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Modeling the spatial and temporal heterogeneity in malaria transmission and control in urban Ghana

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ABSTRACT

In West Africa malaria is an endemic disease and a leading cause of mortality and morbidity. Over the years advances in mathematical modeling have improved understanding of the disease's operational mechanisms. However, the heterogeneity in malaria epidemics as well as the impact of human behavior toward the adoption of protective measures, such as the use of the insecticide-treated bed nets (ITNs), have not yet been sufficiently documented using a mechanistic modeling approach.

In this study, i) the spatial and temporal heterogeneity in the transmission of malaria at a fine-scale was characterized while identifying the prevailing conditions of association between malaria transmission and urbanization; ii) the main drivers of heterogeneity in the transmission and control of malaria in urban areas were identified by revealing the interplay between the drivers; iii) the efficiency of the insecticide-treated bed-net rolled out in Accra was modeled by accounting for the spatial heterogeneity of the uptake behavior of communities.

The characterization of the epidemic in urban settings was done using statistical modeling approaches. A participatory system thinking approach was used, combined with network analysis to assess the key covariates that contribute to the persistence of malaria in urban settings. A mathematical framework that incorporated the empirical findings was developed to show the impact of human behavior on the persistence of malaria.

Malaria incidence proved to be highly heterogeneous over spaces, seasons, and age. Beyond, the association between malaria and urbanization is not always linear and in urban settings, malaria can be higher than in rural areas. Additional sources of heterogeneity in urban malaria epidemics are vegetation cover and population density. The denser both the population and the vegetation are, the higher is malaria incidence. Moreover, malaria transmission in big cities such as Accra and Kumasi follows a diffusion process, with the center of the cities having the highest incidences.

On the other hand, 45 interactive drivers of the transmission and persistence of malaria in urban settings were recorded. Among this set of determinants, human

behavior, revealed by the network analysis, turned out to be a major contributing factor that hinders the control of malaria in urban settings. No evidence of a relationship between uptake and ownership of ITN in the communities surveyed in Accra was found. Several reasons explain the reluctance of ITN adoption such as the decay of the nets. The model demonstrated that the infectiousness of malaria is underestimated when space and human behavior heterogeneities are not accounted for.

Therefore particular emphasis should be given to the education of communities. This will foster the uptake of the ongoing non-pharmaceutical measure and allow reducing the malaria burden in cities.

MODELLIERUNG DER RÄUMLICHEN UND ZEITLICHEN HETEROGENITÄT DER MALARIAÜBERTRAGUNG UND -KONTROLLE IM URBANEN GHANA

KURZFASSUNG

Malaria ist eine endemische Krankheit in Westafrika und dort eine Hauptursache für Mortalität und Morbidität. Im Laufe der Jahre haben Fortschritte in der mathematischen Modellierung das Verständnis von funktionellen Mechanismen dieser Krankheit verbessert. Die Heterogenität bei Malaria-Epidemien sowie der Einfluss des menschlichen Verhaltens auf die Akzeptanz und Annahme von Schutzmaßnahmen, wie zum Beispiel dem Einsatz von mit Insektiziden behandelten Moskitonetzen, wurden jedoch bisher nicht ausreichend mittels eines mechanistischen Modellierungsansatzes dokumentiert.

In der vorgelegten Arbeit wurden i) die räumliche und zeitliche Heterogenität bei der Übertragung von Malaria auf einem feinen Maßstab charakterisiert und gleichzeitig die vorherrschenden Bedingungen der Assoziation zwischen Malariaübertragung und Urbanisierung identifiziert; ii) die Haupttreiber der Heterogenität bei der Übertragung und Kontrolle von Malaria in städtischen Gebieten erkannt, indem das Zusammenspiel zwischen den Treibern aufgezeigt wurde; iii) die Effizienz der mit Insektiziden behandelten Moskitonetze in Accra unter Berücksichtigung der räumlichen Heterogenität des Aufnahmeverhaltens der Gemeinden modelliert.

Die Charakterisierung der Epidemie in städtischen Umgebungen erfolgte mit statistischen Modellierungsansätzen. Ein partizipativer System-Ansatz wurde mit einer Netzwerkanalyse kombiniert, um die wichtigsten Kovarianten zu bewerten, die zur Persistenz von Malaria in städtischen Umgebungen beitragen. Des Weiteren wurde ein mathematischer Rahmen unter Einbezug der empirischen Ergebnissen entwickelt, um den Einfluss menschlichen Verhaltens auf die Persistenz von Malaria aufzuzeigen.

Die Malaria-Inzidenz zeigte eine hohe Heterogenität in Bezug auf Raum, Jahreszeit und Alter der betroffenen Personen. Darüber hinaus stellte sich heraus, dass der Zusammenhang zwischen Malaria und Urbanisierung nicht immer linear ist und Malaria in städtischen Umgebungen höher sein kann als in ländlichen Gebieten. Weitere Ursachen der Heterogenität bei urbanen Malaria-Epidemien sind Vegetationsbedeckung und Bevölkerungsdichte. Je dichter die Bevölkerung und die

Vegetation, desto höher ist die Malaria-Inzidenz. Die Malariaübertragung in Großstädten wie Accra und Kumasi folgt einem Diffusionsprozess, wobei die inneren Bereiche der Städte die höchsten Inzidenzen aufweisen.

Insgesamt konnten 45 interaktive Treiber für die Übertragung und Persistenz von Malaria in städtischen Gebieten aufgezeigt werden. Menschliches Verhalten war im Zuge der Netzwerkanalyse ein wichtiger Faktor, der die Malariabekämpfung in städtischen Umgebungen erschwert.

Im Rahmen der Befragungen von unterschiedlichen Gemeinden in Accra ergaben sich keine Hinweise auf einen Zusammenhang zwischen der Akzeptanz und dem Besitz von Bettnetzen. Mehrere Gründe erklären die Zurückhaltung bei der Einführung dieser, wie zum Beispiel der oftmals schnelle Verschleiß der Netze. Das mathematische Modell zeigte, dass die Infektiosität von Malaria unterschätzt wird, wenn Heterogenität bezüglich Raum und menschlichen Verhaltens nicht berücksichtigt wird.

Die Ergebnisse dieser Studie unterstreicht die Bedeutung von zielgerichteter Aufklärung von betroffenen Gemeinden. Nur so kann eine verbesserte Akzeptanz von nicht-pharmazeutischen Maßnahmen zur Malariaprävention erreicht werden, was eine Verringerung der Malariabelastung in den Städten ermöglichen würde.

DEDICATION

To my family

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LIST OF ACRONYMS AND ABBREVIATIONS

ACT	Artemisinin-based combination therapies
BIC	Bayesian information criterion
CLD	Causal loop diagram
DDT	Dichlorodiphenyltrichloroethane
GHSL	Global human settlement layer
GMAP	Global malaria action plan
GMEP	Global malaria eradication program
GOG	Government of Ghana
GPM	Global precipitation measurement
IBMs	Individual-based models
ICC	Intra-class correlation coefficient
IRS	Indoor residuals spray
ITNS	Insecticide-treated bed nets
LISA	Local indicators of spatial association
LOESS	Locally estimated scatterplot smoothing
NA	Network analysis
NDVI	Normalized vegetation difference index
OBE	Out-of-box error
PCA	Principal component analysis
R_0	Basic reproductive number
RF	Random forest regression model
SIR	Susceptible infectious removed
SSA	Sub-Saharan Africa
STL	Seasonal-trend decomposition
WHO	World health organization

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1. GENERAL INTRODUCTION

1.1. Malaria transmission and socio-economic heterogeneity

Malaria is a communicable disease that kills daily 2,000 children worldwide, with 90% of the victims located in sub-Saharan Africa (SSA) (Sachs and Malaney 2002; Ndugwa et al. 2008; CDC 2017). Due to its endemism in West Africa, malaria represents a major economic constraint for the region (Sachs and Malaney 2002; Asare and Amekudzi 2017). For instance, Ghana invested more than US$ 37.8 million into preventive measures against malaria infection in children below 5 years old in 2009 (Sicuri et al. 2013). At the household level, the incurred expenses to treat a single malaria episode in Ghana can reach 34% of the yearly income of a poor household (Akazili et al. 2008). A similar trend was described in Nigeria where the monthly out-of-pocket expenditure for malaria treatments was 8.5% and 5.5% for low and high-income households, respectively (Onwujekwe et al. 2009). Recent studies showed that the relationship between national economic growth and malaria control expenditure is negative and characterized by a vicious reinforcing feedback loop, i.e., infected people are unable to produce wealth, and if wealth is low, the risk of exposure to the disease increases (Sachs and Malaney 2002; Jowett and Miller 2005). Consequently, malaria can be considered both as a cause and consequence of poverty (Wells et al. 2009).

Furthermore, malaria infection patterns change due to interventions such as the use of insecticide-treated bed-nets (ITNs), and in-door residual (insecticide) spraying (IRS). The heterogeneity in the use of ITNs and IRS due to the variability in their uptake leads to spatio-temporal heterogeneity in malaria transmission that is lower in cities compared to peri-urban and rural areas (Robert et al. 2003; Hay et al. 2005b; Tatem et al. 2013).

1.2. Mechanism of malaria transmission

Malaria infectious protozoans (of the genus *Plasmodium*) are injected into the human bloodstream (host) after an effective biting of a female mosquito vector that occurs when an infectious mosquito successfully injects the parasites into its host. During the egg-laying period, the female mosquitoes lack protein and or plant sucrose necessary for egg maturation and consequently blood-feed on vertebrate hosts that can subsequently become infected by the pathogens transmitted by the mosquitoes during this process (Harrington et al. 2001; Arifin et al. 2014).

Mosquitoes often found in West Africa belong to the genus *Anopheles* (Li et al. 2005), and here in particular to *An. gambiae* Giles. This species is anthropophilic, i.e., it prefers using human blood to complete its gonotrophic cycle, bites preferably indoor (endophagic), and rests inside the rooms (endophilic). Considering its feeding habit, *An. gambiae* is the major malaria vector in West Africa (Sinka et al. 2010). However, other vectors such as *An. arabiensis*, *An. funestus* and *An. melas* can also transmit *Plasmodium falciparum*, the causal agent of tropical malaria. Like *An. gambiae*, *An. funestus* is also anthropohilic, endophagic, and endophillic (Sinka et al. 2010; Asare and Amekudzi 2017). Conversely, *An. arabiensis* is zoophilic (i.e., prefers to blood feed on animals), exophilic (i.e., bites outdoor), and exophagic (i.e., rests outdoor) (Li et al. 2005). *Anopheles melas* is also anthropophagic, exophagic, and exophilic (Tuno et al. 2010). Thus, *P. falciparum* is highly adaptive to *Anopheles* species, thereby increasing the hosts' vulnerability to malaria. This large variability in the vectors' living environment and feeding habits expands the geographical heterogeneity in the transmission (Childs et al. 2015).

The life cycle of the *Anopheles* spp. is divided into the aquatic/juvenile phases (eggs, larva, and pupa), followed by the adult phases (immature adult, mate-seeking, blood meal seeking, blood meal digesting, and gravid) (Arifin et al. 2014). The length of the life cycle of the vector depends on climatic conditions, namely temperature and humidity (Mordecai et al. 2013; Eikenberry and Gumel 2018). Hence, the vector density, longevity, biting habits, and efficiency, as well as the intensity of malaria transmission, decrease under unfavorable conditions (White et al. 2014; Chaturvedi et al. 2014; Adu-Prah and Kofi Tetteh 2015). Nonetheless, vectors' feeding habits and effectivity can change over time as shown for instance in a long term (1999-2010) in Kenya (Mwangangi et al. 2013). To sum up, the interplay between mosquitoes and their environment depicts a complex and extremely dynamic system, which can negatively affect the control of malaria.

There are some heterogeneities in mosquito biting, which implies that the transmission intensity can significantly vary across host populations (Busula et al. 2017). The composition of the human body microflora and the reaction to the bite of mosquitoes elicit differences in the behavior of mosquitoes (Verhulst et al. 2011). For instance, an infected host is more attractive to the mosquitoes than a non-infected one (Lacroix et al. 2005). Similarly, as the sweat composition changes during and after the puberty of a human host, mosquitoes prefer the scent of children to that of adults (Schneider et al. 2004; Busula et al. 2017).

In SSA, infectious protozoans are*, P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi,* with *P. falciparum* accounting for 95% of malaria cases (Kafy et al. 2017; Karnad et al. 2018). The complete life cycle of *P. falciparum* is divided into an incubation period of 10 days within the vector and from 7 to 20 days within the vertebrate host (Institute of Medicine (US) Committee for the Study on Malaria Prevention and Control 1991; White et al. 2014). During the blood-feeding of the vector, *P. falciparum* protozoans are injected through the vector's saliva into the host bloodstream, where the protozoans complete the last part of their life cycle. Once in the host bloodstream, the sporozoites (i.e., the asexual protozoans) move into the host liver, where they penetrate the host's liver cells (hepatocytes). Within the host's hepatocytes the parasite proceeds to multiple asexual divisions, a process termed schizogony (Yam and Preiser 2017; Karnad et al. 2018). Eventually, the hepatocytes break releasing merozoites (protozoan in the feeding stage produced by multiple fission capable to initiate a sexual or asexual cycle of development) in the host bloodstream, which subsequently invade red blood cells. After multiple divisions in the red blood cells, the parasites start their sexual differentiation and develop into gametocytes (Talman et al. 2010). Before and during this differentiation stage, hosts can express clinical symptoms such as fever, chill, and sweat; therefore this period is often referred to as the symptomatic phase of malaria. Nonetheless, some hosts may express no clinical symptoms during the differentiation stage and thus this phenomenon is termed asymptomatic malaria (Bousema et al. 2014). When blood-feeding on infected patients who may or may not express symptoms mosquitoes mainly ingest these gametocytes (Talman et al. 2010).

Hence the human reservoir of parasites includes both symptomatic and asymptomatic cases. The identification of asymptomatic cases is difficult since it requires systematic testing of a large fraction of the population and is consequently financially demanding (Sturrock et al. 2013). This adds another layer of complexity to the overall management strategy, hampers malaria control, and eases its persistence.

The life cycle of *P. falciparum* can speed up or slow down depending on the host's exposure to mosquito bites, e.g., night-time activities of the human host, seasons of the year. A set of within-host factors, such as the genetic make-up (e.g., sickle cell, thalassemia), immunity, and age can also impact the life cycle in ways that are not yet fully understood (Miller et al. 2002; Casuccio et al. 2014; Tubman and Makani 2017). Besides, the migration pattern of both the hosts and vectors, the housing conditions, abundance of breeding sites, and the host culture, norms, beliefs, and overall behavior further play a role in both the transmission pattern of the disease and in the proliferation of mosquitoes (Fobil et al. 2012; Agusto et al. 2015; Diallo et al. 2017; Sumankuuro et al. 2017; Yam and Preiser 2017; Cohen et al. 2017; Sriwichai et al. 2017; Maity et al. 2017). The biology of malaria encompasses several layers of complexity going from the environmental factors to the within-host factors that make the mechanism of transmission intricately complex and multifactorial.

1.3. Complexity of the prevention and cure of malaria

Since malaria transmission requires the recursive interaction between humans, mosquitoes, and parasites, the existing control methods are suboptimal as they target either mosquitoes or parasites. The control of mosquitoes can be done either through the interventions at the larval or adult stages and in general, they intend to diminish the entomological inoculation rate, i.e., the number of infectious bites per person per year, through physical, biological, or chemical alterations of the vector living and reproduction conditions. The physical modification comprises the management of the living environment of the larvae through the removal of breeding sites, often using drainage and weeding (Tusting et al. 2013). However, this approach requires a constant working force for weeding and drain cleaning which led SSA governments to abandon it despite its proven effectiveness (Fillinger and Lindsay 2011; Tusting et al. 2013). The chemical interventions in the larval environment imply the application of larvicides and insecticides. This method is also costly and often leads to the development of insecticide resistance in mosquitoes populations (Liu 2015). Biological and microbiological control methods use the natural enemies of mosquito larval such as larvivorous fish and mosquito pathogens like the bacteria *Bacillus thuringiensis* ssp. Israliensis (Bti), respectively, but is hindered by the short time persistence of natural enemies in the environment (Tusting et al. 2013).

Control of adult mosquitoes primarily relies on the use of IRS and ITNs. These two vector-control strategies have been adopted by the Global Malaria Action Plan (GMAP) of the World Health Organization (WHO) since 2010 (Wayback and WHO 2010). Synthetic pyrethroids (especially deltamethrin and permethrin) are the main chemical compounds in ITNs and IRS, that are lethal, repel mosquitoes, highly persistent in the environment, but also not toxic for mammals (Narendra et al. 2008). In the past, the use of insecticides led to a sharp decrease in mosquito densities and consequently to a considerable decrease in the malaria transmission rate. For example, in Ghana because of the successful control of mosquitoes, there was a decline in malaria cases by 41% from 2005 to 2010 (Aregawi et al. 2017). Since the same synthetic pyrethroids are also used in agriculture there is an increased incidence of insecticide resistance in *An gambiae* populations (Kudom et al. 2018). In addition, because of the widespread use of ITNs and IRS malaria-transmitting mosquitoes species, especially populations on *An. gambiae,* have developed different coping mechanisms like earlier biting, and outdoor bitting behavior (Mwangangi et al. 2013; Moshi et al. 2017).

The main approaches to target the parasite within the human host are the use of different antimalarial drugs, seasonal prevention, and in the future possibly also the use of malaria vaccines. In terms of drugs, GMAP is presently advocating the use of Artemisin-based Combination Therapies (ACT) as the first-line curative measure. ACTs are highly potent against *P. falciparum* with the highest clearance rate of the parasite compared to other curative therapies (Eastman and Fidock 2009). Yet recently, *P. falciparum* has started developing resistance to ACT (Dondorp et al. 2009; Tusting et al. 2013; White et al. 2014). Malaria parasite resistance in SSA is exacerbated by the use of falsified ACTs drugs (Yasuoka et al. 2014; Kaur et al. 2017). Another preventive measure is intermittent prevention, which is the administration of a single curative dose of an anti-malaria drug to pregnant women regardless of their malarial serological status (Briand et al. 2007). This includes the combinations of primaquine, sulfadoxine-pyrimethamine, and amodiaquine, or methylene blue, and dihydroartemisinin-piperaquine which have been proven be able to prevent the transmission of *P. falciparum* (Dicko et al. 2018). In terms of vaccines, a seasonal vaccine denoted “RTS, S/AS01” was effective in protecting children under five years old for a short time and was capable of reducing the malaria incidence rate by 82% (Otieno et al. 2016; Greenwood et al. 2017).

