of HSS was quantified via mixed-effects logistic regressions.

Results: The HSS intervention was associated with a significant increase in immunization rates (Odds Ratio between 1.22 for measles and 1.49 for DTP), which diminished over time. Outreach activities were associated with a doubling in immunization rates, but their effect was smaller in the HSS catchment. Analysis of cohort data revealed that HSS was associated with higher vaccination coverage (Odds Ratio between 1.18 per year of HSS for measles and 1.43 for BCG), a reduction in economic inequality, and a higher proportion of timely vaccinations. Yet, the lower contribution of outreach activities in the HSS catchment was associated with persistent inequalities in geographic coverage, which prevented achieving international coverage targets.

Conclusion: Investment in stronger primary care systems can improve vaccination coverage, reduce inequalities and improve the timeliness of vaccination via increases in RIs.

Key questions

What is already known?

- Reaching the minimum recommended vaccination coverage of 90% for childhood illnesses remains a substantial challenge for low- and middle-income countries (LMICs).
- Understanding how vaccine delivery strategies can be improved to achieve coverage targets in rural areas of LMICs is essential due to the fragility of health systems and associated health budgets.
- While evidence exists on the impact of outreach activities and other targeted interventions aimed at improving immunization coverage, it is unclear how strengthening local health systems can help improve key indicators of vaccination coverage, via its different impacts on routine and outreach immunizations.

What are the new findings?

- A HSS intervention in a rural district of Madagascar improved overall vaccination coverage, reduced economic inequalities in vaccination coverage, and increased the proportion of timely vaccinations via an increase in RIs.
- The contribution of outreach activities was lower in the HSS catchment area than in the rest of the district, which was associated with a persistence of geographic inequalities in vaccination coverage.

What do the new findings imply?

- Strengthening local health systems can help improve key indicators of vaccination coverage in rural, low resource settings, even when those interventions do not target specifically vaccine improvements themselves.
- Explicit efforts are still necessary in areas undergoing HSS to vaccinate children in remote areas so that immunization goals can be reached.

Introduction

Vaccination is one of the most effective public health interventions to reduce the burden of infectious diseases, particularly among children [144,145]. To increase vaccination coverage around the world, the Global Alliance for Vaccines and Immunization (GAVI) was created in 2000 to mobilize funds and technical expertise for child vaccination in the poorest countries in the world [146,147]. As a result, from 2000 to 2015, global vaccination coverage has increased from 72% to 86% [148]. As of 2018, 760 million children have been immunized and an estimated 13 million deaths have been prevented in GAVI-supported countries [149]. Future impacts of immunizations are estimated to be larger with the introduction of new vaccines (e.g. rotavirus, papillomavirus) and the expansion of coverage for existing vaccines [150,151]. Based on the Global Immunization Vision and Strategy, the goal of the Global Vaccine Action Plan was to reach a national coverage of 90% for basic vaccines in all countries in 2020 [150,152], with at least 80% coverage in every district [153]. Despite great progress, vaccination coverage remains low in many areas of the developing world due to many reasons [154]. For instance, while average coverage for third dose of the DTP vaccine increased from 60% to 81% between 1999 and 2018 in LMICs, it remained under 40% for the bottom ten performing countries [148]. Failure to achieve critical population-level thresholds for herd immunity has resulted in sustained transmission, periodic epidemics and has slowed-down progress towards the elimination of vaccine preventable diseases such as polio, measles and rubella [155–157]. Beyond 2020, the new objective of the GAVI strategy is to reduce the number of “zero-dose” children by 25% in 2025 and by 50% in 2030 [158].

National strategies for vaccination in most LMICs typically involve RI at primary health centers, complemented with additional outreach activities to increase coverage such as periodic vaccination weeks (VW) and supplementary immunization activities (SIAs) such as mass vaccination campaigns. RI, where a child is brought to a health facility to receive the recommended shots, usually free of charge, represents the most reliable way of vaccinating children at the right time in order to maximize immunity [159]. However, its reach is undermined by the fragility of health systems in LMICs and multiple barriers faced by local populations for accessing health care [160]. In particular, geographic distance to primary health centers is associated with important inequalities in vaccination coverage [161]. Vaccination campaigns, which involve the mobilization of health workers to administer vaccines where populations live during VW and SIAs, are a very effective way to cover large geographic areas over short periods of time and to reduce geographic inequalities in vaccination coverage [162,163]. Consequently, significant funding has been mobilized towards increasing coverage via vaccination campaigns [163,164], but the low frequency of these campaigns can result

in heterogeneous coverage across age groups [161,165], insufficient number of recommended doses per vaccine [166], and important delays in immunization relative to the recommended age of vaccination [167–170]. In addition, vaccination campaigns can have negative impacts on subsequent rates of immunization via RI [155,171], which could exacerbate these issues. To address this, investments in vaccination campaigns could be accompanied with broader HSS efforts to increase the contribution of RI to overall immunization coverage [171,172].

Madagascar is illustrative of the challenges and potential solutions to achieving global goals for immunization in LMICs. Since its launch in 1976, the national Expanded Program on Immunization (EPI) has contributed to a substantial uptake in immunization [173,174] which seems to have been an important driver in improvements in life expectancy [175]. In addition to supporting RI activities, the EPI launched biannual VWs in 2006 (“mother and child weeks”, which generally take place in April and November) [176–178], and conducts occasional SIAs to further increase coverage and prevent disease outbreaks [155,179]. As of 2018, vaccination coverage goals for Madagascar had not yet been achieved for any of the recommended vaccines [180]. Suboptimal vaccination coverage can lead to larger-than-usual outbreaks (known in epidemiology as “post-honeymoon” epidemics) [155]. For instance, insufficient coverage for measles vaccine (~80% by 2017) [181] led to the largest known measles outbreak in Madagascar history in 2018-2019 [182], which accounted for one fourth of global cases [183] that year with nearly 225 000 cases registered [184]. Achieving vaccination coverage targets is particularly challenging in rural areas of the country, where the majority of the population lives, and where coverage is over 10% lower than in urban areas [180] for all recommended vaccines.

In 2014, the Ministry of Public Health (MoPH) partnered with the nongovernmental healthcare organization PIVOT to strengthen the rural health district of Ifanadiana, located in southeastern Madagascar, to improve local health conditions and serve as a model health system for the country (Bonds et al., 2017). Though the partnership does not include a particular focus on immunization (which is managed directly by the MoPH), it supports a large range of interventions at health centers and community health sites in approximately one third of the district, which has resulted in substantial increases in primary health care access and utilization [186]. Those programs include improved ‘readiness’ of health facilities (staffing, training, equipment, infrastructure, supply chain) and clinical programs that can directly influence adherence to vaccinations schedules, such as family planning, antenatal care, postnatal care, and deliveries at health facilities.

The goal of this study was to assess the impact of HSS on the relative contribution of RI and vaccination campaigns over time, and the impact of these changes on key features of immunization at the population-level. In particular, we assessed changes between 2014 and 2018 in the HSS catchment and in the rest of the district in a) the delivery of recommended vaccines, b) population-level vaccination coverage, c) geographic and economic inequalities in coverage, and d) timeliness of vaccination. For this, we combined immunization data from all health centers in Ifanadiana District with information from a district-representative longitudinal cohort conducted every two years in nearly 1600 households in the district (~8000 individuals).

3.1. Methodology

3.2.1. Study site

Ifanadiana is a rural district in the region of Vatovavy Fitovinany, located in southeastern Madagascar. It comprises about 200 000 people distributed in 13 communes, with 2 additional communes created during the study period. The district's health system consists of one hospital and at least one health center (CSB2) per commune that provides primary health care. Six communes have additional health centers (CSB1) with more limited health services. The initial HSS catchment comprised 4 out of the 13 communes in the first three years (2014 to 2016). One additional commune was added in 2017 to the HSS catchment, with plans to progressively cover the entire district over the following years [187]. The HSS intervention spans across all levels of care (hospital, health centers and community health) and combines horizontal support to health system readiness (e.g. infrastructure, staffing, equipment, removal of user fees, social support to patients) with vertical support to clinical programs (e.g. malnutrition, emergency care, tuberculosis) and improved information systems [187,188]. More details are available in the Annexe, Table A-2 [189]. Delivery of child immunization is similar to the rest of Madagascar, combining RI with biannual VWs and other outreach activities. Only one SIA took place during the study period in Ifanadiana, a measles mass vaccination campaign in October 2016.

3.2.2. Data collection

Health system data collection

Data on monthly immunization rates from 2014 to 2018 were obtained from all 19 primary health centers in Ifanadiana district. Two health centers that were recently built and lacked consistent data across the study period were excluded. Data were obtained on all recommended vaccines in the Madagascar EPI, which included tuberculosis (BCG), measles, poliomyelitis (polio), and the

combined vaccine for diphtheria, tetanus and pertussis (DTP). For polio and DTP, only the number of third doses administered was considered, which indicates completion of all the required doses for these two vaccines. Immunization information was derived from the health centers' monthly reports to the district, which are aggregated from the health centers' registers every month by MoPH staff. From these, the number of children immunized per month for each of these vaccines was obtained for each health center (CSB1 or CSB2), which included all children vaccinated through both routine services and outreach activities. The population of children aged 12-23 months was also obtained for each health center catchment from official MoPH records [190]. Data qualities were monitored by joint PIVOT-MoPH supervisions every three months. During each supervision, data from the health center paper registries, containing each individual visit, were used to calculate several indicators (though the number of immunizations was not among them); values for each indicator were then compared to those reported in the monthly report to the district [191]. Information on the geographic extent and timing of the HSS intervention was obtained from the NGO's internal records.

Cohort data collection

We obtained population-level information from the Ifanadiana Health Outcomes and Prosperity longitudinal Evaluation (IHOPE), a district-representative longitudinal cohort study initiated in Ifanadiana district in 2014 [192]. It consists of a series of surveys conducted in a sample of 1600 households every two years, with questionnaires modeled after the internationally validated Demographic and Health Surveys (DHS) [193]. A two-stage sample stratified the district by the initial HSS and control catchments. Eighty clusters, half from each stratum, were selected at random from enumeration areas mapped during the 2009 census, and households were then mapped within each cluster. Twenty households were selected at random from each cluster. 1522 households were successfully interviewed in 2014 (95.1% acceptance rate), 1514 and 1512 households were revisited during the follow-up in 2016 (94.6% acceptance rate) and in 2018 (94.5% acceptance rate) respectively. Data collection, survey coordination and training were conducted by the Madagascar National Institute of Statistics (INSTAT).

The survey included a household questionnaire and individual questionnaires for all men and women of reproductive age (15-59 years and 15-49 years, respectively). All eligible women and men who were in the households sampled (usual residents or visitors) were interviewed. Data collected through the questionnaires included general information about household composition (size, genders, ages); living conditions, education, and other indicators of socio-economic status; recent illness, care seeking for illness and preventive behaviors; women's reproductive history and care seeking behavior for reproductive health; children's health, development, preventive behaviors, and care seeking for

illness; and child, adult and maternal mortality. For vaccination specifically, information about vaccination status of the children under 5 years was obtained from the individual interviews with their mothers. Vaccination status and history was assessed from the children's vaccination cards when available, or from the mother's report otherwise.

3.2.3. Ethical considerations

The IHOPE cohort study was reviewed and approved by the Madagascar National Ethics Committee and the Harvard Medical School Institutional Review Board. Use of aggregated HMIS data was authorized by the Ministry of Public Health's Medical Inspector in Ifanadiana District.

3.2.4. Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

3.2.5. Data analysis

Analysis of immunization rates at health centers

We studied the effect of the VWs and the HSS intervention on monthly immunization rates at health centers over the study period. For this, we first estimated monthly per capita rates (age-specific) at each health center for each vaccine (BCG, polio 3rd dose, DTP 3rd dose, and measles). Per capita immunization rates were modelled separately for each vaccine via binomial regressions in generalized linear mixed models (GLMM), including a random intercept for each health center. All explanatory variables (see below) were included as fixed effects. To study the effect of VWs and of the HSS intervention on immunization rates, we built dummy variables coded as 1 for the CSBs and months where each program was in place (discrete for months with VWs, and constant from the moment the HSS started until the end of the study period). We also studied the interaction of the HSS intervention with a linear annual change and VWs, to account for the additional effect of the HSS intervention over time, and for changes in the contribution of VWs to overall immunization rates due to the HSS intervention, respectively. We controlled our analyses for baseline differences in health system factors and time-varying factors, which is akin to a difference-in-differences analysis. For health system factors, we controlled for baseline differences between health centers in the initial HSS catchment and in the rest of the district, as well as between different types of health center (CSB1 and CSB2). For time-varying factors, we controlled for annual linear and seasonal changes in immunization rates in the district. Seasonal changes were studied using a sine function with a period of one year and the

horizontal shift that best fitted the data. We excluded from the analysis the measles immunizations delivered via SIAs in October 2016 because the target age was children up to 5 years of age, which differed from the population group used in the analyses (12-23 months).

Univariate analyses were first performed for each explanatory variable and those with p-value below 0.1 were retained for multivariate analysis. From this full model, a reduced model that included only variables reaching statistical significance (p-value < 0.05) was obtained via backwards selection. Effects are reported as adjusted Odds Ratios (OR).