Besides, there are prospects to prevent and treat malaria using homeopathy and phytotherapy. For example, a study on phyto-compounds identified more than 20 local plants and herbs in Central Africa that can heal and prevent malaria transmission (Vlietinck et al. 2015) with almost zero risks for *P. falciparum* to develop resistance against these natural compounds (Vlietinck et al. 2015; Tarkang et al. 2016; Cheuka et al. 2016). This is due to the synergistic interplay between a wide range of phyto-compounds with a considerably reduced risk of resistance development of the pathogens (Ginsburg and Deharo 2011; Tarkang et al. 2016).

Development of resistance results either from increased detoxification or decreased sensitivity or a complex combination of the two mechanisms (Liu 2015). Resistance against insecticides and drugs by the mosquitoes and *P. falciparum*, respectively, hinder the control of malaria in SSA. It leads to the genetic changes of both the transmitting mosquitoes and the parasite *P. falciparum* that can be difficult to track.

1.4. Mathematical modeling of malaria transmission

Mathematical modeling of malaria transmission started in 1911 with the Susceptible Infectious Removed (SIR) model, which compartmentalized the population of hosts and vectors into three (Ross 1911a, b). The compartments were denoted susceptible (S), referring to the population likely to become infected, infectious (I), composed by the infected fraction of the population, and removed/ recovered (R), accounting for the fraction of the population that either died or recovered from the disease. The SIR model assumed a finite and closed population, a homogenous biting rate by the mosquito-vectors, and a well-mixed population (Martcheva 2015). Although the Ross model failed to adjust with new incidence data due to its limited predictability, the SIR model provides insights into the intricate relationship between the number of infected hosts and the density of mosquitoes. Because Ross' model was theoretical and simulation-based it failed to document proof for campaigns of mosquito's eradication.

Subsequently, George Macdonald complemented Ross' (1911a) by feeding the model with real data and embedding an additional compartment for the latency period between the bite of mosquitoes and the onset of symptoms denoted Exposed (E). Furthermore, Macdonald's research theorized on superinfection (Macdonald 1950) providing arguments to support a massive campaign of the eradication of mosquitoes. Consequently, the WHO through the Global Malaria Eradication Program (GMEP) implemented widespread and rigorous mosquito eradication campaigns from 1955 to 1969. In these campaigns, the pesticide Dichlorodiphenyltrichloroethane (DDT) was successfully applied to control malaria in major European and Latin American countries (Nájera et al. 2011). However, GMEP failed to eradicate malaria worldwide due to the increasing resistance of mosquitoes to DDT (WHO 1969). In SSA, aside from the insecticide resistance of mosquitoes, the absence of basic healthcare services, the high intensity of malaria transmission, and other socio-ecological factors weakened the success of the eradication campaigns (Smith et al. 2017).

Since then, the mathematical epidemiology of malaria has evolved steadily from "toy models" (i.e., those that are not realistic but capture only the key features of the disease) to "high-level models" (which are more realistic, precise, and sacrificing generality) (May 1973). Complex models display a common feature such as having interplaying between a large number of components and their resilience (Colizza et al. 2007).

An important metric that summarizes the transmission of a disease is the reproductive number (R_0) which represents the expected number of infected hosts after effective mosquito bites in a fully susceptible population (Macdonald 1950; Aikins and Pickering 1994; Smith et al. 2005, 2009). R_0 provides, thus, a measurement for the intensity of transmission and contributes to the definition of disease-endemic areas when surpasses one (R_0>1) (Smith et al. 2007b). Henceforth, heterogeneity was incorporated in populations for the computation of R_0. These include, for example, the age structure of the hosts (Heesterbeek et al. 2015), migration of the vectors and hosts (Cohen et al. 2017), host beliefs and practices (Agusto et al. 2015), and host income classes (Ross 1902; Mushayabasa et al. 2012; Agusto et al. 2015; Cohen et al. 2017). R_0 also varies with the degree of complexity introduced into the compartmentalization of the population (Agusto et al. 2015). The more the modeling framework embodies the heterogeneity in the host populations, the closer to real-life transmission dynamics the value obtained for R_0 becomes (Smith et al. 2007a; Xia et al. 2017). Although pioneering models helped to provide insight into the dynamics of malaria and the means for its controls, they are not realistic for different reasons, and the maximum control is hardly reached (Smith ehht al. 2017). Most specifically, a large R_0 indicates a higher density of mosquitoes that reduces the effectiveness of ITNs in a large and likely heterogeneous host population (Smith et al. 2007a).

Upon those advances, a wide range of mathematical models was developed combining the compartments S, E, I, and R (e.g., SIR, SIS, SI, SIRS, SEIR, SEIRS, SEI) and including the heterogeneity of the populations (i.e., meta-population modeling approaches) s(Hethcote 1994). Nonetheless, these models are hardly capable to capture sub-population dynamics of malaria as most models assume large and homogenous populations, and where the existence and particularities of sub-populations tend to be neglected (Mandal et al. 2011; Mecoli et al. 2013). Furthermore, they often omit host behavior that confounds the dynamics of the disease (Agusto et al. 2013) as well as its control (Agusto et al. 2013; Ngonghala et al. 2014). Moreover, compartmental models are either knowledge and data-driven, like the Ross model and Macdonald models. In both cases, the models are unable to address the complex interactions and dynamics of the transmission. For example, socio-economic determinants interfere with the parameters generally considered in the calculation of R_0 such as mortality, mobility, and the birth rate (Agusto et al. 2015). Thus, models that capture realistically the transmission process of malaria are still missing.

1.5. Problem statement

The urbanization in Africa set by the rapid development of cities and the anarchic occupation of the space, often in unsanitary conditions, has created conditions prone for malaria spreading (Traoré et al. 2019). Although a large body of literature depicted the proneness of the urban epidemic, the conclusions on the effect of urbanization on malaria are still mixed. This is essentially due to the level of granularity considered to describe the relationship between malaria and urbanization. While some studies documented a significant reduction in urban malaria (Hay et al. 2005a; Tatem et al. 2013; Kabaria et al. 2017), others proved that the urbanization process will rather inflate the current transmission (Klinkenberg et al. 2005; Donnelly et al. 2005). Hence, to consider the heterogeneity in the malaria epidemiology modeling, and to assess at a fine-scale of granularity the prevailing conditions of the association between urbanization and malaria, could result in better strategies to combat malaria in cities and contribute to an improved malaria control (Snow 2015). The assessment of the heterogeneity in the transmission of malaria is even more acute in cities since dwellers are considered at higher risk of severe malaria (Hay et al. 2005b).

The heterogeneity in urban malaria epidemiology results from the complex interplay of interacting determinants, which are: environmental-, policy-, human-, vector-, and parasite-related determinants. Mapping the interplay between them, e.g., by identifying the sources of heterogeneity in urban malaria transmission, could help to design improved interventions (Woolhouse et al. 1997). Besides, disclosing the interplay between different determinants, reduce the data granularity of some variables in the transmission and the control of malaria (Midega et al. 2012; Irvine et al. 2018).

Yet, the interplay among determinants is not well documented by the complex and nonlinear nature of their interactions. Moreover, studies to display the interplay among determinants are scarce, since the quantification of factors is costly and the scale of these factors are not the same (Bannister-Tyrrell et al. 2017; Kabaghe et al. 2018). Identifying the key drivers of the heterogeneity in the transmission and control of malaria allows the design of more suitable pharmaceutical (e.g., seasonal malaria chemoprophylaxis) and non-pharmaceutical (e.g., ITNs) interventions chemoprophylaxis

(Walker et al. 2013; Amratia et al. 2019). So far, the key drivers of heterogeneous transmission of malaria in cities remain poorly documented.

The mathematical modeling of malaria transmission took a new direction when the heterogeneity started to be accounted for (Woolhouse et al. 1997; Cooper et al. 2019). Woolhouse et al. (1997) and Cooper et al. (2019) proved that a small group of super-spreaders that had been heavily bitten amplified the risk of transmission in the population. These studies demonstrated that the risk-taking behavior of a community could hamper control interventions; and on the other hand, that the efficacy of ITNs used as a frontline non-pharmaceutical intervention in urban settings is often limited by a compliant human behavior (Ngonghala et al. 2014). Not accounting for human behavior leads to an overestimation of the performance of ITNs and an underestimation of the transmission of the disease. More specifically, the potential of transmission calculated after the basic reproduction rate is higher in a heterogeneous compared to a homogenous population (Woolhouse et al. 1997). Therefore, it is hypothesized that part of the dynamics of the disease transmission and its control with ITNs is not shown when the population heterogeneity is not accounted for in the mathematical model.

In African cities such as Accra, pioneer spatial modeling has shown uneven transmission patterns of malaria but failed to characterize and identify the sources, and model the heterogeneity of this spatial pattern (Fobil et al. 2012).

1.6. General and specific objectives

This thesis overall objective is to disclose the spatial and temporal heterogeneity of urban malaria transmission and ITNs interventions rolled out in Accra

More specifically, this thesis intends to:

i) To characterize the spatial and temporal heterogeneity in the transmission of malaria at a fine-scale while identifying the prevailing conditions of association between malaria transmission and urbanization.

ii) To identify the main drivers of heterogeneity in the transmission and control of malaria in urban areas by revealing the interplay between the drivers.

iii) To model the efficiency of ITNs rolled out in Accra by accounting for the spatial heterogeneity of the uptake behavior of communities.

1.7. Organization of the thesis

In the first chapter, the spatial and temporal heterogeneity of malaria is described, aiming at substantiating the problem that malaria modeling intends to answer: how disclosing the malaria transmission and infection heterogeneity can be used to reduce its transmission and enhance its control in urban settings.

In the second chapter, an overview of the modeling approaches applied is given, as well as the objectives and data they require. In the third chapter, the spatial and temporal heterogeneity of malaria transmission, particularly in relation to the urbanization processes occurring in urban Ghana is characterized. This chapter investigated the question: In which conditions do malaria incidence and urbanization processes are associated in urban Ghana? In the fourth chapter, the drivers of heterogeneity that play a role in the transmission and control of malaria are explored, while answering the following question: What are the major determinants that explain malaria persistence in urban settings? In the fifth chapter, the bias in modeling by accounting for the heterogeneous behavior of communities is estimated. This chapter answered the question: To what extent are classical meta-population (SIR) models underestimated the infectiousness of malaria in Accra? Finally, in the sixth chapter, the findings, strengths, and weaknesses of this dissertation are summarized, and some conclusions and suggestions for follow-up studies are provided. Finally, several “take-home” messages for policymakers with regard to ways of improving non-pharmaceutical malaria-controlling interventions in urban conditions are proposed.

2. MATERIAL AND METHODS

2.1 Study areas

The research was carried out in Ghana working at the scale of the country (chap. 3) and at a scale of Accra (Chap. 4 & 5). With a population estimate at 31,860,142, Ghana is considered the second most populated country in West Africa (UN population estimate and projections 2019). Ghana demographics are dominated by children and Ghana embedded six distinct ecological zones namely the Guinea savannah zone, Forest-savannah transition zone, Semi-deciduous forest zone, Sudan savannah zone, Coastal savannah zone, and the Rain forest zone (Asravor et al. 2019). The ecological differences impact the seasonal pattern on the transmission pattern of malaria with more pronounced variations in the Guinea savannah and Sudan savannah zones (USAID President's Malaria Initiative 2020). A detailed description of Accra is provided in chapters 4 and 5.

2.2. Methods

In this section, an overview of the methods (Table 2.1) for each of the subsequent chapters as well as the data recorded is given. More details on the different modeling approaches are provided in the respective research chapters.

Table 2 1: Synoptic view of the objectives and modeling process of the thesis

Objectives	Sub-objectives	Tested hypotheses	Data used	Modeling process
To characterize the spatial and temporal heterogeneity in the transmission of malaria at a fine scale, while identifying the prevailing conditions of association between malaria transmission and urbanization	i) Model the heterogeneity in the malaria epidemic	There is spatial and temporal heterogeneity in Ghanaian malaria epidemiological data	Epidemiological time series from 2015-2018	Multi-level modeling
	ii) Document the association between malaria and urbanization	The association between malaria and urbanization can be linear or nonlinear	Cross-sectional data on the density of the population Cross-sectional data on the built intensity	Linear and nonlinear correlation

			Cross-sectional data on built areas	
	iii) Determine the prevailing conditions of association	Some conditions determine the existence of an association between malaria and urbanization	Cross-sectional data on mortality of children under five, the proportion of literate men and women, rate of immunization, the proportion of ITNs ownership, the proportion of households that lack toilet facilities, proportion of households using an improved water source, rainfall, and vegetation coverage	Machine learning processes
To identify the main drivers of heterogeneity in the transmission and control of malaria in urban areas by revealing the interplay between the drivers	i) Exhibit the interplay between sources of heterogeneity	There is a causal and complex association between determinants of malaria transmission in cities	Participatory modeling section	Causal-loop diagram
	ii) Identify the key sources of heterogeneity	Among the web of determinants, some can leverage the system of transmission of urban malaria	-	Network analysis
To model the efficiency of ITNs roll-out in Accra by accounting for the spatial heterogeneity of the uptake behavior of communities.	i) Document the empirical knowledge and behavior of communities living in urban malaria hotspots	Knowledge of the disease determine the behavior of the communities toward the uptake of ITNs	Empirical survey on 1028 households	Descriptive and inferential statistics

	ii) Assess the magnitude of bias in modeling by incorporating spatial human behavior heterogeneity	There is a gap in the efficiency of ITNs that can be quantified	Theoretical mathematics and applications	Ordinary differential equations and computer simulations

3. A CONTEXTUAL ASSOCIATION BETWEEN MALARIA AND URBANIZATION: TEMPORAL AND SPATIAL ANALYSIS IN GHANA[1]

3.1. Introduction

Coupled changes in vector ecology and human dynamics are leading to changing risk of malaria incidence, and urbanization is a key factor in this process (Caminade et al. 2014). These changes are notable in the global south where the unprecedented scale and rate of changes in human settlement patterns play a major role in malaria epidemiology. The dominant understanding considers malaria as a rural disease (Awuah et al. 2018) but rural-urban migration, among others, can fuel malaria incidences in urban areas (Wesolowski et al. 2012). In this paper, we examine the prevailing conditions for an association between malaria incidence and urbanization using the case of Ghana.

The majority of Ghana's population lives in urban areas, and the rural-to-urban demographic shift is likely to continue in the future (GSS 2013). By 2050, Ghana's urban population will be over double fold its rural population (UN 2018). Like many developing countries, urbanization in Ghana is accompanied by adverse outcomes such as traffic congestion, unregulated informal economic activities, and social inequalities (Cobbinah and Niminga-Beka 2017). Furthermore, expanding cities tend to hold and increase the rural-urban linkages and intensify human mobility, as happens in Accra and Kumasi, the two larger urban areas of Ghana (Amoateng et al. 2013; Akubia and Bruns 2019). The impending transition, along with other associated socio-demographic shifts and disease ecology, can change the existing malaria burden (Hay et al. 2005a; UN 2018). Still, little is known about the confluence of urbanization dynamics and malaria disease burden.

Urbanization has changed disease epidemiology and favored the spread of emerging and re-emerging diseases (Alirol et al. 2011; Neiderud 2015). Similarly, urbanization has altered malaria epidemiology in urban Africa (Castro et al. 2004; Keiser et al. 2004; Tatem and Hay 2004;

[1]A modified version of this manuscript is submitted with Merveille Koissi Savi, Bhartendu Pandey, Anshuman Swain, Jeongki Lim, Daniel Callo-Concha, Mohammed Wahjib, Caroline O. Buckee, Christian Borgemeister

Hay et al. 2005a; Tatem et al. 2008, 2013), but the conclusions are mixed. Some studies show reduced malaria prevalence in urban areas due to urbanization benefits (e.g. improvement, accessibility, and availability of health system, etc.) (Coene 1993; Snow et al. 2005; Donnelly et al. 2005; Smith et al. 2005; Machault et al. 2010; Noor et al. 2014). For example, the *entomological inoculation rate*, a proxy to assess malaria risk, is lower in urban and peri-urban areas, as compared to rural areas (Hay et al. 2005a) and vegetation loss reduces the potential breeding sites of the *Anopheles* mosquito (Awine et al. 2018). Other studies associate higher malaria risks with increasing urbanization. For instance, the acquired immunization to malaria decreases in urban areas due to the lack of repeated exposure (Baragatti et al. 2009), and unplanned urbanization (Klinkenberg et al. 2005; Fillinger et al. 2008; Eder et al. 2018), poverty, and lack of sanitation infrastructure (Alemu et al. 2011; Awuah et al. 2018) magnify malaria incidence, especially among young children (Awolola et al. 2007). Furthermore, people living close to urban and peri-urban farms are more exposed to malaria than people living far away (Hay et al. 2005a; Stoler et al. 2009). These interdependencies between urbanization and malarial incidence suggest a rather contextual association. Therefore, we hypothesize that some prevailing conditions are determining the association between malaria and urbanization.

Urbanization has been diversely defined and different spatial analysis approaches and analytical techniques have been used to explore its impact on malaria (Hay et al. 2005a, b; Omumbo et al. 2005; Tatem et al. 2013). Multiple dimensions of urbanization and multiple ways of measuring them present an important challenge to malaria control in urban settings, given the nature and extent of the problem in urban localities are both underappreciated and under-researched. In many studies urbanization is reported as a singular metric (based on the administrative definition of urbanization), whereas it is a multidimensional phenomenon and process. Similarly, studies often focused on average malaria incidences whereas there can be inter-generational and sex disparities.

In this paper, we analyze how urbanization is associated with heterogeneity in malaria incidence in Ghana, and identify factors undergirding this association. To this end, we examine the role of urbanization by using estimates from census and satellite data and perform a novel spatially detailed examination of urbanization and malaria incidences at the national scale in Ghana, which includes sex- and age-categorized numbers of cases at the district level.