Analysis of vaccination coverage in the longitudinal cohort

While an analysis of health center immunizations can provide some basic understanding about the impact of the HSS intervention on RI and outreach activities over time, it does not allow for obtaining accurate measures of vaccination coverage due to known inaccuracies in target population estimates, which are often based on extrapolation of data from censuses conducted very far apart in time [194–196]. In addition, aggregated information reported by the health system does not allow us to evaluate changes in economic or geographic inequalities in vaccination coverage, or for the assessment of the timeliness of vaccination, all of which can be affected by the relative contribution of RI and outreach activities in the area. For this, we conducted a complementary analysis of vaccination coverage at the population-level using data from the IHOPE cohort.

Vaccination coverage was estimated for 2014, 2016 and 2018 from individual level data for children 12-23 months or 12-59 months (depending on the analysis, see below), as the proportion of the target group immunized at the time of the interview. Similar to our analysis of health center immunization rates, we studied separately each of the recommended vaccines, namely BCG, polio 3rd dose, DTP 3rd dose and measles. We also estimated whether the child had received all of these recommended vaccines. For each child surveyed, vaccination status for each vaccine was coded 1 if the child was vaccinated based either on the vaccination cards, or on the mother's report, and 0 otherwise. To assess the impact of economic and geographic inequalities in vaccination coverage, we estimated a household wealth score via principal components analysis of household assets following standard DHS methods [193], and we estimated the shortest path distance from the villages in each cohort cluster to the nearest health center using the Open-Source Routing Machine engine. For this, we had previously mapped the entire district of Ifanadiana on OpenStreetMap, resulting in over 23,000 km of footpaths and 5,000 residential areas mapped [72]. Households were ordered based on their wealth score and distance to the nearest health center and were classified into five quantiles with 20% of observations in each category (Q5 = wealthiest or closest to the health center; Q1 = poorest or most remote). Vaccination coverage in children 12-23 months was estimated inside and outside of the HSS

catchment at the beginning and at the end of the study period (2014-2018), disaggregated by wealth quantile and by distance quantile. Consistent with previous studies, changes in inequalities were measured as the gap in vaccination coverage between the worst-off quantiles (Q1-Q2) and the best-off quantiles (Q3-Q5) over time[186,197,198].

We then modelled changes in vaccination coverage over the study period, studying baseline differences and annual changes in overall coverage and in economic and geographic inequalities for the HSS catchment and the rest of the district. For this, we performed a separate logistic regression mixed model for each vaccine, with the household cluster as random intercept. To study baseline differences between HSS catchments we included a dummy variable reflecting whether clusters were located in the initial HSS catchment. We included the natural logarithm of the wealth score to study differences in socio-economic groups, and distance to health center (in tens of kilometers) to study differences in geographic groups, both as continuous variables. We included two time-varying variables, one to reflect annual changes in vaccination coverage in the whole district, and another to reflect changes per year of HSS intervention in the HSS catchment. Finally, we included interaction terms of these two variables with wealth and distance to study the evolution of inequalities in each area. We included children aged 12-59 months in these analyses to allow for adequate sample sizes for each model. Model selection procedures were identical to those described above for the analysis of health system data. To understand which population groups could reach recommended vaccination coverage targets in the HSS catchment and in the rest of the district, we predicted in-sample vaccination coverage for 2018 from each of the reduced multivariate models, at varying levels of socio-economic class and proximity to health centers.

Finally, we studied the difference in timeliness of vaccination between the HSS catchment and the rest of the district in the subset of children 12-59 months with vaccination cards at the time of the interview in any of the cohort waves (N=786). For this, we estimated the child's age at vaccination from the date of birth and the date of vaccination. Timely vaccination was estimated for each vaccine based on the recommended age of vaccination by the national EPI in Madagascar: in the first month of life for BCG (recommended to be given at birth), in the fourth month for polio 3rd dose and DTP 3rd dose (recommended to be given the 14th week), and in the ninth month for measles [180].

3.2. Results

3.3.1. Trends in the rates of per capita immunization at Ifanadiana's health centers

Between January 2014 and December 2018, a total of 28,407 BCG, 31,476 polio 3rd dose, 33,241 DTP 3rd dose, and 30,371 measles immunizations were delivered by the 19 health centers in

Ifanadiana District. Average monthly per capita immunization rates (age specific, children 12-23 months) at health centers varied from 0.02 to 0.21, with an average of 0.08. Higher rates were observed on average in the HSS catchment, during months where VWs took place, and with an apparent increase over time in the whole district (Figure 3-1). These immunization trends were similar for all the different vaccines considered (Figure 3-1). Results from multivariate analyses revealed that per capita immunization rates were similar for different types of health center and HSS catchment at baseline (Table 3-1). Immunization rates for all vaccines increased over time and varied seasonally, with higher rates during the dry season (peak in August) and lower rates during the rainy season (bottom in February). Annual increase was higher for BCG and measles (OR 1.23 and 1.1 respectively), which require one single dose, than for polio and DTP (OR=1.06 for both), which require three doses. VWs were associated with approximately a doubling in immunization rates in the months where they took place (OR between 1.88 measles and 2 for polio).

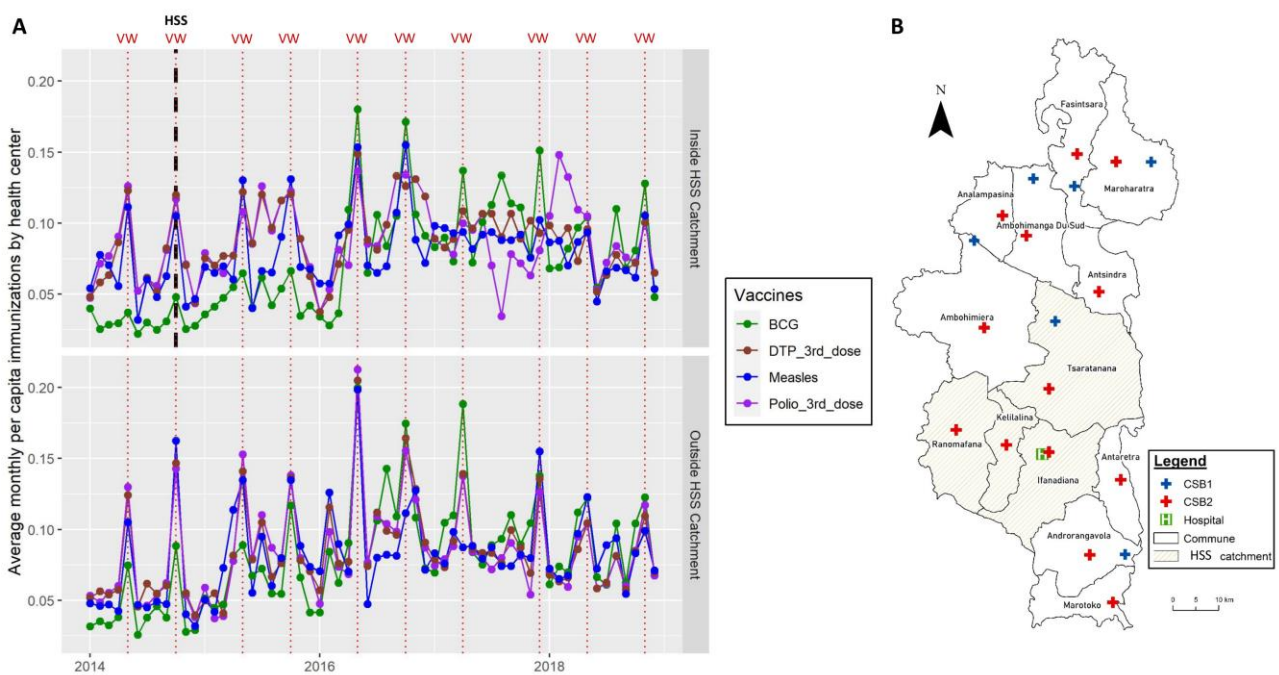


Figure 3- 1: Changes in monthly immunisation rates for children 12–23 months at health facilities in Ifanadiana District, 2014– 2018.

(A) Average number of monthly immunisations per capita (age-specific, 12–23 months) delivered by health centres over time in the HSS catchment and in the rest of the district, with colours representing different vaccines. (B) Map of Ifanadiana district and its health facilities. The initial HSS catchment is shown as yellow shaded areas, whereas the rest of the district is shown as white areas. DTP, diphtheria, tetanus and pertussis;

Table 3- 1: Determinants of per capita monthly immunizations at health centers in Ifanadiana district, 2014-2018 (GLMM, multivariate results1).

Variable	BCG immunizations	Polio immunization (3rd dose)	DTP immunization (3rd dose)	Measles immunization
Monthly coverage at baseline (intercept)	0.04 (0.03-0.04)	0.06 (0.06-0.07)	0.06 (0.06-0.07)	0.06 (0.05-0.06)
Time-varying factors				
Annual change	1.23 (1.22-1.25)	1.06 (1.05-1.07)	1.06 (1.05-1.07)	1.1 (1.09-1.11)
Seasonal changes	1.05 (1.03-1.07)	1.05 (1.03-1.07)	1.06 (1.04-1.08)	0.98 (0.96-1)
Effect of programs and policies				
Mother and child week (2 months per year)	1.95 (1.89-2.02)	2 (1.93-2.06)	1.95 (1.89-2.01)	1.88 (1.82-1.95)
HSS	1.4 (1.29-1.52)	1.34 (1.25-1.44)	1.49 (1.39-1.6)	1.22 (1.14-1.32)
HSS x Annual change	0.95 (0.93-0.97)	0.92 (0.91-0.94)	0.91 (0.9-0.93)	0.92 (0.91-0.94)
HSS x Mother and child weeks	0.73 (0.69-0.77)	0.62 (0.58-0.66)	0.65 (0.61-0.69)	0.77 (0.73-0.82)

¹ Results are expressed as probabilities for the intercept and as Odds Ratio with associated 95% confidence intervals for all other variables. Models initially controlled for health system factors (type of health center and baseline differences in HSS catchment vs. control) but these were removed in the final reduced models for lack of statistical association

The HSS intervention, implemented since October 2014 in a third of Ifanadiana district, was associated with a significant increase in immunization rates (OR between 1.22 for measles and 1.49 for DTP), although this effect diminished over time (OR for interaction of HSS with annual change between 0.91 for DTP and 0.95 for BCG). Interestingly, the relative contribution of VWs to overall immunization rates was lower in the HSS catchment following the HSS intervention, with an OR for the interaction with VWs between 0.62 for polio and 0.77 for measles (Table 3-1). Full multivariate models that included all explanatory variables regardless of statistical significance (Table A-5) had results consistent with those described here using reduced models, although estimates of HSS impact were smaller in considering the full set of control variables.

3.3.2. Changes in population-level vaccination coverage from the longitudinal cohort

Trends in vaccination coverage and inequalities

In total, data from 2,699 children between 12 and 59 months of age were obtained from the longitudinal cohort. Of these, 651 were between 12 and 23 months old, the age at which all four immunizations studied here should be completed. Vaccination coverage for children 12-23 months was very low at baseline, ranging from about 54% to 59% depending on the vaccine. Only 34.6% of children 12-23 months were fully vaccinated in 2014. Consistent with analyses of health system data, coverage for most vaccines improved substantially during the study period, especially in the HSS catchment (Figure 3-2). In 2018, 63.6% were fully vaccinated in the HSS area, compared with only 37.5% in the rest of the district. Coverage in 2018 varied for each vaccine considered; BCG had the highest coverage (80.8% inside and 70.3% outside the HSS catchment), whereas measles had the lowest coverage (73.2% inside and 49.2% outside the HSS catchment). The minimum recommended coverage of 90% was not reached for any of the vaccines, either inside or outside the HSS catchment.

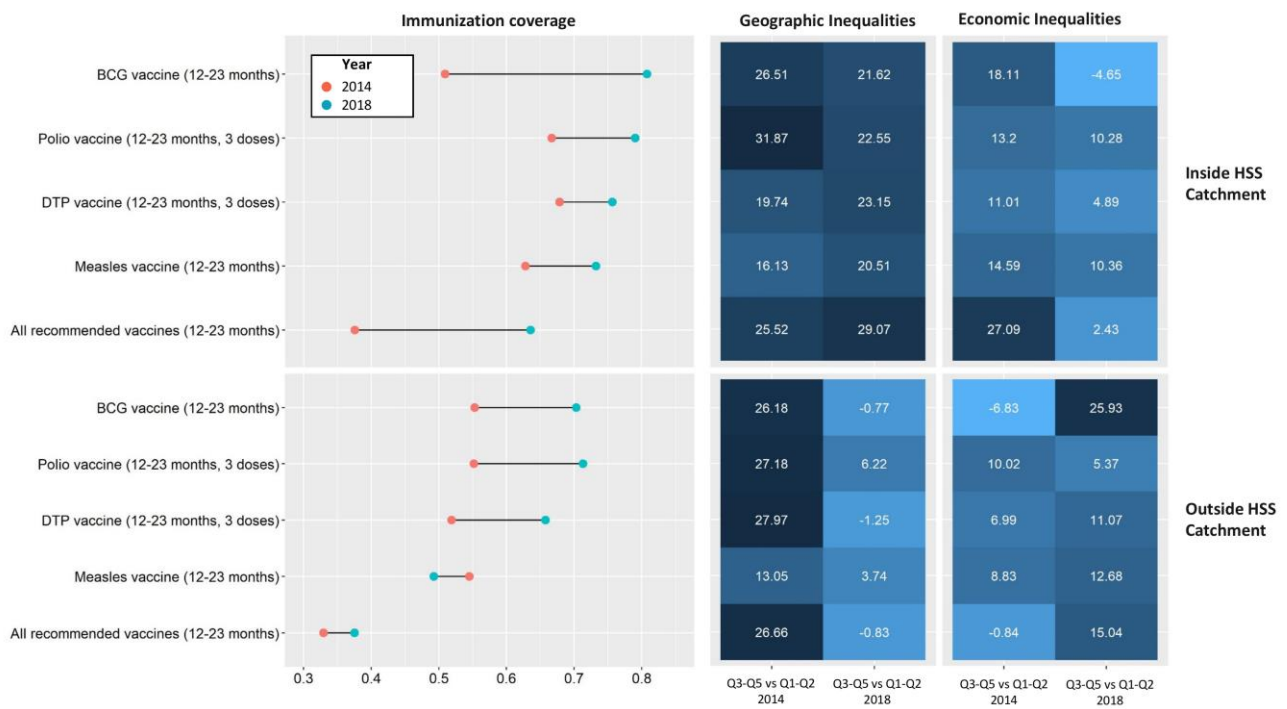


Figure 3- 2: Changes in vaccination coverage for children 12–23 months and associated inequalities in Ifanadiana district, 2014–2018.

(A) shows changes in immunisation coverage over time, split by HSS catchment and type of vaccine. (B) shows inequalities in coverage over time, according to geographical quantiles (distance to health centre, left panel) and economic quantiles (wealth score, right panel). Colour gradient shows the difference in coverage between the best-off groups (quantiles 3–5) and the worst-off groups (quantiles 1 and 2), from dark blue (greater difference, more inequalities) to light blue (smaller difference, less inequalities). Results from an equivalent analysis of inequalities but comparing Q4–Q5 vs Q1–Q2 is available in annexe figure A-2. DTP, diphtheria, tetanus and pertussis; HSS, health system strengthening.

Disparities in immunization coverage were observed according to households’ geographic distance to health centers and wealth, with different trends in the HSS catchment and in the rest of the district (Figure 3-2). In 2014, the difference in coverage between households living closer (quantiles Q3-Q5) and further (Q1-Q2) from health centers ranged from 25% to 32%, except for measles vaccine. Differences between wealthier (Q3-Q5) and poorer (Q1-Q2) households were smaller, between 5% and 15% for most vaccines. After four years, economic inequalities in vaccination coverage were substantially reduced in the HSS catchment, with little change in geographic inequalities. In contrast, in the rest of the district geographic inequalities were greatly reduced, while economic inequalities increased for all vaccines except for polio. Table A-3 shows vaccination coverage rates in each of the cohort years (2014, 2016, and 2018) and these different population groups.

Determinants of vaccination coverage trends and predictions of coverage targets

Multivariate analyses of vaccination coverage trends between 2014 and 2018 revealed consistent predictors for most of the vaccines studied (Table 3-2). Baseline differences between the HSS catchment and the rest of the district were observed for only two vaccines, BCG (OR=0.6) and DTP (OR=1.65). Coverage of each of the four vaccines was positively associated with household wealth and negatively associated with household distance to health centers. The odds of vaccination for children in remote households was between half (OR=0.52, measles) and a fifth (OR=0.22, BCG) for every additional 10 km from the nearest health center. Vaccines with three required doses were the most associated with household wealth, with an OR of 2.58 for DTP and 2.85 for polio. District-wide improvements in vaccination coverage were associated with a reduction in geographic inequalities over time and not with a homogeneous improvement for all population groups. Indeed, the OR of the interaction between annual change and distance to health center ranged from 1.17 (all vaccines) and 1.31 (BCG and polio), meaning that each year households living far from health centers had progressively better coverage, closing the gap with those living in proximity. Changes in the HSS catchment were distinct from the rest of the district. First, every year of HSS intervention was associated with an increase in the odds of vaccination in the HSS catchment between 1.18 (measles) and 1.43 (BCG), except for DTP. Unlike the rest of the district, children from wealthier households in the HSS catchment had lower odds of vaccination over time (OR of interaction ranging from 0.73 to 0.83), meaning that baseline economic inequalities were progressively reduced. However, the decrease in the odds of vaccination over time for more remote households in the HSS catchment (OR of interaction ranging from 0.72 to 0.84) effectively compensated the positive effect observed in the district as a whole, meaning that geographic inequalities were only reduced outside the HSS catchment. Full multivariate models that included all explanatory variables regardless of statistical significance (Table A-6) had results consistent with those described here using reduced models.

Table 3- 2: Determinants of vaccination coverage at the population level in Ifanadiana district, 2014-2018 (GLMM, multivariate results¹).

Variable	BCG immunization	Polio immunization (3rd dose)	DTP immunization (3rd dose)	Measles immunization	All recommended vaccines
Immunization coverage at baseline (intercept)	0.8 (0.73-0.86)	0.77 (0.71-0.83)	0.71 (0.62-0.78)	0.68 (0.61-0.75)	0.47 (0.38-0.56)
District-wide differences	-	-	-	-	-
Baseline differences in HSS catchment vs. control	0.6 (0.39-0.92)	-	1.65 (1.12-2.44)	-	-
Socio-economic class (log of wealth score)	2.18 (1.51-3.15)	2.85 (1.92-4.23)	2.58 (1.75-3.8)	2.3 (1.6-3.32)	2.68 (1.84-3.91)
Distance to health center (every 10 km)	0.22 (0.12-0.4)	0.3 (0.17-0.51)	0.31 (0.18-0.53)	0.53 (0.33-0.85)	0.35 (0.19-0.62)
Changes in the district					
Annual change	-	-	-	-	-
Annual change x Socio-economic class	-	-	-	-	-
Annual change x Distance to health center	1.31 (1.21-1.41)	1.31 (1.21-1.41)	1.23 (1.14-1.33)	-	1.17 (1.08-1.27)
Changes in the HSS catchment					
Change per year of HSS	1.43 (1.22-1.66)	1.19 (1.04-1.36)	-	1.18 (1.04-1.34)	1.22 (1.08-1.38)
Change per year of HSS x Socio-economic class	-	0.75 (0.6-0.95)	0.83 (0.67-1.03)	0.78 (0.63-0.97)	0.73 (0.59-0.9)
Change per year of HSS x Distance to health center	0.81 (0.65-1)	0.72 (0.58-0.9)	0.84 (0.73-0.96)	0.76 (0.62-0.91)	0.81 (0.66-1)

¹ Results are expressed as probabilities for the intercept and as Odds Ratio with associated 95% confidence intervals for all other variables. A sign

“-“ means that the variable was not part of the final reduced model for lack of statistical association.

In-sample predictions from these multivariate models for 2018 revealed stark differences for achieving international coverage targets depending on HSS support and population characteristics (Figure 3-3). Overall, a 90% coverage (recommended coverage at the national level) could only be achieved for BCG, and just for populations who live in close proximity to a health center with HSS support and who are among the wealthiest in the area. When the target is relaxed to 80% coverage (minimum coverage recommended for every district), there were some population subgroups for which this target could be achieved in the HSS catchment for every individual vaccine. The range of socio-economic and geographic groups for which minimum coverage rates could be reached was much larger for BCG and polio than for DTP and measles (Figure 3-3). Coverage targets for all recommended vaccines simultaneously (instead of each independently) could not be achieved for any population group. In areas outside of the HSS catchment, a 90% coverage was not achieved for any of the recommended vaccines or population subgroups. Only those in the top percentiles of wealth and proximity to a health center achieved an 80% coverage for BCG vaccination without HSS support.

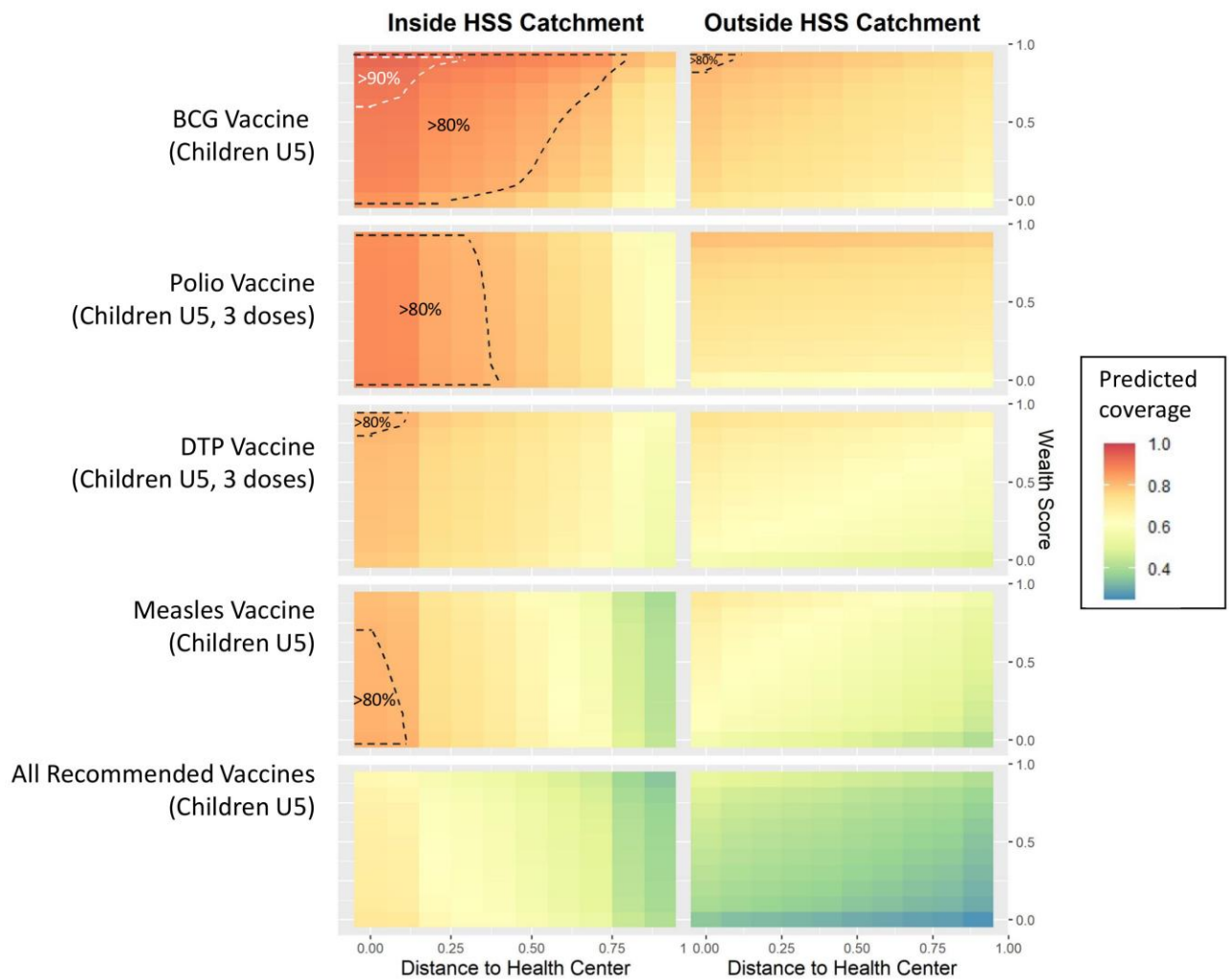


Figure 3- 3: Predictions for achieving vaccination coverage targets for different population groups in Ifanadiana district.

Graphs show in-sample predictions of vaccination coverage for the year 2018, estimated from models fitted with the cohort dataset (coefficients available in Table 3-2). For this, vaccination coverage was estimated for every combination of household distance to health centre and wealth (split into deciles) in the HSS catchment and in the rest of the district, using the fixed effects of each model. Areas with predicted coverage greater than 90% or 80% are surrounded with white dashed lines or black dashed lines, respectively.

Timeliness of vaccination

Among the 786 children aged 12-59 months who had a vaccination card at the time of the interview, timeliness of vaccination varied widely depending on HSS support and the vaccine considered (Figure 3.4). Most children were vaccinated in the first month of life for BCG, at 4-5 months for the third dose of polio and DTP, and at 9-10 months for measles (Figure 3-4.A). Vaccination occurred later than recommended in national policies (see methods section) for many children, especially those outside the HSS catchment. As a result, the proportion of children vaccinated at the recommended age was higher in the HSS catchment, ranging between 58% for BCG and 44% for polio and DTP (Figure 3-4.B). In the rest of the district, this proportion was significantly lower and ranged between 49% for BCG and 22% for polio and DTP. Timeliness of vaccination improved between 2014 and 2018 in the HSS catchment for all vaccines except for BCG, while it only improved for measles in the rest of the district (Figure A-1 in annexe).