3. 2. Data and Methods

3.2.1 Clinical data

We obtained clinical data from the Ghana District Health Information Management System (DHIMS) which is a decentralized system working at different administrative levels, providing preliminary data that helps inform public health policy decisions. Clinical data comprises explicit data of the number of confirmed uncomplicated malaria cases aggregated by month, district (n=216), age categories (n=11), and sex (n=2) over four years from 2015 to 2018. The data contain anonymized outpatient records.

3.2.2 Census and satellite data

We obtained current district boundary data from the Government of Ghana (GoG) website (https://data.gov.gh/dataset/shapefiles-all-districts-ghana-2012-216-districts) and merged it with the clinical data, creating a spatialized version of the clinical dataset. We also acquired the 2010 Ghana census, from the Ghana Statistical Service for erstwhile 170 districts, whose boundary data were gathered from the GoG website (https://data.gov.gh/dataset/shapefiles-all-districts-ghana-170-districts). Due to differences in the number of districts over time, we merged the two datasets using spatial join and spatial intersection tools in QGIS. To correct for differences in the number of districts, we calculated a weighted average of population counts for each district, where built intensities for the year 2014 (built area/total area) derived from the Global Human Settlement Layer (GHSL) were used as weights (Pesaresi et al. 2013). This approach yielded a combined spatially explicit census and clinical malaria cases dataset. In further analysis, we assumed that the cross-sectional distribution of population counts and urbanization levels did not significantly change since the last population census.

In addition to the census-based urbanization measurement, we computed urbanization metrics using a satellite-derived GHSL dataset (v 1.0) for the year 2014, obtained from http://cidportal.jrc.ec.europa.eu/ftp/jrc-opendata/GHSL/GHS_BUILT_LDSMT_GLOBE_R2015B/.

For each district, we calculated the total built area (km^2) and built intensity (built area/total area) as two additional measures of urbanization.

We estimated the density of socio-demographic groups in each district from 2015 to 2018 with a gridded population estimated at 100m spatial resolution WorldPops' dataset (GeoData Institute 2020). Under-five mortality rates, men and women literacy rates, immunization rates, the proportion of insecticide-treated bed-net possession, the proportion of households lacking toilet facilities, and the proportion of households using an improved water source were aggregated at the district level from the Demographic and Health Survey (USAID 2015) gridded dataset. Average precipitation from 2015 to 2018 at the district level was estimated from the Global Precipitation Measurement (GPM)-based merged satellite-gauge precipitation estimates in Google Earth Engine. Similarly, we used Landsat 8-derived normalized vegetation difference index (NDVI) to estimate median vegetation cover from 2015 to 2018 at the district level.

3.2.3 Statistical analysis

3.2.3.1. Malaria incidence across space, time, and socio-demographic groups

We developed a three-level model to examine the heterogeneity in malaria incidence with respect to the socio-demographic groups (age and sex), and location (districts). Detailed identification of the temporal and spatial heterogeneity was done using the seasonal-trend decomposition using locally estimated scatterplot smoothing (LOESS) global and local Moran's I statistics, respectively.

We fit a single-level model, also denoted unconditional means model, (Eq. 3.1) to estimate the overall incidence during the period of data collection for the period of 2015-2018. Here we evaluated the proportion of variation in the incidence due to the location using the intra-class correlation coefficient (ICC).

$$I_{ij} = \mu_0 + \varepsilon_{ij}, \varepsilon_{ij} \sim N\ (0, \sigma_\varepsilon^2) \tag{3.1}$$

where *I* is the malaria incidence of the district *i* (*i=1, …, 216*) for the year *j* (*j=2015,…, 2018*), μ_0 is the average incidence across districts, and ε_{ij} is the residual for a specific district and year (difference between the mean value of incidence and the observed value).

We extended the single-level to a two-level model, also known as the unconditional growth model (Eq. 3.2), where the effect of time (random effect) was measured as nested to the district. We computed the ICC of the unconditional growth model, to malaria incidence way across time and location (district).

$$I_{ij} = \mu_0 + \ (\mu_j + \varepsilon_{ij}), \mu_j \sim N\ (0, \sigma_\mu^2), \varepsilon_{ij} \sim N\ (0, \sigma_\varepsilon^2) \tag{3.2}$$

Where μ_0 represents the average incidence per year associated with the fixed effect. μ_j the variation due to the district is considered as a random effect together with the residual of the model. Both μ_j, ε_{ij} are the random effects of the models assumed to be independent and identically distributed, i.e., assumed to follow a normal distribution with the mean 0 and variance, respectively σ_μ^2 and σ_ε^2.

We further extended the previous model to a three-level model while adding sex (dummy variable) and age groups (with eleven levels) as fixed effects to compare and contrast the effect of sex and age on malaria incidence. μ_j in Eq. 3.3 becomes

$$\mu_j = \ \gamma_{i0} + \ \gamma_{ij} + \ \mathcal{E}_{ij} \tag{3.3}$$

where γ_{i0} represents the average incidence associated with either sex or age; γ_{ij} the effects associated with either the sex at the location or the age group on the location. We selected the better-fit model between the additive and multiplicative using a chi-square test where the additive model was the best fit. Similarly, we used the same test to select the better-fit structure of the matrix of variances-covariance for both the residual and the random components of the model (Eq. 3.3). Then, the matrix of variances-covariance of residuals selected was the first-order autoregressive indicating that the correlation between two observations gets weaker as the distance between them increases, whereas, the unstructured matrix fitted better for the random effects, indicating that there is no constraint across random effects. The statistical difference between socio-demographic groups and location was visualized using histograms and maps. To examine the statistical difference across years, we decomposed malaria incidence time-series using an additive decomposition into seasonality, trend, and remainder components, also denoted seasonal-trend decomposition using LOESS (STL) (Cleveland et al. 1990).

To check the consistency in the spatial structuring of malaria incidence, we computed the Global Moran's I statistic using the Queen's contiguity matrix (Eq. 3.4).

$$I = \frac{N}{W}\frac{\sum_i \sum_j w_{ij}(x_i - \bar{x})(x_j - \bar{x})}{\sum_i (x_i - \bar{x})^2} \qquad (3.4)$$

where N is the number of districts, x the incidence of malaria, $\bar{x}$ their mean, w_{ij} the Queen's contiguity matrix (where $w_{ij} = 0$), and W the sum of all w_{ij}. The local Moran's I was computed to assess the number of spatial clusters and establish the local indicators of spatial association (LISA) map to visualize the most significant local spatial correlations.

3.2.3.2. Association between malaria incidence and urbanization

As we did not assume any nature (linear or not) of the association between urbanization and malaria burden, we examined both linear and nonlinear correlations between three variables quantifying urbanization, i.e., the administrative-defined urbanization, the total built areas, and built intensity against the aggregated median monthly malaria incidence between 2015 and 2018. The linear association was checked with Pearson correlation and the nonlinear association was checked using spatial sampling.

3.2.3.3. Contextual association between malaria incidence and urbanization

The heterogeneity in malaria incidence and urbanization data was first described using a principal component analysis (PCA). As the heterogeneity in malaria is peculiar to geographical space (Klinkenberg et al. 2005) and social factors (Awuah et al. 2018), we defined the contextual association as the set of conditions underneath the relationship between urbanization and malaria burden. These conditions were assessed after clustering and cluster-specific random forest regression model (RF). The clusters of incidences were defined using k-means of district-level data on median monthly malaria incidence across various age and sex groups. The number of clusters and their membership (districts) was optimized using the Bayesian Information Criterion (BIC). The outcome was used for a cluster-specific RF, i.e., RF regression of health and hygiene and education (mortality of children under five, the proportion of literate men and women, the rate of immunization, the proportion of insecticide-treated bed-net possession, the proportion of households that lack toilet facilities, and the proportion of household using an improved water source), environmental (rainfall, and vegetation coverage) and urbanization measures against malaria incidence. Each RF regression was done using 10,000 trees to identify which parameters are the strongest predictors of median monthly malaria incidence. We optimized the number of parameters available for splitting at each tree node in the RF using out-of-box error (OBE).

To get a better understanding of malaria in big cities such as Accra (Greater Accra) and Kumasi (Ashanti), we performed a series of descriptive statistics.

3.3. Results

3.3.1 Spatio-temporal distribution of malaria epidemics across socio-demographic groups

The highest malaria incidence was observed among children from one to five years old, while the lowest was among children less than a month regardless of the location between 2015 and 2018. We found over 19 million clinical cases of malaria in Ghana between 2015 and 2018. The region of Upper East recorded the highest median incidence ~248 per 100,000 cases for children under five years old (Figure 3.1). The lowest maximum of the median malaria incidence was recorded in the region of Greater Accra for women from 20-34 years old, which was ~52 per 100,000 population. The lowest median average was found in the overall region (~ 0.32 per 100,000 population) corresponding to one confirmed case. This lowest record indicates that regardless of the time and the location, there is at least one case of malaria confirming that Ghana is a malaria-endemic region. The overall lowest median was recorded in the Northern region (~7 per 100,000 population) whereas the overall highest median was recorded in both the regions of Brong Ahafo and Western (~21 per 100,000 population) (Suppl. Table 1). Conversely, the overall lowest median was not found in urban areas (Hay et al. 2005b; Kabaria et al. 2017) such as Ashanti and Greater Accra. These findings suggest malaria incidence varies with respect to age and geography, and question precedent narrative stating that the lowest incidences are found in urban settings.

The average incidence of malaria within the country estimated by the unconditional means model (level 1) was 25.66 per 100,000 ± 1.89 ($P < 0.0001$) (Table 3.1- Level 1) and confirmed the spatial clustering since the 16.39% (ICC, Table 3.1) of the total variation in malaria incidence is due to between district variation. The spatial clustering in the epidemics has been confirmed by Moran’s I statistic (see section 3.3.1 last paragraph). The unconditional growth model (level 2) captured more variability than the previous (ICC 19.8, Table 3.1), and there is a significant variation in malaria incidence across years (Table 3.1). A chi-square test confirms the three-level additive model as a better fit than the three-level multiplicative model ($P < 0.01$). Furthermore, this model revealed that malaria incidence varied significantly between years, ages, and sex (Table 3.1 Level 3), with 50.09% due to between-district variations and 49.90% due to within-district variations.

Table 3 1: Multilevel model showing the variation over years, sex, and age

	Null model (Level 1)				Unconditional growth model (Level 2)				Three levels model (Level 3)			
Predictors	*Estimates*	*CI*	*P*	*df*	*Estimates*	*CI*	*p*	*df*	*Estimates*	*CI*	*p*	*df*
(Intercept)	25.66	23.77 – 27.56	**<0.001**	98034	-2489.24	-2848.42 – -2130.05	**<0.001**	98033	-3679.69	-4487.81 – -2871.58	**<0.001**	98031
Year					1.25	1.07 – 1.43	**<0.001**	98033	1.85	1.44 – 2.25	**<0.001**	98031
sex [m]									-6.65	-7.18 – -6.12	**<0.001**	98031
Age									-0.37	-0.38 – -0.35	**<0.001**	98031
Random Effects												
σ^2	1014.21				1012.26				1100.25			
τ_{00}	198.88 District				0.00 District				0.00 District			
τ_{11}					0.00 District.Year				0.00 District.Year			
ρ_{01}					0.89				0.00			
ICC	0.1639				0.1978				0.1978			
N	216 District				216 District				216 District			
Observations	98250				98250				98250			
Marginal R^2 / Conditional R^2	0.000 / NA				0.002 / 0.166				0.087 / 0.087			

Children under five years old recorded the highest incidence, whereas children below a month recorded the lowest malaria incidence (Fig 3.1). Independent of the location female always had the highest incidence than males between 2015 and 2018. There is a variation in the incidence over time regardless of the location with the highest records observed in 2017 (Fig 3.1). The Upper East region has the highest and the Northern region has the lowest incidence (Fig 3.1). We observed that malaria incidence in Ghana varied across years, ages, sex, and locations, corroborating previous evidence (Feachem et al. 2010; Trauer et al. 2019).

Regarding the temporal heterogeneity in malaria incidence, the STL showed an overall decrease in the disease, but at the district level an overall increase in every region except in the Upper West and Upper East regions (Fig. 3.1). Moreover, there are seasonal fluctuations, which are more pronounced in Brong-Ahafo, Eastern, Northern, Upper East, and Upper West regions (Fig. 3.1). The softened peaks of malaria incidence observed in urban dominated regions such as Greater Accra and Ashanti could be explained by the constant influx of people (Molina Gómez et al. 2017), contrary to the other regions where urbanization and immigration are lower.

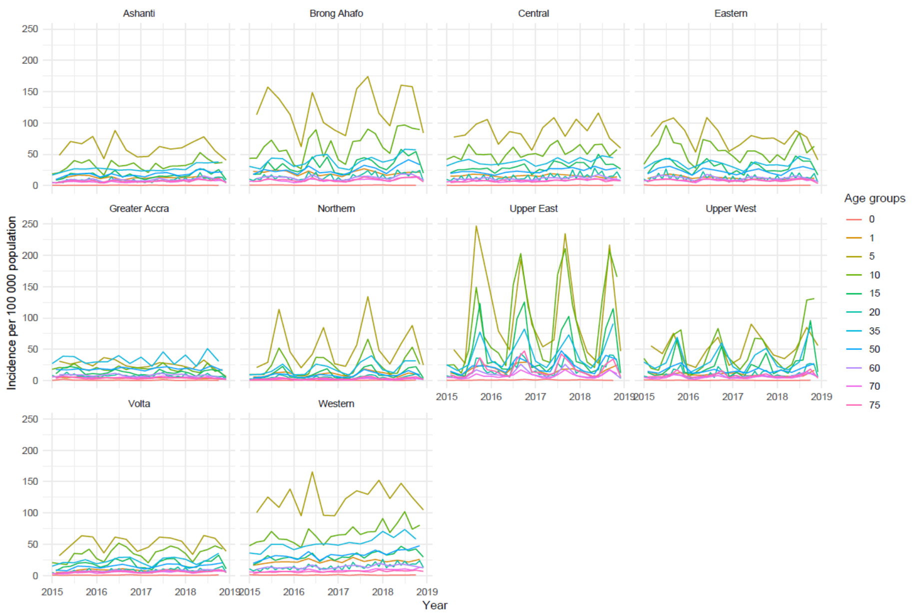

Fig.3. 1: Distribution of the incidence in regions by year and age.

Regarding the above-mentioned spatial heterogeneity, our analysis confirmed a geographic dependence at the district level (Moran's I = 0.2596, P = 2.827e-10). Thus, we found persistent high incidences in 34 districts located in Greater Accra, Western, Upper East, Brong-Ahafo, Ashanti, and Northern regions (Suppl. Fig. 4), which suggests an association of malaria incidence with environmental factors.

3.3.2. Malaria incidence and urbanization

The degree of urbanization differs according to the proxy, i.e., census versus satellite data (Suppl. Fig. 3.4). We found a weak linear and significant correlations (Pearson's coefficient) between median monthly malaria incidence and *administratively-defined* urbanization ($r= 0.32$, $P < 0.001$), and *built areas* ($r = 0.31$, $p < 0.001$) but not significant between median monthly malaria incidence and *built intensity* ($r= 0.07$, $P = 0.32$). The first two linear associations suggest that urbanization increases malaria incidences conversely to the most documented narrative (Hay et al. 2005b; Tatem et al. 2013). However, more than 60% of the association is not explained by a linear relationship. With the spatial sampling method, we found a slightly stronger nonlinear correlation with *administratively-defined* urbanization ($r=0.34$, $P = 0.004$), *built areas* ($r = 0.31$, $P < 0.001$) and malaria incidence. There is not a sufficient argument to conclude in favor of a significant nonlinear correlation between malaria incidence and the *built intensity* ($r = 0.00001$, $P = 0.45$). The two associations are, however, weak since more than 60% of the variations in median monthly malaria incidence are nonlinear. This indicates that the relationship between urbanization and malaria incidence is rather contextual.

3.3.3. Contextual association between malaria and urbanization

Given that the linear and nonlinear associations between malaria incidence and urbanization were not strong, we turned to examine the underlying heterogeneities in the aggregated monthly median malaria incidence and their association with socio-economic, environmental, and urbanization determinants. To understand the gradient of heterogeneities in the median incidence data, the k-means analysis distinguished three clusters of incidence, namely low, high and median monthly malaria incidence. Besides, the PCA revealed variability in the cluster with respect to socio-economic, environmental, and urbanization determinants. The three clusters of monthly malaria incidence spatially coexist, indicating that even in urban areas there are some districts with high, medium, and low monthly malaria incidence, likewise for rural areas (Fig 3.2A).

There is a component of urbanization explaining the spread within each of the clusters (Fig. 3.2B) as indicated by the cluster-specific RF and PRCC. The variance described by the RF models for median incidence for Group 1 to 3 is 67.38%, 51.26%, and 62.93%, respectively. The built areas are the major driver of monthly malaria incidence in the group of low median incidence (group 1, Fig. 3.2B, C). Thus, the transmission gets higher in the cluster of low median incidence when more areas are built, suggesting men-made mosquito breeding sites are the leading cause of malaria infection. This cluster is a mix of varying degrees of low and medium urbanized localities (Suppl. Table 1). Although the overall variance explained by NDVI is low, the more vegetation cover there is, the higher the malaria incidence is (Fig.3.2C).

The built intensity, the built areas, and the NDVI drive malaria incidence in the cluster of median malaria incidence (group 2, Fig. 3.2B, C). Unequivocally, dense vegetation cover and higher built areas fuel malaria incidence whereas a higher built intensity decreases it. This suggests both anthropogenic and environmental factors as drivers of malaria incidence in the cluster of districts having medium monthly malaria incidence. This cluster is situated mostly in peri-urban areas (Fig. 3.2A) where, albeit with a lower percentage of explained variance, the mortality of children under five also influences the incidence.

Administrative-defined urbanization is the main driver of high median monthly malaria incidence (group 3, Fig. 3.2B, C). Administratively, in Ghana, an area with a population surpassing 5,000 people per km^2 is characterized as urbanized (GSS 2013). Thus, the denser the population is the higher the incidence will be. This cluster encompasses mostly the highly urbanized areas (Suppl. Table 1). Notwithstanding the lower percentage of variance explained, the mortality of children under five is negatively associated with median monthly malaria incidence.

Besides, the lack of toilet facilities exacerbated malaria incidence in the three groups.

Concisely, the degree of urbanization solely does not determine median monthly malaria incidence since it depends not only on the degree of urbanization but also on the environment (men-made or natural) and the health and sanitation of the population.

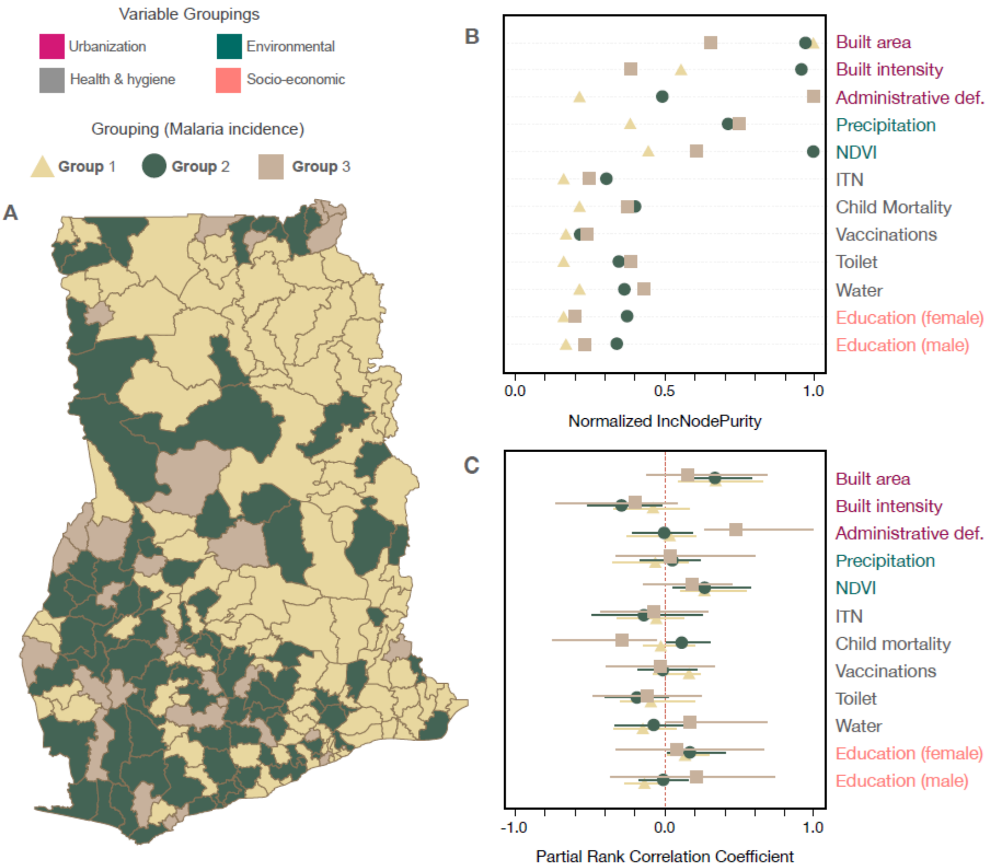

Fig.3. 2: Contextual association between urbanization and the monthly median incidence of malaria: (A) Clusters of districts by the similarity of malaria incidence across all age-sex groups (obtained using k-means clustering); (B) Normalized Variable Importance scores (IncNodePurity) from Random Forest regression analysis of how within each cluster (obtained in [B]), different urbanization features predict average malaria incidence; (D) Partial Rank

Correlation Coefficients (PRCC) of how within each cluster (obtained in [B]), different urbanization features affect median malaria incidence.

Besides, in the region of bigger cities in Ghana such as Greater Accra and Ashanti, there is a positive association between built areas, built intensity, and median monthly malaria incidence, confirming that men-driven malaria incidence in Accra and Kumasi (Fig.3.3). However, the ITN coverage and the vegetation cover have an adverse effect on malaria incidence. The latter should be read the less there is a vegetation cover and the more malaria increases (Fig. 3.3). Moreover, there is a positive association between population density and median monthly malaria incidence in the Ashanti and Greater Accra regions.

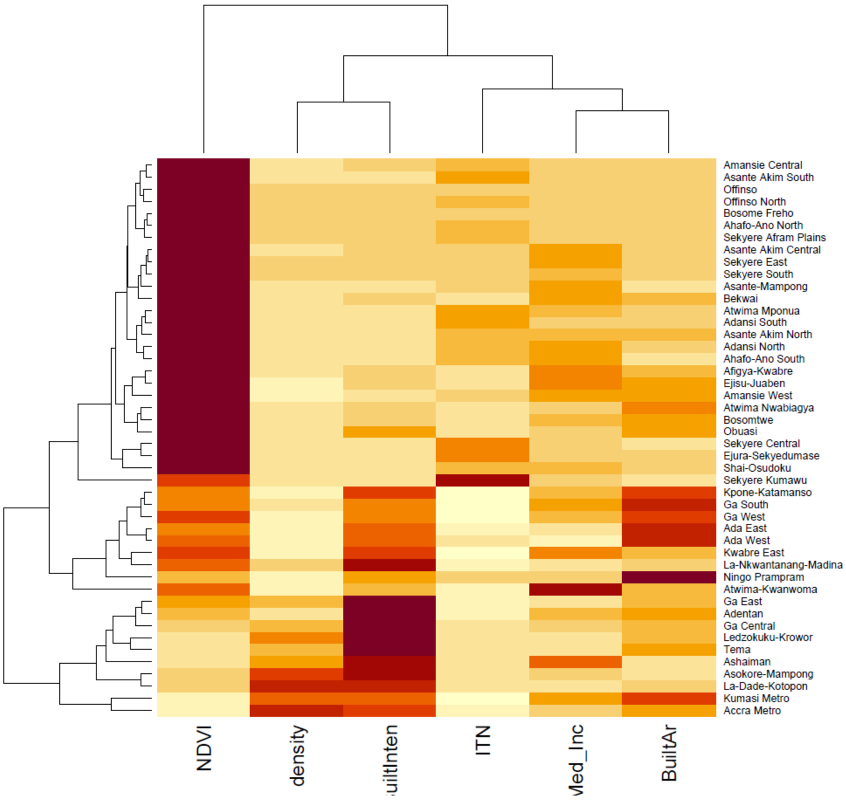

Fig.3. 3: Heat map showcasing the visualization of the normalized value of some key covariates in the district located in the Greater Accra and Ashanti regions NDVI is the vegetation cover; BuiltIten represents the built intensity, ITN represents the use of ITN, Med_Inc represents the median monthly incidence and BuiltAr represents the built area

The spatial distribution showed (Fig.3.4.) that at the district level even in these regions, the repartition of the covariate is highly heterogeneous with Accra and Kumasi having the highest incidence. Most importantly, the surrounding of Accra and Kumasi also recorded a higher incidence of malaria. Hence, there is likely diffusion of malaria incidence from urban to peri-urban areas. However, this hypothesis has not been explicitly tested in the scope of this study. Surprisingly, Accra and Kumasi also recorded the lowest use of ITN (Fig. 3.4) conversely to the neighboring district where the coverage rate of ITN increases as the gyration radiation increases. Besides, the density of the population in the neighboring districts does not follow a diffusion. Accra and Kumasi concentrate the highest density of population whereas in the neighboring district the density of population is lower.

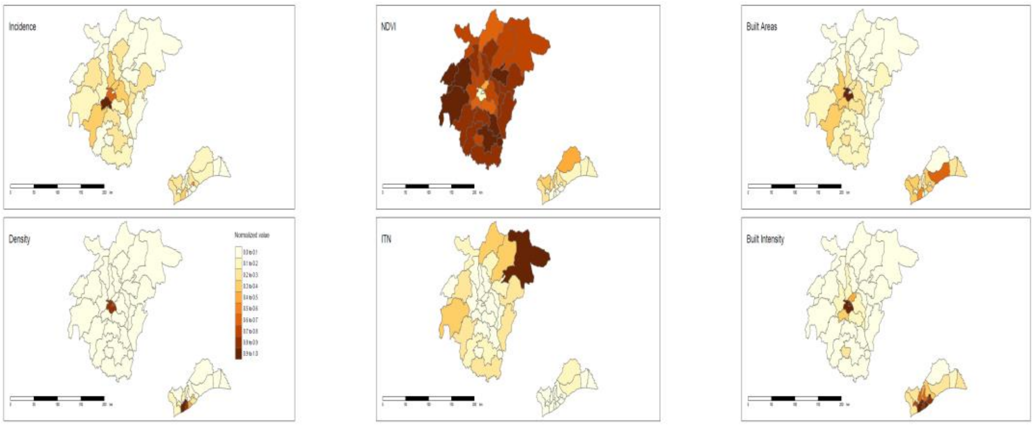

Fig.3. 4: Thematic map of the spatial repartition of the normalized value of key covariate that explains the incidence of malaria in the Greater Accra and Ashanti regions

3. 4. Discussion

3.4.1 Malaria pattern in Ghana

Although at the country level malaria incidence decreased over time, at the regional level, the incidence increased almost everywhere, except in the Upper East and Upper West regions. This is probably the result of an increase in awareness of the population that is now inclined to healthcare support upon the onset of malaria symptoms. Since 2005, Ghana is implementing universal health coverage for all the citizens through its National Health Insurance (NHI) scheme (Ministry of Health 2004). The implementation of the NHI in Ghana fivefold increased the willingness of the population to seek treatment in healthcare facilities (Fenny et al. 2015). Besides, the increase in malaria incidence can be attributed to changes in factors influencing malaria epidemiology. For instance, the 3.5% increase in malaria incidence in 2016 was associated with the use of falsified drugs and the practice of self-medication (Ghana Health Service 2016). An increase in precipitation can equally exacerbate malaria incidence, where a monthly augmentation of 10 mm of rainfall increases clinical malaria by 1% (M'Bra et al. 2018). While factors like greater awareness, access to healthcare, and monitoring impetus suggest a positive change in health-seeking behavior, changes in the social and physical environments can support the factors increasing the epidemiology of the disease. Due to limited data used in the scope of this study, we cannot elaborate on the healthcare-based drivers and their association with the observed trends, and thus, we focus on spatial analysis. Alternatively, the decreasing rate in Upper East and Upper West is possibly associated with the use of indoor residual spraying since 2016; however, stronger evidence is needed to confirm this association (Gogue et al. 2020).

We observed a strong seasonality in malaria incidence which is associated with rainfall patterns where the increase in the incidence coincides with the peaks in rainfall but differs slightly from one region to another along a north-south gradient (Awine et al. 2018). Donovan et al. (2012) and Awine et al. (2018) explained that the clinical cases rise during rainy seasons and fall during dry seasons, the latter likely due to a decrease in vector density.

Regardless of location (urban versus rural) and socio-demographic groups, the highest incidence was recorded for children under five years old with children below one year as the group with the lowest risk. Two major reasons can be attributed to the latter observation: (1) the positive outcome of malaria policy and (2) evidence of maternal immunity. Children-targeted interventions have been proved to reduce malaria mortality and morbidity by up to 18.8% in Ghana (Afoakwah et al. 2015), and through poorly understood mechanisms, children under six months are protected by maternal antibodies (Dobbs and Dent 2016). Arguably, such antibodies are acquired by juveniles through maternal parity, intermittent preventive drugs, and recall response of juvenile blood lymphocytes to malaria antigens (Dent et al. 2006; Metenou et al. 2007; Apinjoh et al. 2015). We suspect a reporting bias for women, especially since we found a higher incidence in women especially in urban areas in Ghana where they are given insecticide-treated bed-net and malaria chemotherapy on antenatal visits (Afoakwah et al. 2018). We hypothesize that women in cities are more informed about the World Health Organization (WHO) policy on intermittent preventive treatment in pregnancy than those in rural areas. This hypothesis was supported by a recent study in neighboring Burkina Faso where urban women are more aware of malaria causes, symptoms, and preventions than rural ones (Yaya et al. 2017).

3. 4.2 Malaria and urbanization in Ghana

We found that even in cities the seasonal decomposition of the incidence time series revealed an increasing malaria rate. Besides, the LISA map showed that in some districts, such as Accra, there is a locally higher and significant incidence. Similar observations were made in other cities such as Douala and Yaoundé (Cameroon) where *Anopheles gambiae* thrive in complex human habitats and even adapt to pyrethroid-polluted water where their larvae develop (Tene Fossog et al. 2012). The adaptation of *An. gambiae* to the urban environment cut across their entire life cycle and was shown to be a signature of the human-driven evolution of the genetic make-up of the species (Alberti et al. 2017; Hendry et al. 2017). Similarly, the recently introduced Asian *Anopheles stephensi* could colonize 22 urban settings in Africa, including Accra, putting more than 40% of the continent's urbanites at high risk of malaria (Surendran et al. 2018; The World Bank 2020; Sinka et al. 2020). *An. stephens*i is more effective at transmitting the disease than *An. gambiae* since it can bite outdoors from 6 PM to 6 AM (Massey et al. 2016).

Different predictors were relevant to explain the association between the incidence of malaria and the degree of urbanization. In poorly to moderately urbanized areas the incidence of malaria is mainly driven by vegetation cover and man-made environments. There is an inverse association only when the vegetation cover is sparse. Moderate or dense vegetation is a necessary ecological condition that enables mosquito vectors to forage in urban environments. The vegetation provides refuge for adult mosquitoes during the daytime, while precipitation allows the female mosquito to breed (Ricotta et al. 2014). The interaction between vegetation cover and men-made breeding sites is particularly acute in urban settings where mosquitoes' ideal reproductive sites (clean and shallow water and vegetation) are not always present (Mattah et al. 2017). Because of the unfavorable breeding conditions of mosquitoes, urbanites are less exposed to their bite leading them to be more vulnerable to malaria (Gardiner et al. 1984; Frank et al. 2016; Kabaria et al. 2017). A loss in the vegetation cover generates an increase in local temperature and consequently alters the risk of contracting malaria (Olson et al. 2010). Nonetheless, Afrane et al. (2005) demonstrated that an increase in the local temperature in Western Kenya caused by deforestation increased the vectorial capacities of *An. gambiae.* According to the same authors, this increase reduces the sporogonic cycle and triple the risk to contract malaria.

In highly urbanized areas instead, population density is the main driver of malaria incidence. This can probably be explained by the immigration and the accessibility to primary care facilities in urban settings. People from peri-urban and rural centers move to better and affordable healthcare facilities especially when the travel time is below two hours (O'Meara et al. 2009). Therefore, such imported malaria cases are counted in cities such as Accra and Kumasi where the incidence is then higher than in the neighboring districts. More specifically, healthcare facilities are more accessible in Accra and Kumasi although efforts have been made to reduce the burden of these healthcare delivery systems (Frimpong 2013). For example, a recent study showed that people living in the rural Ashanti Region travel a long distance to Kumasi to access healthcare (Ashiagbor et al. 2020). On the other hand, in Tema, a district located in the Greater Accra region, there is a high prevalence of malaria among the mobile population of hawkers and long-distance truck drivers (Diallo et al. 2017). A cross-sectional study conducted in Accra and Kumasi revealed the presence of *Plasmodium falciparum* in the blood smear of children under five of people who traveled the last three weeks before the study (Klinkenberg et al. 2006). Consequently, Accra and Kumasi represent healthcare catchment accounting for malaria imported cases.

We found that the lack of toilet facilities increased malaria incidence regardless of the degree of urbanization. In highly urbanized areas in Ghana, private toilet facilities are often missing in deprived communities populated by poor urbanites. This lack of toilet facilities can be considered as a cofactor underpinning the poverty of citizens who due to their activities, are more exposed to mosquito bites (Awuah et al. 2018).

We used datasets generated from satellite images or spatial modeling techniques. Thus, each of the variables has its bias that may affect our estimation of the incidence as well as the prevailing conditions of an association between malaria incidence and urbanization. These biases could be multiplicative or additive, and consequently, our conclusion could have over- or underestimated the prevailing conditions. Therefore, there is a need to validate our findings with empirical data. Nonetheless, our study went beyond an assessment of association and revealed some sets of the prevailing conditions for an association between malaria incidence and urbanization. Importantly, the current study reunited the two postulates and revealed that malaria in urban settings is more complex than that described by urbanization level, regardless of how we measure urbanization. Instead, understanding the association between malaria and urbanization will require a focus on social and ecological heterogeneities. Our results suggest that examining whether urbanization or urbanicity uniquely increases or decreases malaria incidences in Ghana requires a contextual lens. Examining the association and drawing inferences can benefit from a focus on the socio-ecological contexts and how they vary with human settlements. A chief implication of our study is on the complexities of malaria epidemiology and urbanization, and addressing these complexities would need a multidisciplinary approach.

3. 5. Conclusion

In this study, we analyzed a recent spatially- and temporally-detailed dataset of malaria incidence in Ghana from 2015-2018. Our analysis derived a series of stylized facts about malaria incidences in Ghana, suggesting significant underlying complexities in malaria epidemiology. Chiefly, we find evidence of heterogeneity in malaria incidence that varies across regional and urban contexts. The drivers of malaria incidence depend on the degree of urbanization opening up avenues for future research on the marginal effect of the drivers on malaria disease dynamics in urban malaria-endemic areas. Observations derived from our analysis, therefore, will be useful in future modeling work to understand the implications of climate change and urbanization-led changes in malaria dynamics for health inequities in Ghana and beyond.

4. EMERGING PROPERTIES OF MALARIA TRANSMISSION AND PERSISTENCE IN URBAN ACCRA, GHANA: EVIDENCE FROM A PARTICIPATORY SYSTEM APPROACH[2]

4.1 Introduction

Malaria is still the deadliest infectious disease, responsible for more than 380,000 deaths in 2018 only (WHO 2020). In endemic areas of sub-Saharan Africa (SSA), the expenses for its control and prevention reach up to 40% of all public health expenditures (WHO/UNICEF 2015), and its effects were estimated to have reduced the GDP by 9% in 2010 in affected countries in SSA (Mwabu et al. 2011). Due to the collaborative efforts of governments and development partners, malaria mortality has been reduced by 66% from 2007 to 2017 (World Health Organization 2017), but the challenge is yet far from being solved.