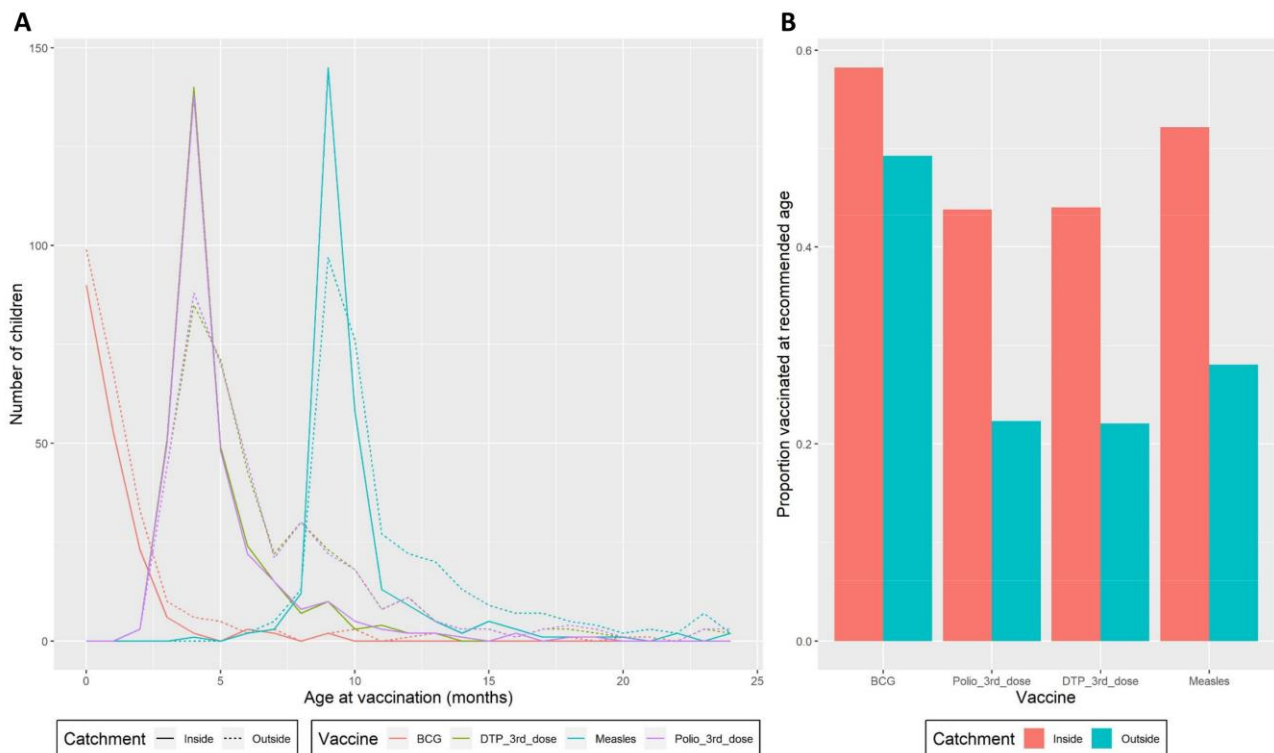


Figure 3- 4: Timeliness of vaccination among children 12–59 months in Ifanadiana district.

(A) Age of vaccine administration (in months) as reported in children’s vaccination cards inside the HSS catchment (solid lines) and in the rest of the district (dashed lines), with colours representing each type of vaccine. (B) Proportion of children vaccinated at the recommended age for BCG (1st month), third dose of polio (4th month), third dose of DTP (4th month) and measles (9th month).

(B)

3.3. Discussion

The COVID-19 pandemic has brought renewed attention to the benefits and challenges of ensuring global access to vaccines as the most effective means to reach herd immunity, halt epidemic spread, and save countless lives [199,200]. For routine childhood immunizations, delivery strategies have not substantially changed in decades: vaccines are delivered by healthcare professionals, either at health facilities or through outreach activities in the form of vaccination campaigns. Understanding how these delivery strategies can be improved in order to achieve vaccination coverage targets is essential, especially in rural areas of the developing world where delivery is significantly more challenging due to the fragility of health systems and associated health budgets. Using a comprehensive dataset on childhood immunizations at both the health system and population levels in a rural district of Madagascar, we show here how strengthening local health systems can help improve key indicators of vaccination coverage, with different impacts on routine and outreach immunizations. The HSS intervention led to an increase in RIs, resulting in higher vaccination coverage, a reduction in economic inequalities, and a higher proportion of timely vaccinations. Yet, these gains disproportionately benefited those who lived in closer proximity to health facilities. Lower contribution of outreach activities in the HSS catchment was associated with a persistence of inequalities in geographic coverage in the area, which prevented achieving international coverage targets for many population groups.

There is widespread agreement that RI should be the basis and the foundation of immunization programmes, but questions remain on how to optimize the delicate balance between providing long-term support to RI and improving short-term access via outreach activities [159] [201]. The multiplicity of barriers to accessing health facilities for populations in low-resource settings requires mass vaccination campaigns and other outreach activities to maintain or increase coverage, but these strategies can have, in turn, negative effects on the rates of RI [155,171]. For instance, RI in Madagascar decreased in the months after SIAs and VWs, resulting in seasonal gaps in immunization and delays from the recommended age of vaccination [155]. Here, we provide complementary insights: where RI improved due to ongoing HSS efforts, the contribution of outreach activities to overall vaccination coverage diminished, with mixed impacts on coverage inequalities. Timeliness of vaccination was better in the HSS catchment, with twice the proportion being vaccinated at the recommended age for polio, DTP and measles in the HSS catchment than in the rest of the district. Timely vaccination is key to ensuring that children are

fully protected against common childhood illnesses by the time when they are most at risk and can help prevent episodic outbreaks [169].

We found that the HSS intervention was associated with a 20-50% increase in the odds of monthly per capita immunizations, which resulted in a 20-40% increase in the odds of coverage per year from 2014 to 2018, and a reduction in economic inequalities over time. This effect may seem counterintuitive, as immunizations are provided free of charge at health facilities across Madagascar as part of the national EPI. However, it has been widely reported that despite childhood vaccines being free of charge, children of poorer households frequently have lower vaccination coverage than their peers [202–205], which is consistent with our findings. Seeking health care for healthy children may not always be a priority for people living under severe poverty, especially given the disproportionate impact of the loss of income associated with seeking care, indirect transportation costs, and lower reported awareness of the long-term benefits of vaccination [202–205]. This may explain why BCG vaccination coverage decreased significantly as a function of distance to the health center, as most deliveries in remote areas occur at home.

The HSS intervention included, among others, renovations to health facilities, hiring of additional health staff, community sensitization and expanded support for reproductive health, including deliveries in health facilities, antenatal and postnatal care, all of which could have improved the confidence on the health system and increased awareness, particularly among mothers of young children. In addition, the removal of user fees at health facilities, which resulted in a tripling of primary care utilization for individuals of all ages over this period and significant increases in maternal health services [197], could have had the indirect benefit of increasing health seeking for services that were already free of charge, as adults and mothers get more used to visiting health centers. An increase in perinatal health services could indeed explain why BCG vaccination coverage was consistently higher than measles coverage, since BCG is delivered right after birth as opposed to measles, which is delivered 9 months later. Health system approaches such as the one implemented in Ifanadiana are increasingly recognized as potential solutions to achieve, not only vaccination coverage targets, but also progress towards universal health coverage [206,207].

Despite HSS efforts to support vaccination delivery at the community level during VW and other outreach activities, geographic inequalities in vaccination coverage persisted or even increased for certain vaccines in the HSS catchment, probably as a consequence of the higher contribution

of facility-based immunizations to overall vaccination coverage in the area. Distance to health care facilities is a known determinant of low vaccination coverage [202,208,209], especially in countries like Madagascar, where coverage is lower than average [160]. Outreach activities during VWs and mass vaccination campaigns can be effective ways to reduce geographic inequalities [164], and these took place in both the HSS catchment and the rest of the district. The higher contribution of outreach activities to overall vaccination coverage in Ifanadiana not supported by the HSS intervention would explain why most of the gains in vaccination coverage were seen via a reduction of geographic inequalities over time (remote populations benefited more than populations living closer to health centers). However, previous modeling studies have shown that eliminating geographic inequalities alone will not achieve coverage targets across Africa, and that parallel increases in routine vaccination rates are necessary [160]. This is consistent with our results, where only certain population groups in the HSS catchment (those of higher socioeconomic level and living in proximity to health centers), but none in the rest of the district, reached international coverage targets required for herd immunity. Additional efforts are therefore necessary to sustain improvements in the district, including the geographic expansion of HSS efforts, and a particular focus on supporting outreach activities in the HSS catchment (e.g. more frequent vaccination campaigns, routine expeditions by mobile teams, etc.).

Our study had several limitations. First, we used official MoPH data on population size for children aged 12-23 months in our analysis of per capita immunizations at health centers. These are notoriously inaccurate and can lead to estimated coverage rates above 100%, which would be the case in our setting if we had used annualized rates. This is unlikely to have affected our analysis unless inaccuracies in population data were highly structured across health centers (much overestimated in some and underestimated in others). The consistency between health system and cohort results suggests that there was limited bias in the analyses of per capita immunizations. Second, less than one third of the children studied in the cohort had a vaccination card at the time of the interview, so their vaccination status (and therefore estimates of coverage) depended largely on the mother's report. Although potentially flawed due to recall bias, vaccination coverage figures used by most international organizations and national governments are based on surveys (DHS, Multiple indicator cluster survey (MICS), etc.) that use the same methods, and the proportion of children with vaccination cards was not lower here than in other settings [210]. Third, our analysis of vaccination timeliness used exclusively children with vaccination cards and we observed that this group was significantly wealthier and closer to health facilities than children without vaccination cards (Annexe Table A-4), so timeliness results may not be

generalizable to the whole district population. Fourth, although we account for baseline differences between the two areas in our models, the HSS catchment had significantly better socio-economic indicators than the rest of the district [187], which could have impacted the positive results observed in the HSS catchment over time. Finally, although the IHOPE cohort includes over 8000 individuals, the sample size for children aged 12-23 months is relatively low, which precludes the robust estimation of vaccination coverage predictors with complex statistical models. For this reason, we expanded the age range of the cohort statistical analyses to children aged 12-59 months. This could have had an impact in the interpretation of results if trends observed for children 12-59 months were greatly different from those in children 12-23 months.

In conclusion, our study shows that strengthening local health systems can help improve vaccination coverage and timeliness of immunization in rural, low resource settings, even when those interventions do not target specifically vaccine improvements themselves. By increasing the contribution of RI over other immunization strategies such as VVs or mass campaigns, the intervention helped reduce economic inequalities in vaccination coverage, but failed to reduce geographic inequalities. Overall, the target of 90% immunization coverage was not achieved for any vaccine, but many populations in the HSS intervention area achieved immunization levels above 80%. Explicit efforts are necessary in areas undergoing HSS to vaccinate children in remote areas so that immunization goals can be reached.

Discussions générales

Cette thèse vise à approfondir la compréhension des barrières à la mise en œuvre des stratégies de lutte contre les maladies infectieuses à Madagascar, en mobilisant des méthodologies propres à l'épidémiologie quantitative, telles que la modélisation statistique et mathématique. Elle se focalise sur deux stratégies de lutte majeures, à travers des cas particuliers i) des campagnes de DMM réalisées par le PEFL, dont l'objectif est d'atteindre l'élimination en 2030 [211], et ii) des stratégies de vaccination des enfants (vaccination de routine (VR) et vaccination de masse (VM)) mises en place par le programme élargi de vaccination, dont l'objectif est d'atteindre un seuil international de couverture de 90% [30]. Etant donné que Madagascar est loin d'atteindre les objectifs fixés pour ces deux programmes les résultats de cette thèse peuvent contribuer à l'amélioration de ce genre de stratégies. Le tableau suivant offre un aperçu synthétique des étapes qui ont été établies dans les deux chapitres de la thèse mettant en évidence la similitude et les différences entre les chapitres.

Tableau récapitulatif

Table 4- 1: Synthèses des deux grands chapitres de la thèse: similitude et différence

	Lutte contre la filariose lymphatique	Vaccination infantile
Objectif	Elimination en 2030	Atteindre le seuil minimal recommandé
Stratégie	DMM	VM & VR
Méthode utilisée pour identifier les barrières	Modélisation mathématique	Modélisation statistique
Etapes	Observation des données Calibration des paramètres Intégration de la migration dans le modèle Simulation et prédiction	Utilisation des données de la cohorte et des données de CSB Identification des déterminants de la couverture vaccinale Simulation et prédiction
Principaux résultats	Il y a une hétérogénéité selon l'âge et une hétérogénéité spatiale de la prévalence de la FL L'hétérogénéité selon l'âge peut être due à la différence de la compliance entre enfants et adultes	Il a des inégalités économiques et géographiques en matière de vaccination Le RSS et la campagne de vaccination ont augmenté le taux de couverture vaccinale Le RSS a réduit les inégalités économiques

	<p>La différence de la compliance entre enfants et adultes entraîne un risque de résurgence élevée L'hétérogénéité spatiale et la migration entraîne un risque de résurgence élevé</p>	<p>La campagne de vaccination a diminué les inégalités géographiques Le seuil minimal recommandé est atteint seulement dans les groupes de population habitant proche des centres de santé avec un niveau économique élevé.</p>
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4.1. **Barrières à la mise en œuvre du programme d'élimination de la filariose lymphatique**

Le programme national PEFL à Madagascar, en place depuis plus de 20 ans, n'a pu interrompre la transmission de la maladie que dans 4 districts des 98 qui sont endémiques [25]. Ce progrès hétérogène est similaire à des nombreux autres pays où la FL est endémique, comme la Mozambique et le Nigeria [212,213] où seuls 19 sur 114 et 37 sur 584 districts, respectivement, ont réussi à mettre fin à la transmission. Sur la base des résultats d'une étude réalisée en 2016 dans le Sud-Est de Madagascar [129], qui a montré une forte hétérogénéité de la prévalence de FL à la fois selon le groupe d'âge au sein d'un même district, et au niveau spatial entre les différents districts, la première partie de la thèse était consacrée à mieux comprendre d'un point de vue mécanistique quels facteurs pourraient être derrière ces tendances observées. En particulier, ces deux types d'hétérogénéités sont souvent associés à des conditions écologiques et géographiques conduisant à différentes expositions aux vecteurs [83,88,96], mais nous voulions explorer si d'autres facteurs liés à la mise en œuvre du PEFL dans cette zone pourraient également expliquer les résultats obtenus. Pour cela, dans le **Chapitre 1** nous avons fait d'abord une revue de la littérature pour mieux comprendre quels sont les modèles mathématiques utilisés dans le cadre de la FL et comment ils ont été utilisés pour guider les programmes d'élimination, afin de décider la meilleure approche pour notre étude. Ensuite, dans le **Chapitre 2** nous avons adapté un de ces modèles mathématiques, le modèle LYMFASIM, au contexte spécifique du Sud-Est de Madagascar afin de répondre à cette question.