Africa's population is expected to triple by 2050 (Donnelly et al. 2005), with major growth occurring in urban areas. For example, the population of major Ghanaian cities has grown by 3.5% per annum from 1984 to 2010 (Owusu and Yankson 2017). Urbanization has shifted the priorities of the public health system from the control of vector-borne diseases such as malaria to environmental public health challenges, such as traffic congestion, slumming, and pollution (Cabannes 2015). For example, in Accra, the capital of Ghana, urbanization-related issues often overshadow the infectious diseases related ones, with the local government investing less than 50USD per person per year on health (Elsey et al. 2019). Moreover, the poorest communities experience the greatest harm (Elsey et al. 2019), like Accra's head porters, especially challenged by the nature of their work and often not able to afford the national insurance scheme (Lattof 2018).

A pressing public health issue is the prevalence of vector-borne diseases, like malaria (Keiser et al. 2004; Kabaria et al. 2017). Its predominant vector *Anopheles gambiae*, whose customary habitat for reproduction used to be rural, clean, and shallow water ponds surrounded by grassy fields, has now adapted to the urban conditions and

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prospers in polluted waters, such as clogged gutters or puddles, characteristic of poor urban housing (Keiser et al. 2004; Mattah et al. 2017).

This example shows the complex and adaptive character of the malaria transmission system, where the humans, vectors, the environment, and parasites interact in an iterative and nonlinear manner (Endo and Eltahir 2016). Earlier modeling approaches rarely considered such complexity, and instead conceived transmission causal and unilaterally, which contributed to the development of policies favoring the promotion of single-intervention programs, like the free provision of malaria drugs (Van Der Geest 1987; Adome et al. 1996; Williams and Jones 2004).

A complex system is one where its components, apparently disconnected and performing their roles after their interests, align together to perform more sophisticated functions (Mitchell 2011). This tends to be the case for most social and ecological phenomena, as they do not occur in isolation but intermingled (Berkes et al. 2002). The unraveling of complex systems is operationalized through approaches, methods, and tools that instead of assessing the determinants individually, focus on the interactions among them, and the overall function of the system (Ludwig 1950). In that regard, the involvement of local stakeholders appears key, as it reduces the bias of researchers and increases the legitimacy of the outcomes (Walker et al. 2002).

We have applied such approaches in this study and visualized the interactions among the determinants of malaria transmission in urban conditions using a Causal Loop Diagram (CLD) and displayed emergent properties of the system via Network Analysis (NA).

CLD can support the visualization of the interplay among determinants and assist in the identification of causal relationships among them (Baugh Littlejohns et al. 2018). Moreover, to better understand the complexity of malaria transmission, CLD can also help to devise improved strategies for more effective control of the disease in cities (and beyond) by scouting underplayed channels (Endo and Eltahir 2016).

NA is based on the principles of network theory, where a system is considered a web of edges (interactions) that connect the nodes (determinants) (Borgatti and Halgin 2011). The examination of the network properties (e.g. density) and its topology, e.g.

centrality, indicate the nature of the information flow and reveal the most sensitive determinants and their roles (Sporns et al. 2007; McGlashan et al. 2016). Furthermore, by applying graph theory, NA offers powerful visualizations of the analyzed phenomena (Borgatti and Halgin 2011; Prell 2011). A successful application of NA can display some emerging properties of complex systems, such as McGlashan et al. (2016) did in identifying the leverage points, i.e., where one can intervene to alter the system of childhood obesity in Australia.

We hypothesized that by combining participatory CLD and NA we would be able to better accomplish the aims of this study, that are (i) to understand the interplay between determinants of the system of transmission and persistence of malaria in urban settings, and subsequently (ii) to identify its emerging properties (i.e., properties of the network and leverage points of the system and derive potential interventions on the system).

4.2. Methods

4.2.1. Study area

Accra, the capital city of Ghana, is located on the coast of the West African Gulf of Guinea. Its climate is tropical alternating wet and dry phases, mainly due to the cyclical harmattan winds. The average annual rainfall is 730 mm and bimodally distributed, the temperature average reaches 26.6°C, and the relative humidity rounds 81%, with little variations along the year (Awine et al. 2017; Wikipedia 2020). Accra's current population is 2,3 million, to a great extent composed of migrants from successive waves of rural-urban migration across the last 50 years. Housing is uneven in infrastructure quality and service provision, but standards are generally low. The worst affected areas are old central neighborhoods, where slums abound, and peripheral settlements, where new developments happen (Songsore 2008).

Although malaria is traditionally considered a predominantly country-side disease, recent evidence showed that mortality and morbidity in SSA's urban and rural areas are highly heterogeneous (Donnelly et al. 2005; Tatem et al. 2008, 2014). For example, in Accra, slums and poorly-managed urban areas such as James-Town and

Korle-Dudor districts recorded the highest malaria indices of morbidity and mortality (Austin 2015).

4.2.1.1. Identification of key experts and Causal Loop Diagram elicitation

Initially, we held an informal meeting with district assembly members of James-Town and Korle-Dudor districts and other members of the communities, to identify the key institutions and experts working on the prevention and treatment of malaria. The list of institutions and experts was consolidated to include twelve representatives from the Ghana National Malaria Program, Malaria Initiative/ USAID, World Health Organization, Ghana Health Service, Plant Protection and Regulatory Services/ Ministry of Food and Agriculture, Noguchi Memorial Institute for Medical Research, several NGOs, and local healthcare facilities (Suppl. Table 1).

The experts met in two recorded qualitative workshops, which were facilitated by a modeling team (modeler, facilitator, and wall-builder) following Hovmand's guidelines (Hovmand 2014). The architecture of the workshop is documented by (Hovmand et al. 2013; Hovmand 2014). Most specifically, in the first workshop, we refined the problem, defined the variables of the model using five thematic clusters (vector, parasite, environment, human, and health care system), and drew an initial CLD. A CLD aims to show the interplay between components of a complex system, eliciting the feedback loops, and facilitate the understanding of a given problem (Binder et al. 2004; Purwanto et al. 2019). For that, we set the background by presenting the outcomes of precedent informal interviews; then, together with the experts, the boundaries of the malaria-related transmission and persistence CLD were defined. We set a time horizon of ten years to guide the discussion and the modeling. Consequently, determinants that are not very specific and have long time effects on the overall system (e.g., climate change) were removed from the discussion. However, their specific parameters (e.g. rainfall and temperature) were included.

In the CLD, a *cause* is a determinant from which the arrow emerges, and an *effect* a determinant that receives the arrow. The positive or negative sign of the arrow explains the type of association, i.e., a cause A implying an effect B showing a positive sign should be read: An increase in A implies an increase in B. Inversely, A implying B with a negative sign should be read: An increase in A causes a decrease in B (Fig. 4.1). Subsequently, some determinants that were not locally relevant, e.g., indoor residual spray (not used in Accra) were excluded and exogenous determinants were limited to the minimum as suggested (Sterman 2000).

During the second participatory workshop, we refined and validate the CLD. Thus, new determinants were added whereas others were merged into more inclusive ones, and some determinants judged non-relevant were removed, which led to changes in the causal linkages. The model obtained (Suppl. Fig. 1) was fine-tuned by the modeling team based on the recordings.

All expert participants were informed and agreed to be recorded and consented to the scientific use of those recordings.

4.2.1.2. Network analysis

The emerging properties of the system represented by the CLD were displayed by the properties of the network and its most central determinants. The most central determinants stand for the leverage points for transmission and persistence of malaria in Accra. These points can enhance the control of malaria when they are adjusted according to the properties displayed by the system.

The CLD represents an unweighted directed network $G = (V, E)$, where V and E are respectively the set of the nodes and the edges. The connectivity in G is represented by the adjacency non-symmetric and unweighted matrix A_{ij} (Eq. 4.1) (McGlashan et al. 2016),

$$A_{ij} = \begin{cases} 1, if \ \{i, j\} \in E \\ 0, otherwise \end{cases} \tag{4.5}$$

The properties of the network were estimated through the computation of the density, the average path length, and the modularity of the CLD network. The functional importance of the determinants was captured via the calculation of six measures of centrality, i.e., degree (K), in-degree (K^{in}), out-degree (K^{out}), PageRank (x), closeness (C), and betweenness (B).

The degree centrality (K) assesses the determinants' connectivity. With respect to the adjacency matrix, the degree K_i can be calculated for a network G containing N nodes:

$$K_i = K_i^{in} + K_j^{out} \tag{4.6}$$

where

$$K_i{}^{in} = \sum_{j=1}^{N} A_{ij}, \quad K_j{}^{out} = \sum_{i=1}^{N} A_{ij}, \tag{4.7}$$

$K_i{}^{in}$and $K_j{}^{out}$ stand for in-degree and out-degree centralities and indicate the direction of the connection between determinants, the former as a recipient (effect), and the latter as emitter (cause).

PageRank centrality x_i estimates the influence of certain determinants on the whole network (Golbeck 2015; Newman 2018) and is given by

$$x_i = 0.85 \times \sum_j A_{ij} \frac{b_j}{k_j^{out}} \tag{4.8}$$

where x_i is the out-degree of the node i. Thus, b_j is given by $b_j = \begin{cases} 0\, if\ in - degree \\ 1 \quad otherwise \end{cases}$.

The closeness centrality C_i calculates the proximity among determinants and identifies which one spreads more efficiently information in the network (Bavelas 1950; Sabidussi 1966; Sporns et al. 2007; Newman 2018). C_i is defined by

$$C_i = \frac{n}{\sum_j g_{ij}} \tag{4.9}$$

where n represents the total number of the shortest paths (the shortest self-avoiding route that runs from one determinant to another along with the connectivity (Newman 2018)) between the determinant i and j, and g_{ij} is each elementary shortest path or the distance between the determinants i and j.

The betweenness centrality B_i measures how a determinant serves as a bridge between different parts of the network (Freeman 1977; Golbeck 2015; McGlashan et al.

2016; Newman 2018). Assuming that g_{st} is the total number of shortest paths from s to t then n_{st}^{i} is the number of shortest paths from the determinants s to t. Simply $n_{st}^{i} = \begin{cases} 1 \; if \; there \; is \; a \; relationship \; between \; s \; and \; t \\ 0 \qquad\qquad otherwise \end{cases}$.

The computation of B_i is given by

$$B_i = \sum_{st} \frac{n_{st}^{i}}{g_{st}} \tag{4.10}$$

All the analyses were run using R (R Core Team 2013).

All participants involved in this study were informed and signed their consent for the recording and the use of the meetings' materials for scientific purposes.

4.3. Results

4.3.1. A system model of malaria transmission and persistence

The transmission and persistence of malaria in Accra are portrayed in a CLD of the complex system model, entailing 56 interactions among 45 determinants (Suppl. Table1). This model shows three sub-models triggered each by a reinforcing loop, i.e., (i) the urbanization-related transmission and acquired resistance of *Anopheles* to insecticides (green), (ii) the human's infection-prone behavior (red), and (iii) the healthcare efficiency and *Plasmodium* resistance (blue) (Fig. 4.1).

Urbanization-related transmission and resistance of Anopheles *to insecticides*

The deficient city planning and planning enforcement, inadequate housing conditions, and limited waste and sewage infrastructure lead to the proliferation of *Anopheles* breeding sites, which is worsened by the excavation of wells for urban and peri-urban agriculture and rainfall. Besides, a temperature range between 26 and 33°C in Accra, contributes to the increase in the reproductive rate of *Anopheles*, their absolute numbers, and finally their survival, augmenting the risk of infection.

Furthermore, the preventive use of insecticides in households, agricultural sites, and healthcare facilities leaves residues that contribute to the development of insecticide resistance in local mosquito populations. Thus, in the reinforcing loop one (R1, Fig4.1), we observe that the transmission of malaria depends not only on the environmental factors, such as temperature and rainfall but also on the lack of regulations to prevent and control the proliferation of mosquito breeding sites. These effects are exacerbated by the widespread use of insecticides. Hence, this reinforcing loop portrayed the environment as a pathway of both, the infection and the development of resistance of mosquitoes to insecticides (Fig. 4.1).

Humans infection-prone behavior

At the individual and household levels, ideally, the awareness of malaria risk leads to the reduction of nighttime activities, as well as the use of protective/preventive measures against mosquito bites, such as the use of insect-proof mesh for doors and windows and insecticide-treated bed-nets (ITNs). The more these measures are accepted and used, the lower the infection will be. In addition, human migration increases the number of infected cases by importation. More infected people in Accra imply a greater number of mosquitoes becoming infected that will subsequently transmit the pathogens to new hosts. This reinforcing loop two (R2, Fig 4.1) highlights the importance of individual and household decisions, and how a changing behavior can prevent the transmission and its persistence by, for instance, reducing the nighttime activities and using protective measures like ITNs. (Fig 4.1.).

Healthcare efficiency and Plasmodium *resistance*

Malaria carriers can be asymptomatic, and as Ghana's healthcare system is often unable to detect them, they frequently remain untreated and thus keep spreading the disease. Knowledge of malaria symptomatology and a sufficient household income leads to more visits to healthcare facilities. If healthcare workers are well trained, adhere to prescription protocols, and patients comply with the prescribed treatment, the reinforcing loop three (R3, Fig4.1) will operate, and trust in the health system will grow. If patients do not trust the health system, the use of inadequate medication and misuse of adequate medication will increase, and alongside the resistance of the *Plasmodium* parasite to preventive and curative drugs. Besides, the free availability of heavily subsidized drug treatments augments self-medication and indirectly enhances drug-resistance development in *Plasmodium*. This loop reveals that a good healthcare system requires to be well endowed logistically and in terms of personnel. Substituting such a healthcare system with highly accessible low-priced drugs can increase the prevalence of resistant strains of *Plasmodium*. Moreover, this loop revealed an unintended pathway of malaria treatment policies (Hovmand 2014), which, although well-intentioned, can be counter-productive. Relatedly, symptomatic patients, unsatisfied with allopathic treatments and drug resistance, may opt for alternative medicines, despite their often uncertain outcomes.

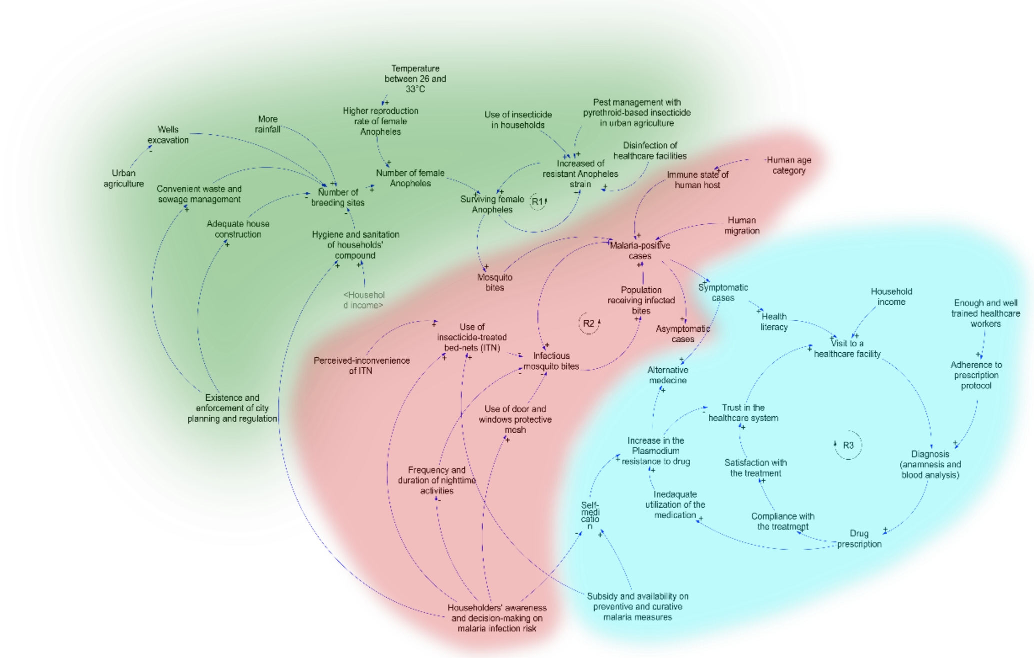


Fig.4. 1: Causal loop diagram depicting the complexity in malaria transmission and persistence in Accra (Ghana). In green the urbanization-related transmission sub-model, in red the human's infection-prone behavior of malaria sub-model, and the healthcare efficiency and Plasmodium resistance sub-model (blue).

4.3.2. Network analysis of the CLD

Properties of the network

The network representing the CLD displayed a structure of *small-world*, meaning that all determinants are not interconnected but are anyhow reachable by a small number of steps (Hexmoor 2016). It shows an average path of 6.309, meaning that each determinant can reach any other on average through 6.309 paths. Still, it has a low density (0.028), presenting only 2.8% of possible edges in a completely interconnected network, and suggesting that a change in a determinant will have only a limited impact on the whole system. This indicates that despite its apparent complexity, there is a small connection path among determinants, allowing the information to spread rapidly (Albert et al. 2002; McGlashan et al. 2016). Furthermore, a modularity of 0.619 implies a structural clustering among determinants, indicating that acting on the determinants of the highest betweenness will have a spillover effect on the whole system (McGlashan et al. 2016). In other words, an effective way to impulse a change in the system is to induce a change in the mediator.

Network metrics

The CLD has a *scale-free* distribution, meaning that its in-degree and out-degree metrics showed a heavy-tailed distribution with values ranging from 0 to 5 (Suppl. Fig. 2). Few nodes show 0 out-degree, indicating that most of the determinants influence other determinants. This configuration describes well real-world networks and suggests a high resilience of the system (Hein et al. 2006) (Table 4.1 & Suppl. Fig. 2). Thus, beyond the mediator of the system, the other leverage points also needed to be strategically adjusted to efficiently fine-tune the system.

The network centrality metrics revealed that *malaria-positive cases*, was the determinant of higher centrality, either impacting or been impacted by seven determinants. Also, the *number of breeding sites* was impacted by five other determinants, ($k^{in} = 5$) namely: 1. *more rainfall*, 2. the *hygiene and sanitation of householders' compound*, 3. the *adequate housing construction*, 4. a *convenient waste and sewage management*, and 5. the *wells excavation.* Conversely, the *householders' awareness and decision-making on malaria infection risk* was the main cause of transmission and persistence, as it impacts five other determinants (k^{out}= 5) namely 1. the *hygiene and sanitation of household compound*, 2. the *use of ITN*, 3. the *frequency and duration of nighttime activities*, 4. the *use of door and windows mesh*, and 5. *self-medication*.