4.1.1 **Utilisation de la modélisation mathématique pour guider les PEFL**

L'utilisation de la modélisation mathématique et statistique sur l'étude de la FL a commencé depuis des dizaines d'années et s'est développée au fil des années [47,48,50,58,80,214]. Ceci a pris encore plus d'ampleur avec l'implémentation du programme de lutte en 2000, intégrant l'évaluation de l'impact de la distribution de traitement de masse [68,77,113]. La revue de la littérature réalisée dans le **Chapitre 1** a révélé que les principaux types des modèles utilisés dans

l'étude des maladies infectieuses, notamment de la FL, comprennent les modèles statistiques et/ou les modèles spatiales, les modèles déterministes, les modèles stochastiques individu-centrés, ainsi que les approches combinant deux ou plusieurs de ces modèles. Le choix du type de modèle à utiliser pendant une étude dépend parmi tant d'autres facteurs de la question de recherche posée, des données disponibles, et de la complexité de la transmission.

Par exemple, l'utilisation des modèles statistiques en particulier spatiaux nécessitent la détention des données de qualité pour garantir la validité et la fiabilité des résultats. Cependant, ceci peut s'avérer coûteux et compliqué logistiquement à obtenir [215], surtout compte tenu de la nécessité de mener une surveillance prolongée de la FL pour certains endroits [216,217]. Les modèles mathématiques déterministes constituent une option valable pour simuler la dynamique de la transmission lorsque les données sont limitées [218]. Ce type de modèle permet d'identifier les conditions sous lesquelles la maladie est endémique et de recommander les mesures à prendre pour interrompre la transmission. Ces modèles sont plus simples à implémenter mais ils ne prennent pas en compte les variations aléatoires qui peuvent survenir dans la réalité [219,220]. Les modèles stochastiques individu-centré sont conçus pour prendre en compte ces variations aléatoires présentes dans la transmission de la maladie, ainsi que la charge parasitaire propre à chaque individu. Bien que ces modèles soient plus complexes, ils parviennent à refléter de manière plus précise la complexité inhérente au processus de transmission de la FL [221]. Dans certaines situations, l'utilisation d'une combinaison de plusieurs modèles s'avère plus efficace pour obtenir une prédiction plus précise [60,62].

4.1.2 Hétérogénéité individuelle, compliance et risque de résurgence

L'utilisation d'un modèle mathématique stochastique et individu-centré dans le **Chapitre 2** nous a permis de montrer que l'hétérogénéité observée entre différents groupes d'âge dans le Sud-Est de Madagascar peut être due à des différences dans la compliance aux traitements entre adultes et enfants. Grâce à la distribution aux enfants dans le milieu scolaire, ceux-ci peuvent être plus enclins à prendre régulièrement les médicaments antifilariens que les adultes, deux études montrent que les enfants d'âge scolaire (6-14) ans affichent le niveau de compliance le plus élevé [222,223]. Ainsi, en simulant différents niveaux de compliance aux traitements chez les adultes et les enfants, nous avons montré que les résultats observés dans le Sud-Est de Madagascar, où la prévalence était plus élevée chez les adultes, pouvait seulement être expliquée par une faible compliance aux traitements chez ce groupe d'âge plutôt que par des différences en termes

d'exposition. Cette conclusion est en accord avec ce qui a été observé dans une étude précédente [123], qui indique qu'en Egypte, la compliance à la prise du médicament est liée à la prévalence de la FL. La prévalence de la maladie dans le groupe de population ayant pris au moins deux fois le médicament est plus de 40 fois plus faible que dans l'autre groupe [123].

Dans notre contexte, une prévalence élevée chez les adultes présente une source potentielle de transmission continue de la maladie, permettant de maintenir la circulation du parasite dans la population même si la prévalence chez les enfants est en dessous du seuil de 1% recommandé par l'OMS. Ainsi, il existe des situations où les conditions de l'enquête d'évaluation de la transmission « TAS » sont remplies, étant donné que cette enquête est basée sur la prévalence chez les enfants [128], alors que la prévalence chez les adultes peut encore être élevée à cause d'une mauvaise compliance. Dans ce genre de situation, nos simulations montrent que le risque de résurgence post TAS peut être très élevé. Ce résultat va dans le même sens qu'une étude précédente [61] qui montrait à travers des simulations les limites des stratégies actuelles de surveillance et évaluation de la FL, et ensemble ces deux études remettent en question la fiabilité de la validation d'arrêt d'intervention par le TAS uniquement.

Une conclusion majeure des résultats du **Chapitre 2** pour maximiser l'efficacité des PEFL est qu'il est essentiel de garantir une compliance élevée aux traitements de la FL chez les adultes, et cela nécessite des approches plus ciblées qui prennent en compte les facteurs qui influencent la prise des médicaments. L'étude menée par Rabindra et.al en Inde a aussi mis en évidence ce besoin urgent d'améliorer la compliance en mettant en lumière les variations au sein de la population en termes de genre et de tranche d'âge [223]. Ainsi, les programmes de DMM au niveau communautaire doivent ajuster leurs stratégies de distribution pour augmenter la compliance des adultes. Pour cela, des études additionnelles pourraient permettre de comprendre les facteurs sous-jacents qui influencent la non-compliance dans chaque groupe d'âge pour élaborer des approches plus efficaces. Dans les études antérieures, les facteurs associés à la non-compliance comprennent entre autres, le système de distribution, la crainte des effets secondaires, ainsi que la manque de conscience et de connaissance aux bienfaits de DMM [110,140].

Dans le Sud-Est de Madagascar, moins de deux tiers des adultes étaient au courant de la FL, et encore moins connaissaient le DMM [129]. Cela souligne la nécessité de mener les campagnes de sensibilisation, de communication et d'éducation sur la FL, ainsi que l'importance de la prise des médicaments pour la prévenir et l'éliminer [25]. Le PEFL devrait, si leur budget et leur

capacité opérationnelle le permettent, surveiller la compliance aux traitements de manière systématique (par exemple, post-campagne DMM dans un échantillon représentatif d'adultes), et utiliser les informations sur l'évolution de la prévalence de la FL par groupe d'âge pour évaluer l'efficacité de la DMM aux adultes au niveau communautaire. Ceci peut permettre d'adapter les stratégies pour maximiser l'impact sur les groupes d'âge les plus touchés.

4.1.3 Hétérogénéité spatiale, migration et risque de résurgence

Les progrès vers l'élimination de la FL sont variables entre les pays endémiques et au sein même de chaque pays endémique [103]. A l'hétérogénéité spatiale de la prévalence de FL liée à des conditions environnementales plus ou moins favorables s'ajoute une hétérogénéité liée à la mise en œuvre programmatique: des zones au sein d'un pays peuvent commencer la DMM à des moments différents, avoir des durées de DMM différentes, et la couverture peut également être variable [212,213]. A Madagascar, cette hétérogénéité spatiale de la prévalence de la FL est toujours présente et était aussi observée dans notre site d'étude [25]. Les trois districts du Sud-Est qui ont réussi à éliminer la FL selon la dernière enquête TAS sont entourés d'autres districts avec des prévalences encore très élevés (29.5-40%) [25]. Les mouvements de population tels que les migrations pour des raisons économiques, sociales ou environnementales peuvent jouer un rôle clé dans la transmission d'une maladie. Par exemple, le mouvement des populations à Madagascar cause l'importation des cas de paludisme des zones côtières vers les hautes terres centrales [224].

Les résultats du **Chapitre 2** montrent qu'en intégrant la migration des individus entre différents districts dans la modélisation de la transmission de la FL, le risque de résurgence augmente rapidement avec la prévalence des districts voisins. Ces résultats sont en accord avec des études précédentes, qui montrent que la migration peut compliquer la surveillance et le contrôle de la FL [141,225]. Par exemple, ces études ont mis en évidence le risque encouru par les zones urbaines face aux migrations des ruraux et qu'avec l'arrivée de seulement deux personnes infectées, une source potentielle de transmission peut être observée. Comprendre comment ces facteurs interagissent peut contribuer à minimiser le risque de résurgence de la maladie due à la migration et à progresser vers l'objectif de l'élimination.

L'implication de ces résultats pour les PEFL est double. D'abord, les campagnes de DMM devraient couvrir un maximum de zones endémiques au sein d'un pays dès le départ du

programme afin de limiter le risque de résurgence dû à l'hétérogénéité spatiale et à la migration. Ce risque peut être élevé lorsque des districts où la DMM a été arrêtée sont entourés par des districts présentant toujours une forte prévalence. Ensuite, dans ce genre de contextes il est particulièrement important de continuer la surveillance post-TAS afin de détecter une possible résurgence et mettre en place des stratégies appropriées. Par exemple, même si le protocole de l'OMS recommande une deuxième évaluation TAS 2 ou 3 ans après l'arrêt de DMM [128], Madagascar n'a pas mené cette deuxième enquête à temps par manque de moyens. Malgré ces recommandations, la complexité de la lutte contre ce genre de maladie tropicale négligée dans un pays à faibles revenus comme Madagascar, où le financement du programme est très limité et se repose fortement sur des bailleurs et partenaires extérieurs (notamment l'OMS pour le PEFL), fait que les autorités nationales ont des marges de manœuvre limitées pour les appliquer.

4.2. Les barrières à l'amélioration de la couverture vaccinale à Madagascar

Dans le cadre du PEV, en place depuis presque 50 ans, tous les enfants doivent recevoir dans leur première année de vie des vaccins contre la tuberculose (BCG), contre la diphtérie, le tétanos, la coqueluche (DTCoq), contre la polio, et contre la rougeole, parmi d'autres. Or, la dernière enquête démographique et de santé menée au niveau national à Madagascar en 2021 a montré que moins de 50% des enfants de 12-23 mois ont reçu tous les vaccins recommandés, et 18% n'ont reçu aucun vaccin [226]. Ceci soulève des questions importantes sur l'efficacité de la mise en œuvre du programme et sur l'atteinte des objectifs internationaux à Madagascar. Dans le but d'évaluer différentes stratégies vaccinales, dans le Chapitre 3 nous utilisons des données d'une cohorte longitudinale en place depuis 2014 et des données collectées auprès de tous les centres de santé du district pendant 4 ans (2014 et 2018) afin de modéliser par des approches statistiques la couverture vaccinale dans le district d'Ifanadiana, dans le Sud-Est de Madagascar.

4.2.1. Inégalités économiques et inégalités géographiques

Malgré la réalisation des campagnes de vaccination régulières, la gratuité des vaccins infantiles, et des efforts de RSS en place, nos résultats ont montré que des niveaux de couverture vaccinale insuffisants sont étroitement liés à des inégalités économiques et géographiques persistantes dans la zone d'étude. La couverture vaccinale était associée positivement au niveau économique des

familles enquêtées et négativement à la distance entre la maison et le centre de santé le plus proche.

Concernant les inégalités économiques, bien que les vaccins eux-mêmes soient gratuits, il est bien connu dans la littérature que les patients peuvent subir des coûts indirects importants tels que les frais de déplacements au centre de santé, où le temps utilisé pour s'y rendre, qui entraînerait une perte de revenu [227,228]. Ceci peut représenter une barrière importante à l'accès aux soins, notamment dans des zones rurales pauvres comme le district d'Ifanadiana, où plus de trois quarts de la population vit en extrême pauvreté et pratique l'agriculture de subsistance [191]. Les familles nombreuses ou celles avec des jeunes enfants peuvent trouver difficile de coordonner la vaccination de tous leurs enfants en même temps, ce qui peut entraîner des retards et des oublis [229,230]. Certains groupes socio-économiques vulnérables peuvent être marginalisés et faire face à des stigmatisations ou discrimination dans les établissements de santé, ce qui peut les dissuader de rechercher des soins, même lorsqu'ils sont gratuits [231].

Madagascar, et notamment la côte Est du pays, est caractérisée par sa géographie diverse et souvent accidentée, ce qui rend difficile l'accès aux services à tous les niveaux d'un système de santé comme celui d'Ifanadiana, y compris pour la vaccination [72,232,233]. Par exemple, l'utilisation des soins de santé primaire diminuait de manière exponentielle par rapport à la distance des populations vers les centres de santé, et ce malgré un programme en place pour renforcer le système de santé et supprimer les paiements directs des patients lors des consultations [234]. Les ressources en matière de santé, le personnel médical qualifié et les infrastructures sont souvent inégalement réparties entre les zones urbaines et les régions rurales [235], entraînant des inégalités dans l'accès aux services de vaccination. La logistique de transport de stockage des vaccins peut être un défi, en particulier pour les régions éloignées, ce qui peut entraîner des retards dans la distribution des vaccins et des interruptions de la chaîne d'approvisionnement. L'instabilité politique et les conflits peuvent perturber les services de santé, y compris les campagnes de vaccinations dans certains endroits [236].

4.2.2. Impact du renforcement du système de santé et des campagnes de vaccination

Tandis que les programmes nationaux de vaccination centrent souvent leurs efforts sur les campagnes de vaccination de masse et les stratégies mobiles pour augmenter de manière rapide la couverture vaccinale au niveau populationnel, notre étude montre que le RSS à Ifanadiana a contribué à l'augmentation de la couverture vaccinale et à la réduction des inégalités économiques en matière de vaccination. Même si l'intervention de RSS mise en place en partenariat entre l'Organisation non gouvernemental (ONG) Pivot et le Ministère de la Santé Publique depuis 2014 ne ciblait pas spécifiquement le programme de vaccination, elle incluait, parmi d'autres, l'amélioration des infrastructures de santé, l'approvisionnement en médicaments et en équipements, et le recrutement et la formation des personnels de santé [189]. Des évaluations d'impact précédentes ont montré que cette intervention était associée à une amélioration de l'accès aux soins de santé et de la qualité des soins en général, permettant une meilleure prestation de santé [186,188]. Ceci a entraîné également un meilleur accès aux soins pour les enfants de moins de cinq ans ainsi qu'une réduction de la mortalité infantiles et néonatale [186,197]. Dans cette étude, nous avons démontré que l'intervention était associée à l'amélioration de la couverture vaccinale et le respect du calendrier vaccinal, notamment par le moyen de la vaccination de routine. Cependant, le problème des inégalités géographiques persistait malgré le RSS, et la couverture vaccinale dans les zones reculées est restée très limitée. Grace aux stratégies avancées, lors des campagnes de vaccination et des « semaines mère et enfant » effectuées deux fois par an, les inégalités géographiques étaient réduites dans la zone d'étude, mais nous avons montré que cette stratégie de vaccination ponctuelle peut favoriser le risque de non-respect du calendrier vaccinale.

La conclusion majeure du **Chapitre 3** pour les programmes élargis de vaccination est que pour atteindre les objectifs internationaux d'immunisation de la petite enfance (90% de couverture vaccinale au niveau national et au moins 80% pour tous les districts) et réduire les inégalités économiques et géographiques, il est nécessaire de combiner un RSS, pour améliorer les taux de vaccination de routine, avec des stratégies avancées ciblées pour augmenter la couverture vaccinale au niveau géographique. Ces actions peuvent inclure l'augmentation des investissements dans les infrastructures de santé et dans la formation du personnel de santé dans les régions sous-desservis, la mise en œuvre de campagnes de sensibilisation et d'éducation dans les régions rurales pour sensibiliser aux avantages de la vaccination et l'amélioration de la chaîne d'approvisionnement pour garantir la disponibilité constante des vaccins dans toutes les régions.

Pour cela, il est indispensable d'établir des mécanismes de coordination rapprochés entre le Ministère de la Santé, les organisations internationales et les ONG afin soutenir la disponibilité, l'accessibilité et la distribution des vaccins au sein des structures de santé et dans les populations vivant dans des zones difficiles d'accès.

4.3. Limites des approches développées dans cette thèse

Une limitation importante qui a influencé le choix des méthodes et l'extension du sujet initial de la thèse qui était la FL vers d'autres programmes de lutte a été l'absence de progrès dans la surveillance et le contrôle de la FL à Madagascar depuis 2016, ce qui a impliqué une insuffisance des données. En effet, lorsque cette thèse a démarré, il était prévu que le PEFL continue les campagnes de DMM et mène des nombreuses évaluations TAS ainsi que d'autres activités de surveillance dans plusieurs zones de Madagascar, dont les informations auraient pu être utilisées pour cette thèse. Néanmoins, des blocages importants dans le financement du PEFL ces dernières années, couplés avec les disruptions liées à la pandémie du COVID-19, ont fait que les seules données disponibles étaient celles d'une étude précédente, collectées entre 2004 et 2016. Ceci a empêché de développer des modèles statistiques sur des facteurs associés à la réussite (ou pas) du PEFL dans différents districts du pays, ou encore de mieux calibrer nos modèles et valider nos prédictions avec des données plus récentes.

La revue de littérature que nous avons effectuée dans le **Chapitre 1** a été tout d'abord limité aux articles publiés dans PubMed et ne présentait pas les articles anciens (avant 1973) qui constituent les premières modélisations de la FL. Nous avons alors inclus des articles cités par d'autres revues comme dans [41,42] pour compléter l'historique de la modélisation de la FL. D'autres limites à notre étude sur la FL dans le **Chapitre 2**, qui était finalement basé sur des simulations théoriques calibrées à un contexte réel, inclut l'intégration de la migration dans le modèle. En effet, le modèle LYMFASIM ne permet pas de considérer la complexité de flux migratoires et donc nous avons dû introduire des paramètres supplémentaires dans l'équation du nombre de parasites pour représenter les parasites apportés par les immigrants. Des modèles spatiaux comme ceux utilisés dans [59] pourraient être utilisés et combinés avec des modèles individu-centrés pour une investigation plus poussée, ce qui pourrait être envisagé comme une piste de développement futur. Malheureusement dans le cadre de cette thèse nous n'avons pas pu intégrer ce type de modèle en raison des contraintes de temps qui ont entravé la mise en œuvre de cette combinaison.

Pour l'étude sur la vaccination dans le **Chapitre 3**, les enfants ayant des cartes de vaccination dans l'enquête auprès des ménages représentaient seulement un tiers des enfants étudiés. Ceci aurait pu entraîner des biais car les deux tiers d'informations restantes étaient collectés grâce aux propos verbaux des parents. En outre, l'estimation du respect du calendrier vaccinal était basée uniquement sur ces cartes de vaccination, et donc le faible nombre des enfants inclus a impliqué une augmentation de l'incertitude autour de ces estimations. Enfin, les données sur le nombre total de population des enfants dans la zone d'intervention de chaque centre de santé, qui ont été obtenus auprès des centres de santé pour estimer le taux de couverture vaccinal par année, était sous-estimé et pouvait conduire à un taux de couverture annuelle au-delà de 100%. Par contre, la combinaison de deux sources de données, d'enquêtes auprès des ménages et des données du système de santé, nous a permis de limiter ces biais et d'obtenir des résultats plus fiables.

Conclusions et perspectives

La lutte contre les maladies infectieuses exige une réponse multidisciplinaire, des investissements dans la recherche et l'innovation, une coordination internationale, une éducation sanitaire, un renforcement des systèmes de santé et une vigilance constante pour faire face aux menaces déjà connues et émergentes. Les défis de la lutte contre les maladies infectieuses dans le cas de la FL et la vaccination infantile dans le Sud-Est de Madagascar incluent l'hétérogénéité (spatiale ou individuelle) de la prévalence de la maladie liée à des défis de mise en œuvre programmatique, ainsi que des inégalités socio-économiques et les géographiques dans l'accès aux soins de santé primaire.

L'objectif ultime de ces programmes est de garantir que tous les individus, quelle que soit leur région géographique, aient un accès équitable aux soins de santé et que les interventions de santé publique soient adaptées aux besoins spécifiques des populations locales pour réduire la prévalence des maladies et améliorer la santé globale. Pour surmonter ces barrières et optimiser la lutte contre la FL en conjonction avec la vaccination infantile, il est crucial de développer des stratégies intégrées, de mobiliser des ressources adéquates, de prendre en compte la coordination entre les parties prenantes et de mettre en place des campagnes de sensibilisation efficaces. Il est aussi indispensable de créer une politique visant à équilibrer la répartition des services de santé en fonction des besoins de la population, en particulier dans les zones moins desservies, ainsi que l'amélioration des infrastructures de santé, le transport et les communications pour faciliter l'accès aux soins.

L'utilisation de la modélisation statistique et mathématique a permis d'améliorer les programmes de lutte contre les maladies infectieuses. Ces modèles ont aidé à comprendre le mécanisme de transmission de la FL, y compris l'interconnectivité entre les humains, les parasites, et les vecteurs. Ils ont permis également d'évaluer l'efficacité des interventions, d'établir des systèmes de surveillance appropriés et de formuler des prédictions sur les évolutions futures post-intervention. Il est généralement recommandé de privilégier l'utilisation du modèle le plus simple qui est capable de fournir les résultats attendus. Cependant, il arrive parfois que des modèles trop simples ne puissent pas saisir toute la complexité d'une situation. Dans le contexte de notre thèse, nous avons fait le choix d'étendre un modèle déjà existant, ce qui nous a permis de mieux appréhender le risque de résurgence d'une maladie dans des endroits qui avaient déjà réussi à l'élimination d'une maladie.

Une direction de recherche prometteuse serait d'explorer des approches novatrices pour combiner des modèles spatiaux et des modèles individu-centrés afin de mieux saisir l'évolution de la charge parasitaire au niveau de l'individu, tout en prenant en compte de la variation spatiale de la prévalence de la maladie ainsi que la possibilité d'une mobilité entre différents endroits. Cette combinaison de modèles pourrait permettre de mieux comprendre la dynamique complexe de la transmission des maladies infectieuses comme la FL, en intégrant des données individuelles sur l'exposition, l'interconnectivité de différents endroits et la réponse immunitaire, avec une représentation spatiale pour cartographier la propagation de la maladie sur différents territoires. Des études de cas dans divers contextes épidémiologiques pourraient être envisagées pour évaluer l'applicabilité de cette approche et son potentiel à fournir des informations cruciales pour la planification et l'évaluation des interventions de santé publique.

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Annexes

Table A- 1 : Age-specific MDA compliance rate that corresponds to a proportion of resurgence greater than 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
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

Table A- 2: Summary of the idHSS intervention carried out by the MoPH-PIVOT partnership in Ifanadiana District in 2014-2017, based upon TIDieR guidance

1. BRIEF NAME
Integrated district-level health system strengthening (idHSS) initiative in Ifanadiana, Madagascar
2. WHY
GOAL/RATIONALE: To create a model public health district with universal access to care aiming for broad-based population health impact on mortality. Based upon the World Health Organization’s building blocks of Health System Strengthening: 1) service delivery; 2) health workforce; 3) health information systems; 4) medicines and supplies; 5) financing; 6) leadership.
WHAT
<p>3. MATERIALS (by level of care and above enumerated building blocks)</p> <p>At district hospital level</p> <p>(1) <u>Service delivery:</u> Overall infrastructure upgrades and outfitting for service delivery, bringing inpatient bed capacity from 25 to 40, upgrades to waste management system, specific renovations of the emergency and triage department, pediatric unit, inpatient ward, isolation ward, and laboratory; support to specific service delivery, including emergency care and provision of a network of 3 ambulances, including 2 new fully equipped ones with 24/7 coverage and 12 PIVOT paramedics for referrals; maternal and obstetrical care; laboratory service were upgraded to include a total of 53 tests, including microscopy and GeneXpert for tuberculosis; social support evolved to support all hospitalized and vulnerable patients; launch of intensive care unit for severe acute malnutrition with complications.</p> <p>(2) <u>Health workforce:</u> Staffing of health workers to reach MoPH norms through joint MoPH-PIVOT hires of 7 clinicians, including a trauma surgeon and an anesthesiologist, which were integrated into the MoPH staff (long term solution); staffing supplemented further with fulltime presence of 2 PIVOT doctors and 4 nurses by end of 2017; non-clinical PIVOT staff including a team of 3 social workers, support staff (janitors, guards, etc.), a laboratory technician, and a radiology technician; ongoing mentorship and frequent trainings of medical staff in key clinical areas, such as emergency medicine and postoperative care.</p> <p>(3) <u>Health information systems:</u> Creation of a hospital-based M&E team to follow progress of activities and improve quality of HMIS data; implementation of a system for baseline and follow-up facility readiness surveys.</p> <p>(4) <u>Medicines and supplies:</u> Supply chain management and reduction of stock-outs, initially through frequent donations which evolved into a reimbursement program paired with pharmacy management training; provision of medical and non-medical equipment for service delivery, including full laboratory capacity. PIVOT became the procurement manager for the hospital pharmacy as of October 2017.</p> <p>(5) <u>Financing:</u> Cost of outpatient and inpatient care fully covered for patients referred by district-wide health centers and self-referred patients who necessitated urgent inpatient care (over 76,000 patients between 2014 and end of 2017); cost of referral to and care at higher levels of care (e.g. university hospital) fully covered for services not available at district hospital.</p> <p>(6) <u>Leadership:</u> Creation of a joint MoPH-PIVOT executive committee for hospital management and transparency; creation of sub committees for specific projects such as infection control or quality of care.</p> <p>At health center level</p> <p>(1) <u>Service delivery:</u> Overall infrastructure renovations and/or extensions for service delivery at 5 target health centers, including ensuring electricity, water, waste management/sterilization capacity, proper pharmacy conditions; provision of medical and non-medical equipment, including beds, armoires, furniture; support to</p>

launching specific service delivery of Integrated Management of Childhood Illnesses (IMCI) and malnutrition protocols for every child under 5 attending the health center; ensuring timely referrals and emergency care. Launch of supervision efforts and quality of care improvement projects with a focus on IMCI and malnutrition.