Predictably, the determinant of highest betweenness that connects most clusters of determinants is the *malaria positive cases* (B = 328); and the one with the highest Page rank, and, thus, the most influential is the *malaria positive cases* ($x =$

0.086). Also, the determinant with the greatest closeness centrality, i.e., with the shortest distance to all others is *drug prescription* (C =0.381) (Table 4.1).

Interestingly, determinants participating directly in the infection process, such as the *number of breeding sites,* the *malaria positive cases*, or not, such as the *drug prescription* and *householders' awareness and decision-making on malaria infection risk* are also important leverage points (influential points in the system where a small change in these determinants can induce a big change in the whole system (Fischer and Riechers 2019)) that can affect the system.

Table 4 1: Metrics of the network analysis of determinants of transmission and persistence of malaria in Accra

Label	K	C	B	x	K^{in}	K^{out}
Existence and enforcement of city planning and regulation	2	0.116	0	0.004	0	2
Adequate housing construction	2	0.119	10	0.006	1	1
Convenient waste and sewage management	2	0.119	10	0.006	1	1
Urban agriculture	1	0.111	0	0.004	0	1
Wells excavation	2	0.119	20	0.008	1	1
Number of breeding sites	6	0.128	147	0.032	**5**	1
More rainfall	1	0.119	0	0.004	0	1
Householders' awareness and decision-making on malaria infection risk	5	0.266	0	0.004	0	**5**
Hygiene and sanitation of households' compound	3	0.119	16	0.007	2	1
Household income	2	0.200	0	0.004	0	2
Temperature between 26 and 33°C	1	0.119	0	0.004	0	1
Higher reproduction rate of female Anopheles	2	0.128	19	0.008	1	1
Number of female Anopheles	3	0.140	192	0.039	2	1
Surviving of female Anopheles	4	0.153	262	0.080	2	2
Use of insecticide in household	1	0.140	0	0.004	0	1
Insecticide resistant Anopheles strain	5	0.134	34	0.050	4	1
Pest management with pyrethroid-based insecticide in urban agriculture	1	0.124	0	0.004	0	1
Disinfection of healthcare facilities	1	0.124	0	0.004	0	1
Mosquito bites	2	0.160	246	0.038	1	1
Use of insecticide-treated bed-nets (ITN)	4	0.160	23	0.011	3	1
Perceived-inconvenience of ITN	1	0.145	0	0.004	0	1
Frequency and duration of nighttime activities	2	0.160	2	0.005	1	1
Use of door and windows mesh	2	0.160	2	0.005	1	1
Infectious mosquito bites	5	0.177	313	0.047	4	1
Population receiving infected bites	2	0.209	298	0.044	1	1
Malaria positive cases	7	0.255	**328**	**0.086**	4	3
Human migration	1	0.214	0	0.004	0	1

Human age category	1	0.186	0	0.004	0	1
Immune state of human host	2	0.214	15	0.008	1	1
Asymptomatic cases	1	0.000	0	0.029	1	0
Symptomatic cases	3	0.250	273	0.029	1	2
Health literacy	2	0.250	224	0.017	1	1
Visit to a healthcare facility	4	0.296	255	0.057	3	1
Enough and well trained healthcare-workers	1	0.233	0	0.004	0	1
Adherence to prescription protocol	2	0.273	9	0.008	1	1
Diagnosis (anamnesis and blood analysis)	3	0.333	239	0.060	2	1
Drug prescription	3	**0.381**	205	0.056	1	2
Compliance with the treatment	2	0.222	61	0.028	1	1
Satisfaction with the treatment	2	0.242	27	0.028	1	1
Trust in the healthcare system	3	0.267	47	0.043	2	1
Inadequate utilization of the medication	2	0.267	68	0.028	1	1
Increase in Plasmodium resistance to drug	4	0.296	61	0.034	2	2
Alternative medicine	2	0.000	0	0.031	2	0
Subsidy and availability on the preventive and curative malaria measures	2	0.236	0	0.004	0	2
Self-medication	3	0.250	18	0.007	2	1

degree (K), in-degree (K^{in}), out-degree (K^{out}), PageRank (x), closeness (C), and betweenness (B); Values in bold represent the higher value of centrality

4.4. Discussion

4.4.1. System model of malaria transmission and persistence in Accra

We found that the most central determinants also standing for the leverage points of the system, aside from the environmental-related ones, are those resulting from the citizens' *awareness of malaria infection risks*, and *household income,* and derived empowerment. These findings corroborate earlier studies that showed that poor-income households are more vulnerable to the disease, by facing a double burden: Malaria hotspots in Accra are in economically deprived communities, where malaria infection risk is additionally fueled by the economic needs, leading to community members to take up jobs that increase their exposure (Fobil et al. 2012); and, poor-income households spend relatively more of their earnings on the treatment of malaria than the higher-income ones (Chuma et al. 2006).

Our results also stress the importance of an efficient healthcare system, a structural issue in most countries of the Global South. We found particularly relevant the *trust in the healthcare system*, which can be reinforced through *training and supervision of health workers* on malaria diagnosis and treatment-related protocols, and the *adherence of the health workers* to it. Supporting this, a system dynamics simulation on policies for improving neonatal health in Uganda demonstrated that the workload of healthcare workers affects the development of trust of patients, especially when it leads to long waiting times for attention (Rwashana Semwanga et al. 2016). Likewise, a study in England and Wales revealed that the reduction of waiting time built the trust of patients and enhanced healthcare efficiency (Calnan and Sanford 2004). On the other hand, the *non-adherence to the prescription and treatment protocols* by health workers can lead communities to underestimate malaria infection and increase its effects, which augments the distrust in the health system.

Relatedly, we found that the *subsidy on anti-malaria drugs* instead of promoting a more holistic public health policy contributes to *patients' self-medication* (Winstanley et al. 2004), highlighting the sometimes counterproductive effects of a sole focus of public health programs on biomedical policies as this ignores the complexity of malaria transmission (Haynes et al. 2020). Previous research showed that patients' self-medication leads to arbitrary dosage and posology of anti-malaria drugs, and tends to exacerbate the symptoms and augments the morbidity and mortality of malaria (Awuah et al. 2018). Such situations are worse in poor-income households, where people often self-medicate with inadequate or counterfeit drugs, and/or inappropriate dosages and posologies at the onset of malaria symptoms (Winstanley et al. 2004).

Humans can be infected with *P. falciparum* and be symptomatic or asymptomatic. The latter is most often undiagnosed because random testing of the population is costly (Sturrock et al. 2013). Besides, the conventional rapid diagnostic test is not sensitive enough to allow efficient screening of low-level parasitemia observed in asymptomatic infections (Yeung et al. 2020). This contributes to feeding a permanent human reservoir of *P. falciparum* and thereby contributing to the persistence of malaria (Tao et al. 2019). Also, imported cases by human migration amplify the number of cases in cities and at times can initiate the resurgence of malaria in locations where it had been previously under control (Martens and Hall 2000; Buckee et al. 2013).

Our findings also suggest that deficient urban sanitation and poor urban planning increase the number of mosquito breeding sites. About 10% of *Anopheles* mosquito breeding sites in Accra are situated around construction sites (Mattah et al. 2017). Similar observations were made in Nigeria and Tanzania, where clogged gutters and sewage channels are playing similar roles (Adeleke et al. 2008). Thus, the ecology- and behavior-related adaptations of the mosquitoes delay control and make such efforts less effective, thereby contributing to the persistence of malaria in cities (Wilke et al. 2019).

4.4.2. Emergent properties of malaria transmission

The *small-world* and *scale-free* properties that feature our CLD indicate that the network is resilient and the identified leverage points could help to set more adequate policy recommendations.

The functional analysis of the network allowed to identify the determinants of the more central standing for potential intervention points such as causal, impacted, spreader, mediator, and influential, and derive from them key leverage points. Thus, we found that the determinant i) the *malaria-positive cases* was both, the most influential and the greatest mediator; and ii) the *number of breeding sites* had the larger effects. These findings align with a recent review of malaria determinants for sub-Saharan Africa (De Silva and Marshall 2012) that highlights the surge of infection as an intricate interplay between mosquitoes, humans, and their environments. Furthermore, i) the *drug prescription* was the determinant with the highest closeness centrality, and ii) the *householders' awareness and decision-making on malaria infection risk* the most important cause. This indicates that malaria transmission and persistence rely heavily on human behavior, which opens opportunities for more targeted policy action.

The CLD was able to disclose the interactions among malaria determinants and also permitted to track the causal links among them that preserve transmission and the feedback loops that reinforce certain sets of determinants (Rickles et al. 2007), which permits signaling emerging properties of the system post the NA (Ahn et al. 2006).

4.4.3. Limitations of the study

The CLD is a systemic tool capable to depict how determinants are interconnected. In our case, the CLD has been collectively built enabling the generation of a group thinking model (Purwanto et al. 2019). As such, CLD may preclude its replicability and reproducibility because the model is contingent on the experts' perception of the system. Therefore, for the same problem, more determinants can be always identified. Thus, the CLD is an over-simplification of the real-world system. Nonetheless, Richardson (Richardson 1986) argues that CLD still contains information that could be further transferred to the decision-makers as it is meant to embody the premises underpinning the functioning of the system (Schaffernicht 2010).

On the other hand, CLD is described as a qualitative and often perception-based model that should be read as a causal-effect model (Sterman 2000). As such it is based on a set of qualitative interviews, workshops, or qualitative reviews. For instance, it has been used to document the interplay between factors that lead to childhood obesity in the US (Allender et al. 2015), to display the obesity-related behavior in youth (Waterlander et al. 2021), and to highlight a pathway for the prevention and the response to covid-19 (Bradley et al. 2020). Since the CLD is not sustained by empirical observations (Sterman 2000), it leaves room to question the causal inferences drawn from its interpretation. Nonetheless, we trust this study shed light on potential avenues for forthcoming empirical test the causality among the determinants of the transmission and persistence of malaria in Accra and other urban settings.

The validation of the topology of a network is often carried out through structural modifications of the network using random addition and removal of nodes and edges (Narayanam and Narahari 2009; Zitnik et al. 2019; Stadtfeld et al. 2020). This operation allows displaying the resilience of the network (Zitnik et al. 2019). It has been extensively used in social networks and protein network analyses to validate the most important nodes (after re-computation of the centrality metrics) without ruining the underlining problem of friendship building or elaboration of proteins. However, as our CLD is a thematic network, a structural modification of the network will also lead to a functional change of the network deviating from the identification of the leverage point of a system of transmission and persistence of malaria in Accra. Nonetheless, the calculation of the metrics combined with the properties of the network enables the identification of potential strategies that may guide policy recommendations for better control of malaria.

4.5. Conclusions

The proposed CLD contributed to illustrating the complexity of malaria transmission and persistence in our case study, Accra, Ghana. It showed that beyond the mere biological processes and the physical environment, the behavior of people plays a key role in malaria transmission and persistence. The CLD embodies three major loops that trigger and maintain transmissions in urban environments. Furthermore, the NA enabled the detection of emergent properties of the system and the identification of the key levering determinants. Besides, the topology disclosed by the CLD revealed that all leverage points need to be accounted for strategic policy development. Hence, major efforts toward preventing malaria transmission are needed, and on that, the key priorities should be: to reduce malaria persistence by reducing mosquito density, for instance, through the regular drainage of gutters or treating breeding sites with larvicides; and reducing infections by increasing the awareness of city dwellers on malaria literacy, for instance, through regular campaigns in deprived communities, both, on the field and social media. Ongoing measures, like, protecting windows and doors with mosquito-proof netting and the use of ITNs, should be intensified. Besides, an improvement of the healthcare system through regular training of the healthcare workers in malaria can enhance trust in the healthcare system and limit the risk of patients' non-compliance to malaria-drugs prescription.

5. MATHEMATICAL MODELING OF SPATIAL-DEMOGRAPHIC HETEROGENEITY IN URBAN MALARIA EPIDEMICS TO ASSESS THE IMPACT OF INSECTICIDE-TREATED BED-NETS IN ACCRA, GHANA[3]

5.1. Introduction

The female mosquito is considered to be the deadliest animal since it is responsible for more than 1,000,000 deaths per year (Prudêncio 2020). As such, mosquitoes are the carrier of the pathogens of several infectious diseases including Chikungunya, Zika, Dengue, West Nile, Yellow fever, filariasis, and malaria, the latter being the leading cause of mortality and morbidity in sub-Saharan Africa (SSA). In 2019, the SSA fatality of malaria was estimated at 384,000 deaths representing a decrease of 67% compared to the early 2000s (World Health organization 2020). This milestone resulted from the use of preventive measures such as i) indoor residual spraying (IRS), ii) the distribution and use of insecticide-treated bed-nets (ITNs), and curative therapy, i.e., Arthemisin-based Combination Therapy (ACT). However, with the surge of the global pandemic of COVID 19 in January 2020, caused by SARS-CoV-2 (Senghore et al. 2020), there was a disruption in the malaria control programs, affecting the use of these preventive measures namely the free distribution of ITNs. Evidence suggested that this disruption will exacerbate malaria-induced death in SSA as was observed during the surge and resurgence of Ebola in West Africa in 2017 (World Health Organization 2020; Sherrard-Smith et al. 2020; Aborode et al. 2021). Likewise, the fatality induced caused by malaria so far exceeded the one of COVID 19 in SSA and could possibly double compared to the number of 2019 if ITNs distribution campaigns are halted (World Health organization 2020). Consequently, the costs for the preventive measures will also be higher than in 2019 (White et al. 2011; Wisniewski et al. 2020).

ITNs are the most prominent malaria preventive intervention whose widespread adoption resulted in an unprecedented level of control of malaria vectors and a substantial decrease in *Plasmodium* parasitemia in SSA (Lengeler 2004; Lim et al. 2011). Impregnated with pyrethroids, ITNs kill and repel mosquitoes with little to no

[3]A slightly modified version of this manuscript will be submitted with Merveille Koissi Savi , Lauren M. Childs , Christian Borgemeister

toxicity to mammals, and are considered cost-effective (Lengeler 2004; Koenker et al. 2018). Despite the huge effort of the Roll Back Malaria initiative to attain the universal ITNs coverage of 80%, today still less than 2% of children sleep under fully functioning ITNs in SSA (Yamey 2004; Lim et al. 2011). This is due to their loss of physical and/ or chemical integrity, their repurposing, being moved out of the target areas, and other human behavior (Ngonghala et al. 2014; Scates et al. 2020). For instance, according to studies from the Coastal region in Ghana, including the capital Accra, between 20% and 40% of people who possess ITNs do not sleep under them. The reasons for the reluctance of use are related to human behavior that is often undermined in the planning and management of the free distribution campaigns (Elder et al. 2011; Ahorlu et al. 2019).

Mathematical models have been widely used to obtain insights into the dynamics of malaria (Ross 1902, 1911b; Macdonald 1950). They have played a valuable role in documenting policy for disease management (Heesterbeek et al. 2015). As such they have been used to design strategies of vector control (Ross 1911a), define vaccination threshold (McLean and Anderson 1988), and evaluate the effectiveness of ITNs (Bhatt et al. 2015). Since Ross's (1911a) susceptible-infected-recovered ordinary differential equations (ODE) model, mathematical models describing malaria have steadily evolved in complexity. This has led to accuracy in the predictability of the model when more data becomes available (Mandal et al. 2011). The increase of model complexity leans on the integration of spatial heterogeneity, i.e. patch models (Lutambi et al. 2013; Bichara and Iggidr 2018a), demographic heterogeneity, i.e., age structure model (Aron and May 1982; Yan et al. 2015), host genetic heterogeneity (Gupta et al. 1994; RodrÍguez and Torres-Sorando 2001), and acquired immunity (Aron 1988; Filipe et al. 2007). An important metric allowing to measure the persistence of the disease is the basic reproduction number (R_0) representing the number of secondary infections produced by a single infected host in an immunologically naïve population. When $R_0<1$ the epidemic will die out whereas the epidemic will persist when $R_0>1$. Thus R_0 assesses the magnitude of the disease and guides the effort for its control (Heesterbeek and Dietz 1996).

Previous mathematical studies assessed the impact of ITNs on the dynamics of the disease and predicted a globally stable mosquito-free equilibrium when $R_0<1$ with a constant rate of ITNs usage underestimating the magnitude of the disease (Ngonghala et al. 2016). In a heterogeneous host population, the increase of ITNs coverage causes a decrease in the proportion of host-seeking mosquitoes, benefiting both the ITN users and the non-users (Chitnis et al. 2009). While comparing different malaria control measures using the ODEs framework, Chitnis et al. (2010) concluded that the ITNs are more effective than the IRS. Okumu et al. (2013) showed that the protection against a malaria infection depends more on individual protection than the efficacy of the ITNs and the IRS. Most of the models implicitly associated the coverage rate, i.e., possession, with the use of ITNs at a constant rate, thus, failing to consider the heterogeneity in the use, leading to an overestimation of ITNs' effectiveness (Killeen et al. 2007; Killeen and Smith 2007; Gu and Novak 2009; Govella et al. 2010; Okumu et al. 2013; Agusto et al. 2013; Briët et al. 2013). In Ngonghala et al. (2014) study, the ODEs quantified the impact of physical and chemical decay in ITNs, however, the authors failed to consider both the spatial and demographical heterogeneity in the host population. Human behavior can have a significant impact on the dynamics of the disease. This effect can be beneficial. For example, Funk et al. (2009) demonstrated that increased awareness in communities can reduce the spread of infectious diseases or hinder the control of the epidemics, for the latter for example the social scare of vaccines could exacerbate the spread of an infectious disease (Oraby et al. 2014). Likewise, it was theorized that host behavior can impact the effect of ITNs and hence there is a need to embody human behavior for a more realistic assessment of ITNs use for malaria control (Agusto et al. 2013). So far only a few studies have embedded human behavior in mechanistic frameworks to assess the effectiveness of ITNs.

In the present study, we provide empirical evidence of human behavior and how the misrepresentation in modeling can hinder the control of malaria after surveying two communities in Accra's malaria hotspot. We developed a patch and age-structured model i.e., an extended susceptible-infected-recovered-susceptible – susceptible-infected (SIRS-SI) model. The rationale for developing such a model lies in i) previous studies that revealed spatial heterogeneity in malaria incidence in Accra with high levels in poorly managed areas (Fobil et al. 2012) and ii) the fact that the incidence rate of malaria in Accra is highly heterogeneous in Accra with the respect to the demographic structure of the population (Frank et al. 2016). We integrated the empirical findings into a mechanistic model to mimic the misrepresentation of community behavior to assess the effectiveness of ITNs.