(2) Health workforce: Staffing through joint MoPH-PIVOT hires to bring all 13 primary care health centers up to MoPH norms (1 doctor, 1 nurse, 1 midwife, 1 dispenser, 1 support staff at each facility); 33 PIVOT-MOH hires were integrated into the Ministry of Health staff (long term solution); at target health facilities, hiring exceeded norms and PIVOT clinicians were permanently present (~2 clinicians per health center) to implement service delivery protocols (e.g. IMCI, malnutrition); trainings for medical staff (some district-wide) such as obstetrical and neonatal care; ongoing supervision and mentorship in target centers for IMCI and malnutrition.

(3) Health information systems: Joint MoPH-PIVOT training and supervision to improve HMIS data quality (district-wide); implementation of system for baseline and follow-up of facility readiness surveys.

(4) Medicines and supplies: Supply chain management and reduction of stock-outs, initially through frequent donations which evolved into a reimbursement program paired with pharmacy management training.

(5) Financing: Essential medicines and consumables provided free of charge to all patients (more than 130,000 patients between October 2014 launch and end of 2017); more details of this program are available in Section S1 of the Appendix.

(6) Leadership: Close collaboration with district health managers for the planning and implementation of activities.

At community level

(1) Service delivery: Construction of 21 community health posts; specific service delivery in Integrated Management of Childhood Illnesses and malnutrition protocols for every child under 5, community sensitization and mass testing, urgent care, and mobile clinics with direct care provision by PIVOT clinicians every other month. In 2017 PIVOT started to support monthly supervision of CHWs at the health facilities and doubled the area of the CHW strengthening program (43 community health posts, covering 4 out of 5 communes in the idHSS catchment).

(2) Health workforce: 14 active CHW supervisors – PIVOT staff that are training, coaching and monthly supervision of ~86 community health workers by mobile teams of trained nurses by the end of 2017; community IMCI training provided for CHWs in all of the intervention area

(3) Health information systems: Joint MoPH-PIVOT training to improve HMIS data quality on community health.

(4) Medicines and supplies: Monthly provision and follow-up of MNCH medicine stocks, including malaria diagnosis and treatment, oral rehydration salts, NSAIDS, antibiotics and zinc.

(5) Financing: cost of MNCH medicine stocks fully covered; financial and non-financial incentives to CHWs and local leadership.

(6) Leadership: Community engagement and participation (e.g. community health posts are built by the community, with PIVOT support for roofing, painting, furniture and equipment).

4. PROCEDURES

All interventions were aimed at fulfilling existing Madagascar Ministry of Health protocols and standards.

5. WHO PROVIDED

At district hospital level

Ministry of Health clinicians provided the majority of service delivery. PIVOT clinicians are integrated in the hospital staff and provide direct care as any other clinician during external consultations and clinical rounds, but also carry out frequent training. Non-clinical PIVOT staff provided social support to vulnerable patients, helped manage the patient circuit to benefit from fee exemptions (registration, validation).

At health center level

Ministry of Health doctors and nurses provided the majority of service delivery. By MoPH norms each health center (CSB2) should have 1 doctor, 1 nurse, 1 midwife, 1 dispenser, and 1 support staff. Additional PIVOT clinicians (~2 per health facility) provided some direct care, especially for the implementation of malnutrition and IMCI protocols, but focused mostly on training and supervision.

At community level

Two community health workers per fokontany (a cluster of villages, lowest administrative unit) provided basic MNCH care, supervised monthly by the clinicians of their respective health center. PIVOT mobile teams of nurses provided on-site mentoring and supervision of CHWs every two months. They also provided direct care at community level during on-site supervisions for fokontany located >10 kilometers from a health center.

6. HOW (modes of delivery)

PIVOT employees worked in partnership with existing networks of MoPH clinicians and community health workers within existing public health facilities. Wherever possible, such as in the case of supply chain management, leadership and financing, the intervention deliberately avoids the creation of parallel systems of care.

7. WHERE

At district hospital level

The initial PIVOT catchment area comprised the only district hospital, located in Ifanadiana city. Most referrals to higher levels of care (tertiary) were sent to the university hospital in Fianarantsoa (2h away by car), and some to specialized facilities in Antananarivo (capital, ~1 day by car).

At health center level

Full health center activities were implemented in the health centers of the five communes closest to the hospital on the district's sole paved road (i.e. Ranomafana, Kelilalina, Ifanadiana, Tsaratanana, Antaretra); all 13 health centers in the district received trainings, staffing support to reach MoPH norms, and some access to the referral network (limited by road conditions and accessibility).

At community level

By the end of 2017, community activities had been rolled out in fokontany from four of the five communes within the PIVOT catchment area (43 out of a total of 195 total fokontany in the district).

8. WHEN AND HOW MUCH

All interventions were progressively rolled out during the study period.

The earliest intervention activities implemented (starting in April-May 2014, at the beginning of the study period) included the ambulance network, staffing of health centers and district hospital, and provision of medical equipment in four communes.

The renovation of health centers also began in April-May 2014 but the date of completion varied for each health facility.

The renovation of the emergency and triage unit and pediatric guard at the district hospital were completed by early 2016.

Removal of user fees at health centers and hospital began in October of 2014.

Implementation of IMCI and malnutrition protocols at all health centers began in October 2015.

Community-level activities began in November 2015 in two communes, with an expansion to four communes in February 2017. First expansion of the PIVOT intervention area at health facility level to include a fifth commune in October 2017.

A costing analysis of the idHSS intervention is underway and will be published separately. Preliminary estimates suggest that the annual per capita investment of the idHSS intervention (all in-country costs of the NGO/idHSS catchment population) was about \$35, which added to the investment by the MoPH and other bilateral or multilateral donors represents approximately \$65 per capita.

9. TAILORING

The idHSS intervention in Ifanadiana District was initially modelled after the experience in HSS implementation by the NGO Partners in Health in several districts of Rwanda. A distinct element of the idHSS intervention was a substantial investment in information systems, monitoring, evaluation and research as core elements of the intervention. For M&E, an interactive dashboard allows the visualisation of hundreds of indicators from health system data collected at all levels of care. Key indicators are reviewed in monthly and quarterly reviews with program managers to follow-up the progress of different activities and services (e.g. utilization, quality of care). For research, the I-HOPE cohort study allows conducting impact evaluations every two years, which provides complementary population-level information such as health system coverage, quality, or mortality. Evaluation results are presented to managers and leadership of the MoPH-PIVOT partnership as they become available, but to allow the routine use of this information by program managers, an interactive web application has been developed (main text).

As a result of the iterative learning process integrated in the idHSS intervention, program implementation has been tailored over time to respond to coverage gaps and intervention deficiencies observed in Ifanadiana during monitoring, evaluation and research activities. The most notable example of this is the increasing support to community health after an initial phase where the idHSS intervention focused most of its resources on strengthening the district hospital and several health centers. The data and analyses generated by the I-HOPE cohort study (among other sources) have contributed to this shift, highlighting geographic inequalities in coverage and leading to several programs to address them. First, PIVOT has expanded its support to the community health program, both geographically and in terms of activities implemented. In 2019-2020, PIVOT is piloting the implementation of proactive community health in order to improve access to care for children under 5 years to further reduce geographic barriers in access to care within the communities. Second, the NGO and local government are building houses near health centers for mothers to arrive several days in advance of their delivery date in order to increase geographic access to safe delivery. This is part of a broader effort to improve maternal health coverage, given lags in maternal care improvements observed in the idHSS catchment. Third, PIVOT is increasing its outreach activities, such as on-site supervision of community health workers by teams of nurses (who also provide direct care during field expeditions) and is looking into progressively expanding the scope of work and professionalization of community health workers.

10. MODIFICATIONS

N/A; The intervention is progressively being implemented, as explained in section 8 (when and how much)

HOW WELL

N/A; The aim of this study was to study the evolution of geographic access to primary care in Ifanadiana District. Full details of the impact assessment are available in the main text.

Table A- 3: Vaccination coverage in Ifanadiana for each of the recommended vaccines, result from the longitudinal study between 2014 and 2018

Variables	Statistics of the coverage vaccination (%)														
	2014					2016					2018				
	BCG	Measles	DTP	Polio	All	BCG	Measles	DTP	Polio	All	BCG	Measles	DTP	Polio	All
All	58.8	57.4	57.5	59.2	34.6	68.2	61.7	60.3	70.7	41.3	74.3	58.3	69.5	74.2	47.4
Socio-economic classes															
Poorest (Q1)	51.7	43.2	53.3	56.6	30.0	75.8	75.0	56.7	75.4	44.7	70.5	42.3	61.5	71.5	34.0
Second poorest (Q2)	53.7	57.8	51.4	49.0	28.9	66.2	55.4	53.0	60.2	37.8	71.7	51.4	60.8	67.6	36.6
Middle (Q3)	58.6	56.6	46.4	53.5	32.0	54.9	43.9	52.0	67.2	24.6	60.5	53.5	65.1	68.1	40.6
Second wealthiest (Q4)	44.2	52.1	58.9	57.7	29.0	69.4	59.8	62.3	68.2	44.8	91.1	77.1	85.3	91.3	68.7
Wealthiest (Q5)	61.9	81.1	80.3	83.1	56.2	81.2	85.9	87.9	90.2	65.0	87.0	75.5	81.2	78.3	66.3
Geographical distance to health center															
<5km	66.8	71.4	72.3	75.9	52.9	71.3	70.7	70.2	78.6	49.3	78.2	63.3	72.1	79.5	59.7
Between 5km and 10km	43.3	50.1	50.6	51.5	22.3	65.3	52.0	51.7	63.5	33.2	68.6	53.0	68.0	70.5	42.6
>10km	40.0	26.8	21.2	18.0	05.1	64.1	53.2	45.5	59.8	32.1	73.9	52.1	62.4	62.0	39.7
HSS Catchment															
Outside	55.3	54.6	51.9	55.2	37.6	64.7	54.8	53.3	66.3	35.8	70.3	49.2	65.7	71.3	37.5
Inside	50.9	62.8	67.9	66.7	32.9	73.9	73.1	71.7	78.1	50.4	80.0	73.2	75.6	79.0	63.6

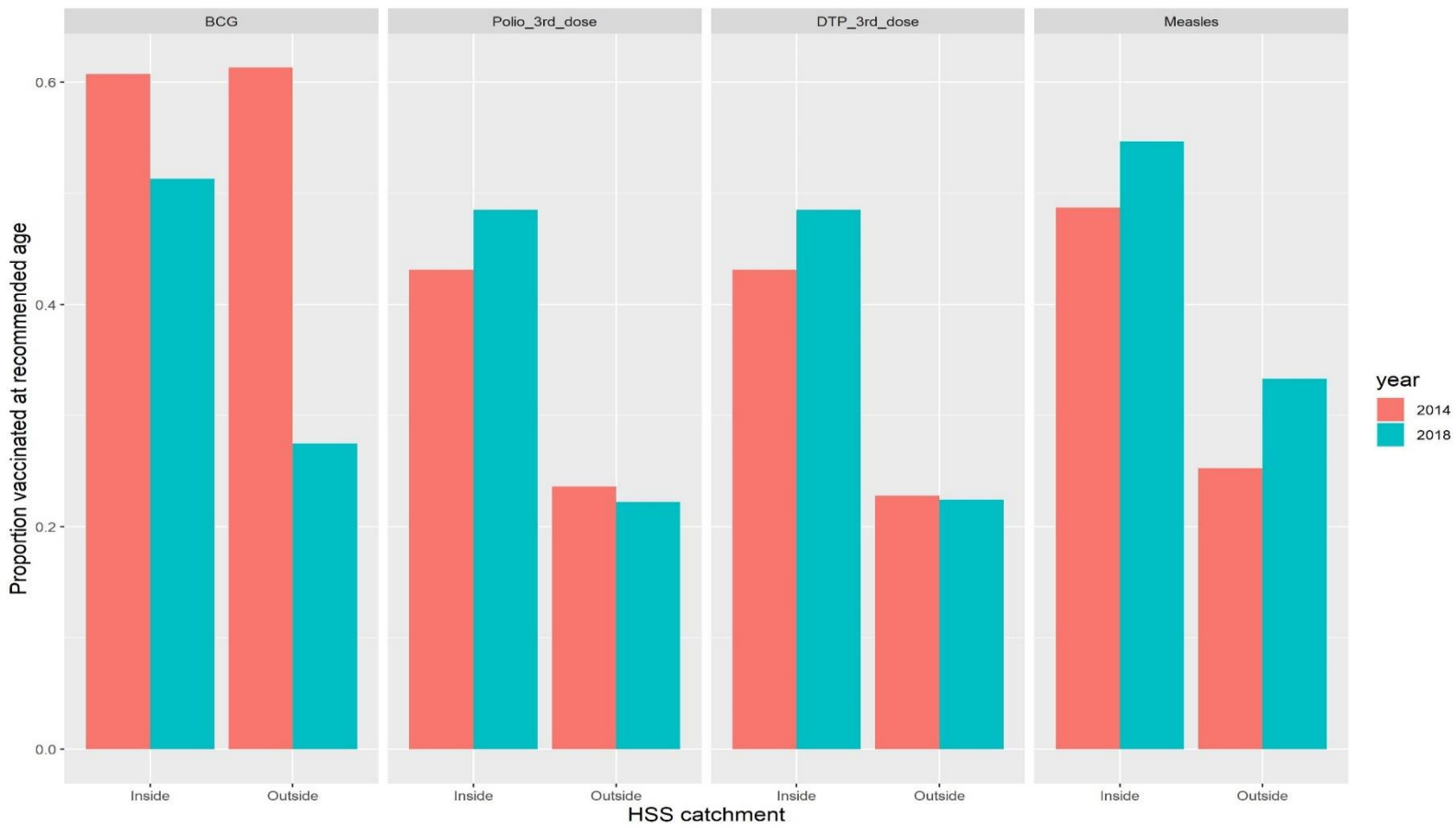


Figure A- 1: Timeliness of vaccination over time for each of the recommended vaccines in Ifanadiana, inside and outside the HSS catchment