5.2. Method

5.2.1. Study area

Accra is located in the Greater Accra Metropolitan Area (GAMA), which stretches between 5° 28' N to 5°52' N and 0° 32' W to 0°02' E. It is one of the fastest-growing cities in Western African with an annual population growth rate of 3.1% (GSS 2013). GAMA is a densely populated area with 1,236 people per km^2. Accra is the main administrative and economic center of Ghana with 69.7% of the national private informal workforce employment, 15% of the private formal, 12.8% of the public, and 2.2% of other workforce employed in 2008 (GSS 2008).

The rapid urbanization in Accra generated an increase in the price of affordable accommodation, compelling 15% of Accra's population to live in informal settlements, i.e., poorly managed areas and slums (UN-Habitat Ghana 2009). Accra is facing a heavy burden of malaria, driven by the fast-growing population density, especially in the deprived community areas. The mortality and morbidity of malaria remain high in such neighborhoods, for instance in Korle-Dudor and James Town (Fobil et al. 2012; Austin 2015).

The James Town community is a poorly managed area designed by the Accra Metropolitan Assembly as a tenure-secured slum (Tutu et al. 2017). Accounting for an averagely of 8.5 occupants per room, this community is facing serious sanitation problems underpinned by public garbage disposal (Awuah et al. 2014; Tutu et al. 2017). The Korle-Dudor community exhibits some characteristics of a slum such as the self-made drains and the inexistence of the tared roads (Awuah et al. 2018). Korle-Dudor is populated mainly by migrants coming from all parts of Ghana and who often work in the informal sector.

Since 2007, Ghana has initiated a policy of extensive and free distribution of insecticide-treated bed nets (ITNs) that has reached a coverage rate of 85% in 2017 (Awine et al. 2017). However, the expected reduction of malaria incidence due to the implementation of the ITNs distribution policy is still far below the predictions.

5.2.2. Community survey

To assess the perception of malaria in an urban setting such as Accra, we surveyed the two poorly urbanized communities (James Town and Korle-Dudor). Prior to that, in August 2018, we identified gatekeepers and community leaders. The community entry and the identification of the gatekeepers granted support to conduct a cross-sectional household survey from January to February 2019. Twenty enumeration areas were randomly selected out of a total of 53 in the two communities. Following the randomized selection of the enumeration areas, the data collection team proceeded to perform a detailed enumeration of the households in each of the 20 enumeration areas. We randomly selected 1,200 households for a cross-sectional in-depth interview. Out of the selected households, we obtained a response rate of 85.67% that represented 1,028 households that participated in the survey. Within each household, we applied Kish criteria (Kish 1949) considering that any resident of a given household who was between 18 to 82 years old and who had spent at least the last six months in the household has good knowledge of the disease situations. Therefore, regardless of gender, any member of the household > 17 years had a chance to participate in the study on behalf of the household.

5.2.3. Statistical analysis

Community perception was assessed based on the general knowledge about malaria, the care-seeking behavior as well as the assessment of the risk factors of ITNs use. Descriptive statistics were used to assess the general knowledge assessment as well as health-seeking behaviors. We ran two generalized linear models to assess i) the relationship between the use and ownership of ITNs, and ii) the determinants of ITNs use.

To assess the relationship between use and ownership of ITNs, we regressed the number of households who used the ITNs against the possession of ITNs. We estimated the probability value of the statistics using 1,000 Monte Carlo permutations of Poisson regression. Robust standard errors were used for parameters estimation to control for over-dispersion around the mean as suggested by Cameron and Trivedi (2009). The goodness of fit of the model was substantiated using a chi-square test.

We applied the same procedure to explain the determinants of ITNs use with the help of logistic regression. The reasons for the non-use of ITNs were analyzed by means of descriptive statistics.

5.2.4. Mathematic model formulation and assumptions

We developed a SIRS-SI model incorporating both patches and the age structure of the population. The SIRS structure for each age group of the host population is located in each patch and SI structure for the population of mosquitoes within each patch. We assumed that depending on the disease state and the spatial location, the total population of humans in a patch j is N_j^H and the total *An. gambiae* in the same patch (which is the main mosquito species transmitting malaria in Accra) population is N_j^V. The total populations of both humans and mosquitoes are arbitrarily structured in v patches. In addition, within the hosts' population, there are interactions among i age groups. Thus, we are accounting for both spatial and group heterogeneity as suggested by Bichara and Iggidr (Bichara and Iggidr 2018a). We assumed that the risk of getting infected depends on the location. For instance, the exposure risk to malaria is higher in slums and poorly managed areas than in standard and well-managed areas (Fobil et al. 2012). We also assumed the migration rate m_{ij} between patches is serological status specific. Thus, susceptible and removed compartments can freely move from one patch to another whereas the infected compartment has reduced the mobility that tends to 0 with the duration of the disease ($\lim_{t \to \infty} m_{ij} = 0$). As a patch represents the location where an individual spend the majority of the time, we assumed that the likelihood of an individual to spend a long time in a patch that is not where she/he lives is very low. At a time t the population of a given human group j ($i = 1, \dots, u$), is structured into susceptible (S_j^H), infected (I_j^H) and recovered with partial immunity (R_j^H), while the population of mosquitoes was divided into susceptible (S_j^V) and infected (I_j^V).

The model assumed that: a) there is no incubation period prior to potential transmission; b) every infectious person is symptomatic; c) the life span of the mosquito is so short that they are unable to recover from their infection before they die and ; d) the group of humans and mosquitoes spend the maximum time in their respective patch, $(j = 1, \ldots, v)$. The total human population N_j^H in a patch j at the time t is

$$N_j^H = S_j^H + I_j^H + R_j^H$$

Similarly, the total population of mosquitoes N_j^V at this same time t is

$$N_j^V = S_j^V + I_j^V$$

β_i is the risk of malaria infection for the group i, γ_i is the recovery rate of the infectious individuals of the same group, Λ_i^H as the recruitment rate of the susceptible human population. μ_i^H is the natural mortality rate, and σ_i the rate of immunity lost. The remaining parameters of the model are described below (Table 5.1) and the interactions between humans and mosquitoes are represented in the flow diagram (Fig. 5.1).

Table 5 1: Descriptions, ranges of values of parameters for the malaria model Eq. (5.1)

Parameters	Description	Range	Unit	References
Λ_i^H	Recruitment rate of each group	0.000001-6.438356e-05	day^{-1}	(GSS 2013; Awine and Silal 2020)
β_i^H	Probability of transmission from infected human group	0.1-0.24	day^{-1}	(Smith et al. 2012)
μ_i^H	Natural death rate of each human group	1/63.48*365-23.5/1000	day^{-1}	(GSS 2013; Awine and Silal 2020)
δ_i^H	Malaria-induced death rate of each group	0.000174-0.00035	day^{-1}	(Forouzannia and Gumel
σ_i^H	Proportion of getting immune of each human group	5.5/52	-	(Awine and Silal 2020)
Λ^V	Recruitment rate of mosquitoes	0.35-0.5	day^{-1}	Estimated
μ^V	Death rate of mosquitoes	0.1	day^{-1}	Estimated
γ_i^H	Recovery rate of each human group	0.00274	day^{-1}	(Nakul et al. 2006)

β^V	Probability of transmission from infected mosquitoes	0.024	-	(Chitnis et al. 2009)
ψ_i^H	Function of ITNs use	-	-	Estimated
ζ	Efficacy of ITNs	0.398	-	(Awine and Silal 2020)
a	Biting rate of mosquitoes	0.35-0.5	day^{-1}	(Forouzannia
m_{ij}	Migration rate of the human group i between patches j	-	day^{-1}	Estimated

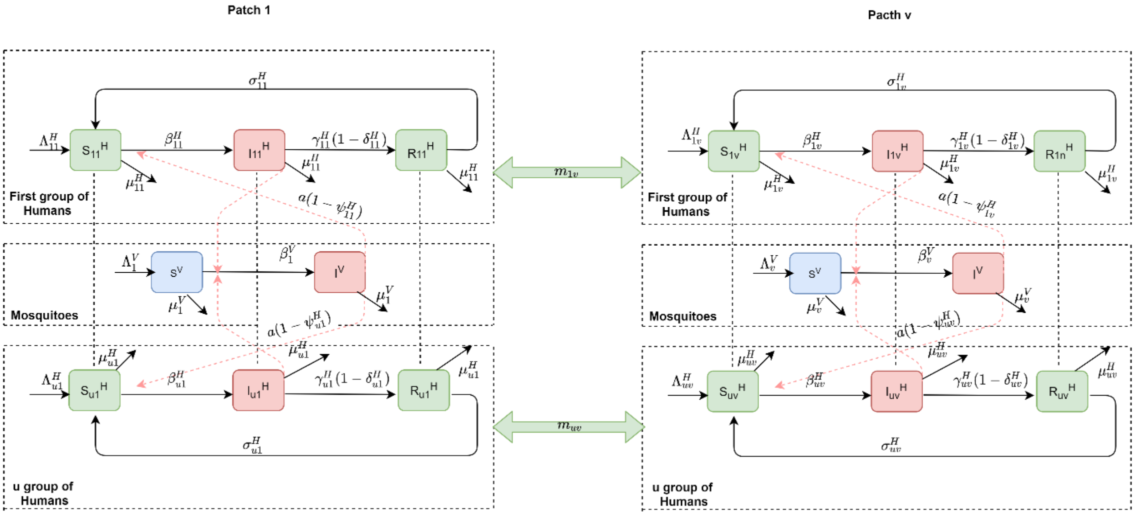


Fig.5. 1: Flow diagram of patch model of malaria. In green, the human compartments move from one patch to another, in red the compartment of infectious humans and mosquitoes; in blue the compartment of susceptible mosquitoes move freely within their specific patch. The dotted red arrows represent the interaction between humans-mosquitoes while the plain arrows show the flow from one compartment to another.

The interactions between hosts and vectors within patches j are described by the following system of non-linear ordinary differential equations:

$$(5.1)\begin{cases}\frac{dS_j^H}{dt} = \Lambda_j^H - \frac{\beta_j^V a\left(1-\zeta\psi_j^H\right)I_j^v(t)}{N_j^H} S_j^H + \sigma_j^H R_j^H - \mu_j^H S_j^H + \sum_{j=1}^{v} m_{ij} S_i^H \\ \frac{dI_j^H}{dt} = \frac{\beta_j^V a\left(1-\zeta\psi_j^H\right)I_j^v}{N_j^H} S_j^H - \left(\gamma_j^H + \mu_j^H + \delta_j^H\right)I_j^H \\ \frac{dR_j^H}{dt} = \gamma_j^H I_j^H - \left(\mu_j^H + \sigma_j^H\right)R_j^H + \sum_{j=1}^{v} m_{ij} R_i^H \\ \frac{dS_j^V}{dt} = \Lambda_j^V - \mu_j^V S_j^V - \frac{\beta_j^H I_j^H a\left(1-\zeta\psi_{ij}^H\right)}{N_j^H} S_j^V - \zeta\psi_j^H a S_j^V \\ \frac{dI_j^V}{dt} = \frac{\beta_j^H I_j^H a\left(1-\zeta\psi_{ij}^H\right)}{N_j^H} S_j^V - \zeta\psi_j^H a I_j^V - \mu_j^V I_j^V \end{cases}$$

Where $\Lambda_j^H = \sum_i^v \Lambda_{ij}$, $\psi_j^H = \sum_i^v \psi_{ij}^H$, $\sigma_j^H = \sum_i^v \sigma_{ij}^H$, $\mu_j^H = \sum_i^v \mu_{ij}^H$, $\beta_j^H = \sum_i^v \beta_{ij}^H$, $\gamma_j = \sum_i^v \gamma_{ij}$, $\sigma_j = \sum_i^v \sigma_{ij}$, $S_j^H = \sum_i^v S_i^H$, $I_j^H = \sum_i^v I_i^H$, $R_j^H = \sum_i^v R_i^H$,

When the rate of change in human and mosquitoes are zero in a patch j ($\frac{dN_j^H}{dt} = 0, \frac{dN_j^V}{dt} = 0$) we can see that $N_j^H = \frac{\Lambda_j^H}{\mu_j^H - \sum_j m_{ij}}$ and $N_j^V = \frac{\Lambda_j^V}{\mu_j^V + a\zeta\psi_j^H}$

5.2.5. Analysis of the model

Positivity and boundedness of solutions

The biological interest of the previous system of nonlinear ODE (Eq.5.1) admit its solutions in a set denoted Ω and defined as follow

$$\Omega = \left\{\left(S_j^H, I_j^H, R_j^H, S_j^V, I_j^V\right) \in \mathbb{R}_+^{5v} \mid S_j^H + I_j^H + R_j^H \le 1, S_j^V + I_j^V \le 1\right\}$$

At a steady-state, the disease-free equilibrium (DFE) of the model in patch j is given by $\varepsilon_0 = \left(\frac{\Lambda_j^H}{\mu_j^H - \sum_j m_{ij}}, 0,0, \frac{\Lambda_j^V}{\mu_j^V + \psi_j a}, 0\right)$.

Using the next-generation method (van den Driessche 2017) we calculated the reproduction number of the system (Eq. 5.1).

The system (Eq. 5.1) has two infected states, I_j^H and I_j^V and three uninfected states S_j^H, R_j^H and S_j^V. At a steady-state $S_j^H = N_j^H$ and $S_j^V = N_j^V$ and DFE of the model is given by $\varepsilon_0 = \left(\frac{\Lambda_j^H}{\mu_j^H - \sum_j m_{ij}}, 0,0, \frac{\Lambda_j^V}{\mu_j^V + \zeta\psi_j a}, 0\right)$. The linearized infected compartments

$$\frac{dI_j^H}{dt} = \beta_j^V a\left(1 - \zeta\psi_j^H\right)I_j^v(t) - \left(\gamma_j^H + \mu_j^H + \delta_j^H\right)I_j^H$$

$$\frac{dI_j^V}{dt} = \frac{\beta_j^H \Lambda_j^V\, a\left(1 - \zeta\psi_{ij}^H\right)\left(\mu_j^H - \sum_j m_{ij}\right)}{\Lambda_j^H\left(\mu_j^V + a\zeta\psi_j^H\right)} I_j^H - \left(\zeta\psi_j^H a + \mu_j^V\right)I_j^V$$

The nonlinear terms with new infection $\mathcal{F}$ and the outflow term $\mathcal{V}$ are given by

$$\mathcal{F} = \begin{pmatrix} \beta_j^V a\left(1-\zeta\psi_j^H\right) I_j^v \\ \frac{\beta_j^H \Lambda_j^V a\left(1-\zeta\psi_{ij}^H\right)\left(\mu_j^H - \sum_j m_{ij}\right)}{\Lambda_j^H \left(\mu_j^V + a\zeta\psi_j^H\right)} I_j^H \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} \left(\gamma_j^H + \mu_j^H + \delta_j^H\right) I_j^H \\ \left(\zeta\psi_j^H a + \mu_j^V\right) I_j^V \end{pmatrix}.$$

This gives the Jacobian matrices F and V at DFE

$$F = \begin{pmatrix} 0 & \frac{\beta_j^H \Lambda_j^V a\left(1-\zeta\psi_{ij}^H\right)\left(\mu_j^H - \sum_j m_{ij}\right)}{\Lambda_j^H \left(\mu_j^V + a\zeta\psi_j^H\right)} \\ \beta_j^V a\left(1-\zeta\psi_j^H\right) & 0 \end{pmatrix} \text{ and}$$

$$V = \begin{pmatrix} \zeta\psi_j^H a + \mu_j^V & 0 \\ 0 & \left(\gamma_j^H + \mu_j^H + \delta_j^H\right) \end{pmatrix}$$

Let us found the inverse of V (V^{-1}) since V is diagonal

$$V^{-1} = \begin{pmatrix} \frac{1}{a\zeta\psi_j^H + \mu_j^V} & 0 \\ 0 & \frac{1}{\left(\gamma_j^H + \mu_j^H + \delta_j^H\right)} \end{pmatrix}$$

Hence, the next generation matrix is given by

$$K = FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_j^H \Lambda_j^V a\left(1-\zeta\psi_j^H\right)\left(\mu_j^H - \sum_j m_{ij}\right)}{\Lambda_j^H \left(\mu_j^V + a\zeta\psi_j^H\right)\left(\gamma_j^H + \mu_j^H + \sigma_j^H\right)} \\ \frac{\beta_j^V a\left(1-\zeta\psi_j^H\right)}{\mu_j^V + a\zeta\psi_j^H} & 0 \end{pmatrix}$$

Given $|K - \lambda I| = 0$ we have

$$\lambda^2 = \frac{\beta_j^H a\left(1-\zeta\psi_j^H\right)\left(\mu_j^H - \sum_j m_{ij}\right)}{\Lambda_j^H \left(\mu_j^V + a\zeta\psi_j^H\right)\left(\gamma_j^H + \mu_j^H + \sigma_j^H\right)} \times \frac{\beta_j^V a\left(1-\zeta\psi_j^H\right)}{\mu_j^V + a\zeta\psi_j^H}$$

Accordingly, the reproduction number is given by

$$\mathcal{R}_0^{NG} = \sqrt{\left(\frac{\beta_j^H a\left(1-\zeta\psi_j^H\right)\left(\mu_j^H - \sum_j m_{ij}\right)}{\Lambda_j^H \left(\gamma_j^H + \mu_j^H + \delta_j^H\right)} \times \frac{\beta_j^V \Lambda_j^V a\left(1-\zeta\psi_j^H\right)}{\left(\mu_j^V + a\zeta\psi_j^H\right)^2}\right)}$$

We can proceed to the study of the local stability of the DFE. The Jacobian of the system (Eq. 5.1) at the DFE is given by

$$J =$$

$$\begin{pmatrix} -\mu_j^H + m_j & 0 & \sigma_j^H & 0 & -\frac{\beta_j^V a\left(1-\zeta\psi_{ij}^H\right)}{N_j^H} S_j^{H*} \\ 0 & -\left(\gamma_j^H + \mu_j^H + \delta_j^H\right) & 0 & 0 & \frac{\beta_j^V a\left(1-\zeta\psi_{ij}^H\right)}{N_j^H} S_j^{H*} \\ 0 & \gamma_{ij}^H & \sum_j m_{ij} - \left(\mu_{ij}^H + \sigma_j^H\right) & 0 & 0 \\ 0 & -\frac{\beta_j^H a\left(1-\zeta\psi_j^H\right)}{N_j^H} S_J^{V*} & 0 & -\left(\mu_j^V + a\zeta\psi_j^H\right) & 0 \\ 0 & -\frac{\beta_j^H a\left(1-\zeta\psi_j^H\right)}{N_j^H} S_J^{V*} & 0 & 0 & -a\zeta\psi_j^H - \mu_j^V \end{pmatrix}$$

Where $S_{ij}^{H*} = \frac{\Lambda_j^H}{\mu_j^H - \sum_j m_{ij}}, S_J^{V*} = \frac{\Lambda_j^V}{\mu_j^V + \zeta\psi_j^H}$.