Table A- 4: Comparison of demographic, economic and geographic characteristics in children with and without vaccination cards

¹ The test used in this analysis is the chi-squared test for independencies

Variables	With Vaccination Cards N (%)	Without Vaccination Cards N (%)	P-value¹
2014			
Gender			
Male	178 (54.44)	324 (49.48)	0.14
Female	149 (45.56)	331 (50.52)	
Wealth index			
Poorest	95 (29.19)	257 (39.28)	0.002
Middle	92 (28.10)	209 (31.96)	
Richest	140 (42.71)	189 (28.76)	
Geographical distance to health center			
<5km	194 (59.44)	254 (38.80)	<0.0001
Between 5km and 10km	113 (34.41)	308 (47.03)	
>10km	20 (06.15)	93 (14.17)	
2016			
Gender			
Male	121(54.83)	352 (47.94)	0.0631
Female	99 (45.17)	371 (52.05)	
Wealth index			
Poorest	57 (26.12)	246 (34.56)	0.0099
Middle	64 (28.91)	265 (37.16)	
Richest	99 (44.97)	202 (28.28)	
Geographical distance to health center			
<5km	128 (46.60)	332 (58.25)	0.023
Between 5km and 10km	78 (38.81)	277 (35.54)	
>10km	14 (14.59)	104 (06.21)	
2018			
Gender			
Male	101 (50.28)	296 (50.84)	0.90
Female	100 (48.72)	287 (49.16)	
Wealth index			
Poorest	45 (22.19)	216 (37.11)	0.053
Middle	56 (27.92)	184 (31.54)	
Richest	100 (49.89)	183 (31.35)	
Geographical distance to health center			
<5km	119 (59.37)	270 (46.39)	0.054
Between 5km and 10km	64 (32.01)	217 (37.24)	
>10km	18 (08.62)	96 (16.37)	

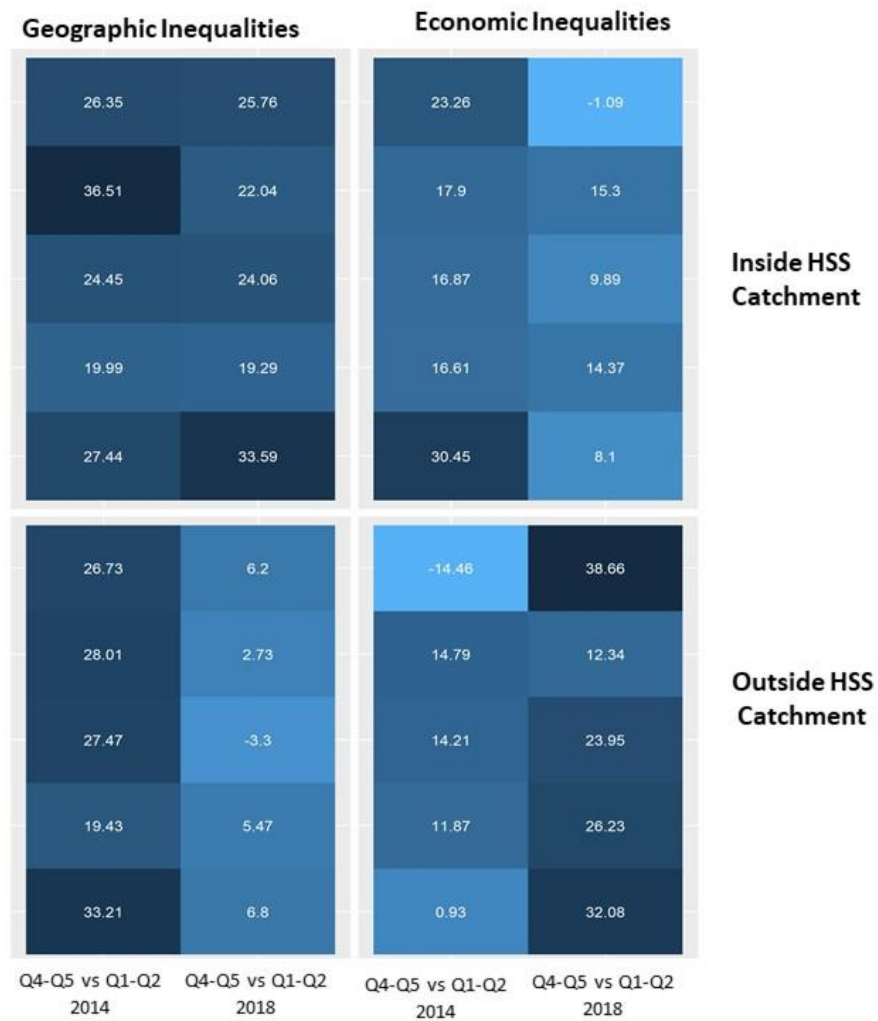


Figure A- 2: Changes in inequalities in vaccination coverage for children 12-23 months in Ifanadiana District, 2014-2018.

Complementary to Figure 3-2 in the main text, showing inequalities in coverage over time, according to geographic quantiles (distance to health center) and economic quantiles (wealth score), respectively. Instead of a comparison Q3-Q5 vs. Q1-Q2 as in Figure 3.2, this figure shows the difference in coverage between the two best-off quantiles (quantiles 4 to 5) and the two worst-off groups (quantiles 1 and 2), from dark blue (greater difference, more inequalities) to light blue (smaller difference, less inequalities).

Table A- 5: Determinants of per capita monthly immunizations at health centers in Ifanadiana district, 2014-2018 (GLMM). Full model, multivariate results including all variables (equivalent to the reduced model presented in Table 3-1).

Variable	BCG immunizations	Polio immunization (3rd dose)	DTP immunization (3rd dose)	Measles immunization
Monthly coverage at baseline (intercept)	0.04 (0.03-0.05)	0.07 (0.05-0.1)	0.06 (0.04-0.09)	0.06 (0.04-0.1)
Health system factors				
Types of health centers(CSB1 or CSB2)	0.87 (0.67-1.13)	0.98 (0.72-1.33)	1.01 (0.75-1.36)	0.88 (0.64-1.22)
Baseline differences in HSS catchment vs control	1.2 (0.89-1.62)	0.91 (0.64-1.3)	1.01 (0.72-1.41)	0.91 (0.63-1.31)
Time-varying factors				
Annual change	1.23 (1.22-1.24)	1.05 (1.04-1.06)	1.06 (1.05-1.07)	1.09 (1.08-1.1)
Seasonal changes	1.09 (1.07-1.11)	1.07 (1.05-1.09)	1.09 (1.07-1.11)	1 (0.99-1.02)
Effect of programs and policies				
Mother and child week (2 months per year)	2.08 (2.01-2.15)	2.21 (2.14-2.27)	2.14 (2.07-2.2)	2.05 (1.98-2.11)
HSS	1.37 (1.26-1.49)	1.35 (1.26-1.45)	1.5 (1.4-1.61)	1.21 (1.13-1.31)
HSS x Annual change	0.95 (0.94-0.97)	0.92 (0.91-0.94)	0.91 (0.9-0.93)	0.92 (0.91-0.94)
HSS x Mother and child weeks	0.84 (0.79-0.89)	0.61 (0.58-0.65)	0.64 (0.6-0.68)	0.82 (0.77-0.86)

Table A- 6: Determinants of vaccination coverage at the population level in Ifanadiana district, 2014-2018 (GLMM). Full model, multivariate results including all variables (equivalent to the reduced model presented in Table 3-2).

Variable	BCG immunization	Polio immunization (3rd dose)	DTP immunization (3rd dose)	Measles immunization	All recommended Vaccines
Immunization coverage at baseline (intercept)	0.79 (0.71-0.86)	0.74 (0.66-0.81)	0.7 (0.6-0.78)	0.66 (0.57-0.73)	0.52 (0.41-0.62)
District-wide differences					
Baseline differences in HSS catchment vs. control	0.61 (0.4-0.94)	1.31 (0.89-1.92)	1.6 (1.06-2.4)	1.26 (0.88-1.79)	0.72 (0.47-1.1)
Socio-economic class (log of wealth score)	2.88 (1.67-4.96)	2.83 (1.66-4.81)	2.63 (1.55-4.45)	2.23 (1.35-3.68)	3 (1.8-5.01)
Distance to health center (every 10 km)	0.25 (0.13-0.48)	0.33 (0.19-0.57)	0.33 (0.18-0.59)	0.5 (0.3-0.85)	0.33 (0.18-0.61)
Changes in the district					
Annual change	1.06 (0.94-1.2)	1.07 (0.95-1.2)	1.01 (0.9-1.13)	1.03 (0.92-1.15)	0.95 (0.85-1.06)
Annual change x Socio-economic class	0.9 (0.71-1.14)	1 (0.79-1.25)	1 (0.8-1.24)	1.01 (0.81-1.24)	0.95 (0.76-1.17)
Annual change x Distance to health center	1.17 (0.99-1.39)	1.21 (1.03-1.43)	1.22 (1.04-1.43)	1.04 (0.89-1.2)	1.22 (1.04-1.43)
Changes in the HSS catchment					
Change per year of HSS	1.36 (1.12-1.64)	1.1 (0.92-1.31)	1.05 (0.88-1.25)	1.13 (0.96-1.33)	1.31 (1.11-1.55)
Change per year of HSS x Socio-economic class	0.84 (0.64-1.09)	1 (0.79-1.25)	0.76 (0.58-1)	0.82 (0.63-1.06)	0.75 (0.59-0.96)
Change per year of HSS x Distance to health center	0.91 (0.68-1.22)	1.21 (1.03-1.43)	0.78 (0.61-0.99)	0.79 (0.62-1.01)	0.78 (0.61-0.99)

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Publications

1. Rajaonarifara E, Bonds MH, Miller AC, et al. Impact of health system strengthening on delivery strategies to improve child immunisation coverage and inequalities in rural Madagascar. *BMJ Glob Heal.* 2022;7(1):1–13.
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Résumé:

Résumé pour le public

Les maladies infectieuses continuent à faire des ravages dans les pays à faibles revenus. Des disparités liées à l'accès aux soins (financier, géographique, etc.), la fragilité des systèmes de santé de ces pays, et des défis persistants dans le financement de la santé, parmi d'autres facteurs, constituent des barrières considérables à la lutte contre ces maladies infectieuses. Cette thèse se concentre sur les barrières à la mise en œuvre de deux stratégies majeures de lutte contre les maladies infectieuses à Madagascar: les campagnes de distribution médicamenteuse de masse, à travers l'exemple du PEFL, et la vaccination, à travers l'exemple du programme élargi de vaccination. Dans une première partie, on présente une revue de la littérature sur les modèles mathématiques existants sur la filariose lymphatique, ainsi que leur application pour guider les programmes d'élimination. Dans une deuxième partie, on utilise un modèle mathématique pour montrer comment l'hétérogénéité sur la mise en œuvre du programme d'élimination de la filariose lymphatique dans le Sud-Est de Madagascar peut augmenter le risque de réémergence. Enfin dans la troisième partie, on étudie l'impact du renforcement de système de santé dans un district du Sud-Est de Madagascar sur l'efficacité des stratégies de vaccination et l'amélioration de la couverture vaccinale. On terminera avec une discussion générale sur comment les méthodes utilisées et les résultats obtenus contribuent à la littérature sur les défis de mise en œuvre des programmes de lutte.

Mots clés: Filariose lymphatique, modélisation, vaccination, maladies infectieuses, Madagascar

Barriers to the control of infectious diseases in low-income countries: a focus on lymphatic filariasis and childhood vaccination in southeastern of Madagascar

Abstract:

Infectious diseases continue to devastate in low-income countries. Disparities in access to healthcare (financial, geographical, etc.), the fragility of healthcare systems in these countries, and persistent challenges in healthcare financing, among other factors, constitute considerable barriers to the fight against these infectious diseases. This thesis focuses on the barriers to the implementation of two major infectious disease control strategies in Madagascar: mass drug administration, through the example of the lymphatic filariasis elimination program, and immunization, through the example of the expanded program on immunization. In the first part, a literature review is presented on existing mathematical models of lymphatic filariasis, and their application to guide elimination programs. In the second part, a mathematical model is used to show how heterogeneity in the implementation of the LF elimination program in southeastern Madagascar can increase the risk of re-emergence. Finally, the third section examines the impact of health system strengthening in a district of southeastern Madagascar on the effectiveness of vaccination strategies and the improvement in vaccination coverage. We conclude with a general discussion of how the methods used and the results obtained contribute to the literature on the challenges of implementing control programs.

Keywords: Lymphatic filariasis, modeling, childhood vaccination, Madagascar, infectious disease