The three first eigenvalues of J are obtained using the Laplace expansion (Poole 2005) of J. We can see that $\lambda_1 = -\mu_j^H + \sum_j m_{ij}$, $\lambda_2 = \sum_j m_{ij} - (\sigma_j^H + \mu_j^H)$ and $\lambda_3 = \mu_j^V + a\zeta\psi_j^H$ Thus, the two remainings are given by the matrix J_1

$$J_1 = \begin{pmatrix} -(\gamma_j^H + \mu_j^H + \delta_j^H) & \frac{\beta_j^V a(1-\zeta\psi_j^H)}{N_j^H} S_J^{H*} \\ \frac{\beta_j^H a(1-\zeta\psi_j^H)}{N_j^H} S_J^{V*} & -a\zeta\psi_{ij}^H - \mu_j^V \end{pmatrix}$$

The determinant of J_1 gives the quadratic function denoted P

$$P = \lambda^2 + \lambda A + B$$

With $A = a\zeta\psi_j^H + \sigma_j^H + \mu_j^H + \mu_j^V + \gamma_j^H$

$$B = (\gamma_j^H + \mu_j^H + \sigma_j^H)(a\zeta\psi_j^H + \mu_j^V) - \beta_j^V a(1-\zeta\psi_j^H) \times \beta_j^H a(1-\zeta\psi_j^H) \times \frac{\Lambda_j^V}{(\mu_j^V + a\zeta\psi_j^H)} \times \frac{\mu_j^H - \sum_j m_{ij}}{\Lambda_j^H}$$

Theorem *If $\mathcal{R}_0 > 1$ the DFE is unstable and $P(\lambda) = 0$ has a real positive zero since $B < 0$ and $\lim_{\lambda\to\infty} P(\lambda) = \infty$; if $\mathcal{R}_0 < 1$ implies that the DFE is locally asymptotically stable and $P(\lambda) = 0$ has only negative*

Proof. Let prove using the Routh-Hurwitz stability criteria (Routh 1877; Hurwitz 1895)

$$\mathcal{R}_0 < 1 \leftrightarrow B > 0$$

$B > 0 \rightarrow (\gamma_j^H + \mu_j^H + \sigma_j^H) > \beta_j^V \beta_j^H a^2 (1-\zeta\psi_j^H)^2 \times \frac{\mu_j^H - \sum_j m_{ij}}{\Lambda_j^H} \times \frac{\Lambda_j^V}{(\mu_j^V + a\zeta\psi_j^H)^2}$ (a)

And $\mu_j^V + a\zeta\psi_j^H < \mu_j^V + a\zeta\psi_j^H + 2\,(\mu_j^H + \gamma_j^H)$ (b). From the inequalities (a) and (b) we have $B > 0$. $A > 0$ as a sum of positive factors (c). From (c) we can conclude that the DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$.

5.2.6. Numerical simulations and scenarios

This model was parameterized using existing data from the literature, the population census of Ghana (2013), and the findings of the community survey (Table 5.1). Moreover, we used a model containing two age groups (juvenile and adults) and two patches (well-urbanized areas and slums) and developed three scenarios to account for misrepresentations in modeling and behavior.

i) The parameter ψ_i^H is considered a constant in the two patches with the condition $\psi_1^H \ll \psi_2^H$ with ψ_1^H standing for the rate of ITNs in the well-urbanized areas, and ψ_2^H in the slum and poorly managed areas;

ii) ψ_i^H stands for a linear association between ownership and uptake where the slope is higher in the well-urbanized areas.

ii) ψ_i^H is decreasing over time, assuming that the ITNs have an exponential decay rate given by f $(\psi_j^H) = \psi_j^H exp^{-\lambda_j t}$, (where λ_j represents the rate of physical and (or) chemical decay of the ITNs in patches with the decay rate higher in the slums j). Scenario i) and ii) account for the common misconceptions whereas iii) stand for behavior toward the use of ITNs.

We quantified the magnitude of the misrepresentation through the computation of the relative error using the basic reproduction rate of the baseline (i.e., constant and homogeneous uptake of ITNs regardless of the patch) as the gold standard of comparison.

5.2.7. Global uncertainty and Sensitivity analyses

A sensitivity analysis was performed, using the Latin Hyper-cube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC) techniques to evaluate the critical inputs (parameters and initial conditions) of the model and quantify how uncertainty impacts the reproductive number of the system (Eq. 5.1) (Marino et al. 2008). More specifically, we performed the analysis on 12 parameters and assessed their influence on the R_0. All the parameters are assumed following uniform distribution and partitioned into 100 equi-probable subintervals.

5.3. Results

5.3.1. Empirical evidence of good knowledge on malaria and its risks

In the two surveyed communities, malaria is perceived as the major threat to health (Suppl. Fig. 1) suggesting that the risk of malaria infection is well perceived. In addition, the major raining season was identified as a critical period of the year where the incidence of malaria is higher (Suppl. Fig.2). These findings corroborated previous studies that showed that from May to June, corresponding to the major raining period (Awine et al. 2018).

To prevent malaria infections, the communities from James Town and Korle-Dudor, primarily used ITNs, followed by repellent coils and other alternative prevention methods (Suppl. Fig. 3). This suggests that the community members perceived ITNs as the most efficient way to prevent mosquito bites, which also implies that they have access to information on the disease.

The model of ITNs uptake is not statistically significant (residual deviance = 17.75675; df = 18 and p value= 0.472) indicating there is no evidence of a linear/ pseudo-linear relationship between ownership and the uptake of ITN across communities (Table 5.2). This finding highlights two major misrepresentations both by modelers and policymakers: i) the coverage rate of ITNs represents the uptake of ITN by communities and ii) the hypothesis of a linear or pseudo-linear relationship between ownership and uptake of ITNs. Furthermore, imposing a threshold of uptake in models is not justified. Overall, the uptake of ITN depends on other co-factors apart from share ownership.

Table 5 2: Relationship between ownership and use of the ITNs in James Town and Korle-Dudor communities of Accra, Ghana

	Estimate	Robust SE	Pr (>|z|)	LL	UL
(Intercept)	13.074	1.216	0.913	8.907	19.190
ITNs ownership	1.012	1.005	0.075	1.001	1.023

LL= Lower limit UL= Upper limit

The results of the logistic regression to assess the other co-factors favoring the use of ITNs revealed that the model with a logit link fit better than the other links and that the model is statically significant (logLik test= 7.069; pvalue= 0.99). Moreover, the variable "*Health checking the week before the survey*" turned out to be significant (Table 5.3). A unit increase in the number of times households checked their health status in the week before the survey increases the odds of ITN use by a factor of 1.53. These findings suggested that the reminding effect is very important to stimulate the use of ITNs and it also corroborates the notion that when people experience their relatives in the hospital they tend to take fewer malaria risks (Bernard et al. 2009). Thus, we can assume that education/ awareness, e.g. using the right channel (one-on-one conversation), can improve the uptake of ITNs in the communities like James Town and Korle-Dudor.

Table 5 3: Determinants of ITNs use

	Estimate	Std. Error	z value	Pr (>|z|)	LL	UL
(Intercept)	0.576	0.120	-4.586	4.52E-06	0.455	0.729
Proximity to a stagnant water	0.997	0.002	-1.581	0.1139	0.994	1.001
Per capita prevalence	1.218	0.126	1.563	0.118	0.951	1.564
Immediate care seeking	1.296	0.146	1.78	0.0751	0.974	1.726
Health check in the week before the survey	1.530	0.178	2.383	0.0172	1.078	2.171

Yet in total less than 40% of the people surveyed used ITNs. Six reasons explain their reluctance to use the ITNs, i.e., by order of importance, (i) heat generated overnight, (ii) lack of space, (iii) itchiness of nets, (iv) the impossibility/ difficulty to breathe properly while using the nets, (v) physical/ chemical decay of the nets, and (vi) repurposing of ITNs (Suppl. Fig. 4).

5.3.2. Magnitude of the epidemics

With a uniform ITNs coverage of 60% in every community in Accra regardless of their location and their age class, the epidemic will die out since the total R_0 is 0.80 with a lesser progression within the group of children (Table 5.4). Besides, due to the difference in parameters (ecological conditions) pre-existing in the two patches (well-urbanized versus surveyed communities i.e., poorly urbanized), in the poorly urbanized areas (mosquito-related parameter higher, Table 5.4), the disease will progress faster than in the well-urbanized areas (Fig. 5.1 A -D).

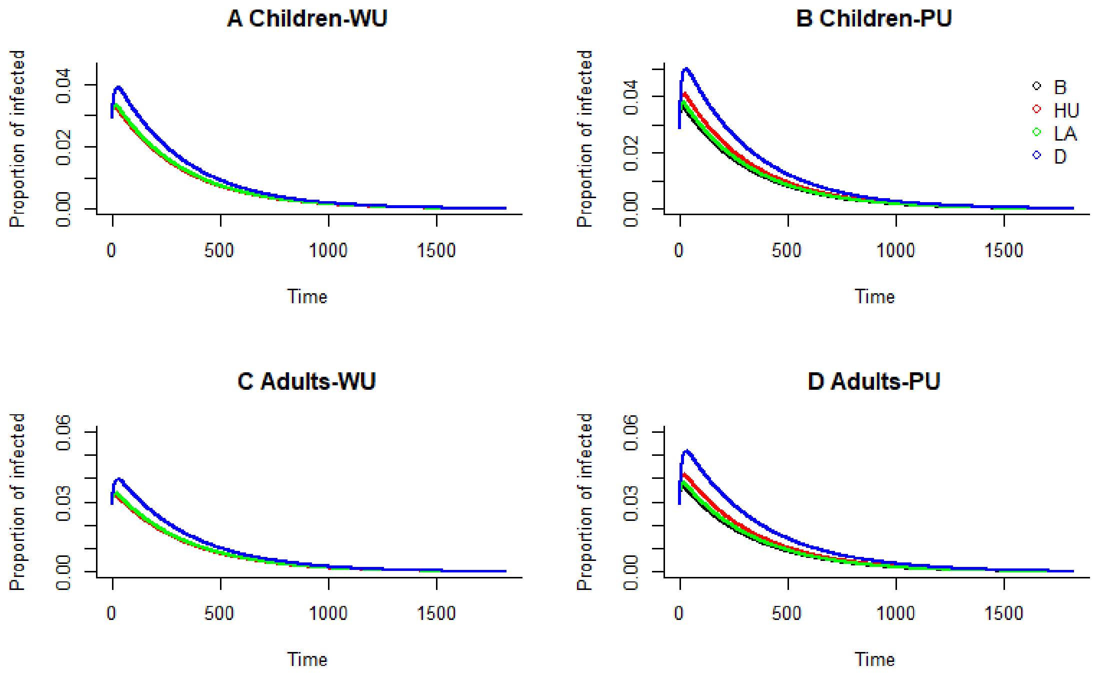


Fig.5. 2: Epidemiological curve showing the fraction of infected for baseline and the three others scenario. B, HU, LA, and D stand for baseline, heterogeneous use of ITN, Linear association between possession and use, and physical or chemical decay of ITN, respectively. WU and PU referred to well-urbanized and poorly-urbanized

With the heterogeneous uptake of ITNs (60% in well-urbanized patches and 30% in poorly urbanized areas), the R_0 increased and the epidemics persist (R_0=1.02). The disease progresses faster in poorly compared to well-urbanized areas (Table 5.4). As observed in the baseline, children record a slower progression of the disease compared to adults (Fig. 5.1A-D). Not considering the heterogeneity in ITN use (e.g. by policy-makers or modelers) results in a relative error of 28.19%.

When a linear association is made between the ownership and the use of ITNs with a heterogeneous uptake rate (80% in well- vs. 30% in poorly-urbanized areas) and homogeneous ownership of 60%, the epidemics progresses faster than both in the baseline and the heterogeneous coverage (Fig. 5.1 A-D) and the persist (R_0= 1.23).

Moreover, the highest progression is observed in poorly urbanized areas. The relative error, while not considering a threshold of use, is 55.23%

When a physical decay is integrated into the model, the epidemics persist (R_0= 2.10; Table 5.4) with the highest records among adults living in poorly urbanized areas. Regardless of the scenario used we observed that both in well- and poorly-urbanized areas, fewer children than adults are infected (Fig.5.1 A-D). The relative error, while undermining the behavioral effect i.e., decay, is 163.68 (Table 5.4).

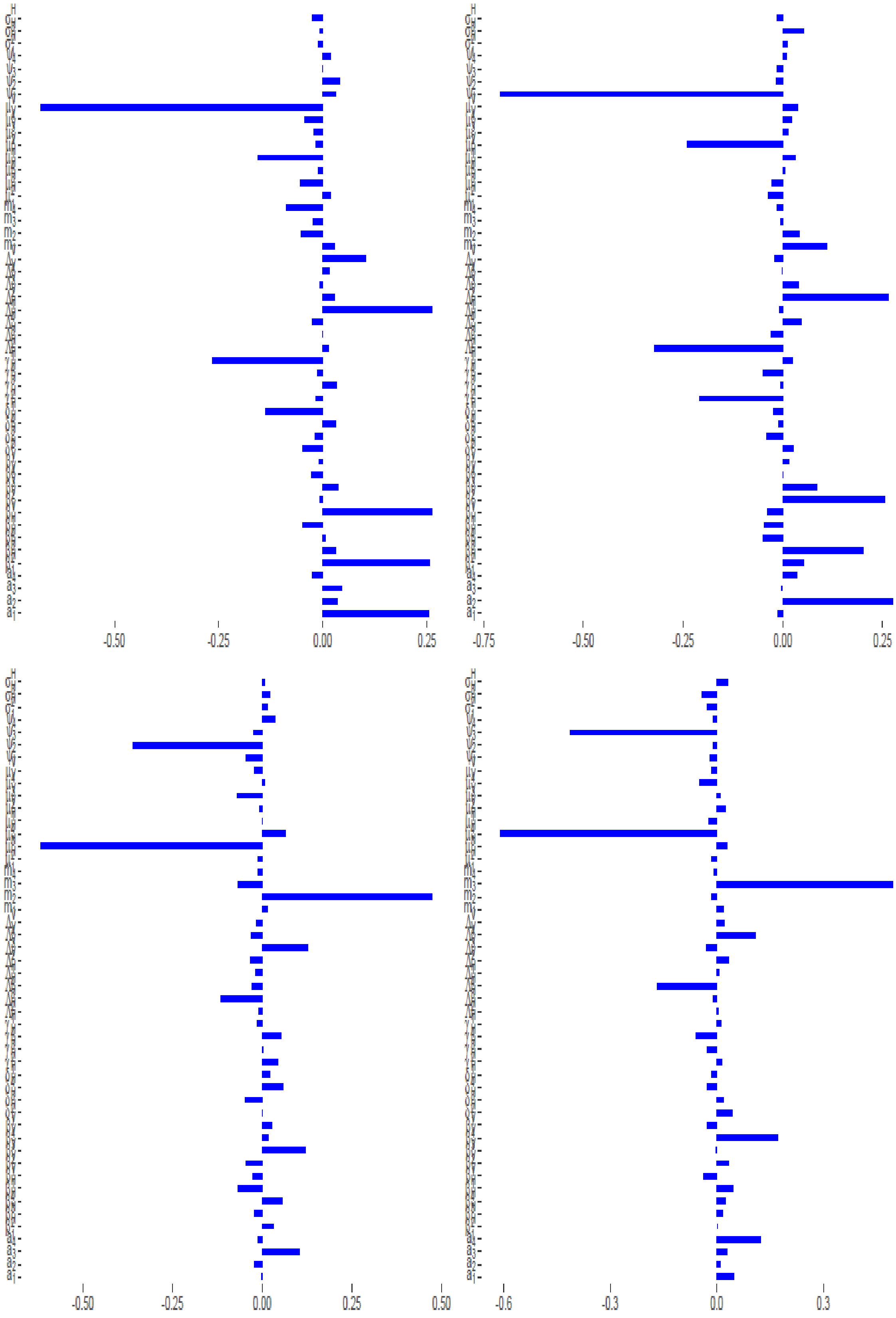
Table 5 4: Reproduction number by patch and age with the respect to the baseline and the scenario mimicking the conceptual misrepresentation and the behavior of the communities towards ITNs.

		Children	Adults	R_0 Total	Relative error
Baseline	Well urbanized	0.0261518	0.3895110	0.7967822	
	Poorly urbanized	0.0428304	0.3382890		
Heterogeneous coverage	Well urbanized	0.02615180	0.38951105	1.021384	28.19%
	Poorly urbanized	0.06807126	0.53764979		
Linear association	Well urbanized	0.03057684	0.45541860	1.236843	55.23%
	Poorly urbanized	0.08438062	0.66646663		
Decay of ITNs	Well urbanized	0.06307077	0.93939094	2.100959	163.68%
	Poorly urbanized	0.12344969	0.97504737		

5.3.3. Sensitivity analysis

The results of the sensitivity analysis carried out on the parameters of the model (Eq. 5.1) with the R_0 as a response function showed that three main parameters are dominant in Accra: i) the migration rate (mobility of the population between ecological patches) (m), ii) the function of the use of ITNs ($f\ (\psi_j^H)$), and iii) the natural death rate of the population (μ_j^H) irrespective of the scenario (Fig. 5.2). The correct identification of these parameters is crucial for improving ITNs use. Regardless of the type of scenario, we found that increasing the uptake of ITNs in every age category and the ecological patch, decreasing the mobility between patches will significantly reduce the spread of malaria in Accra.

A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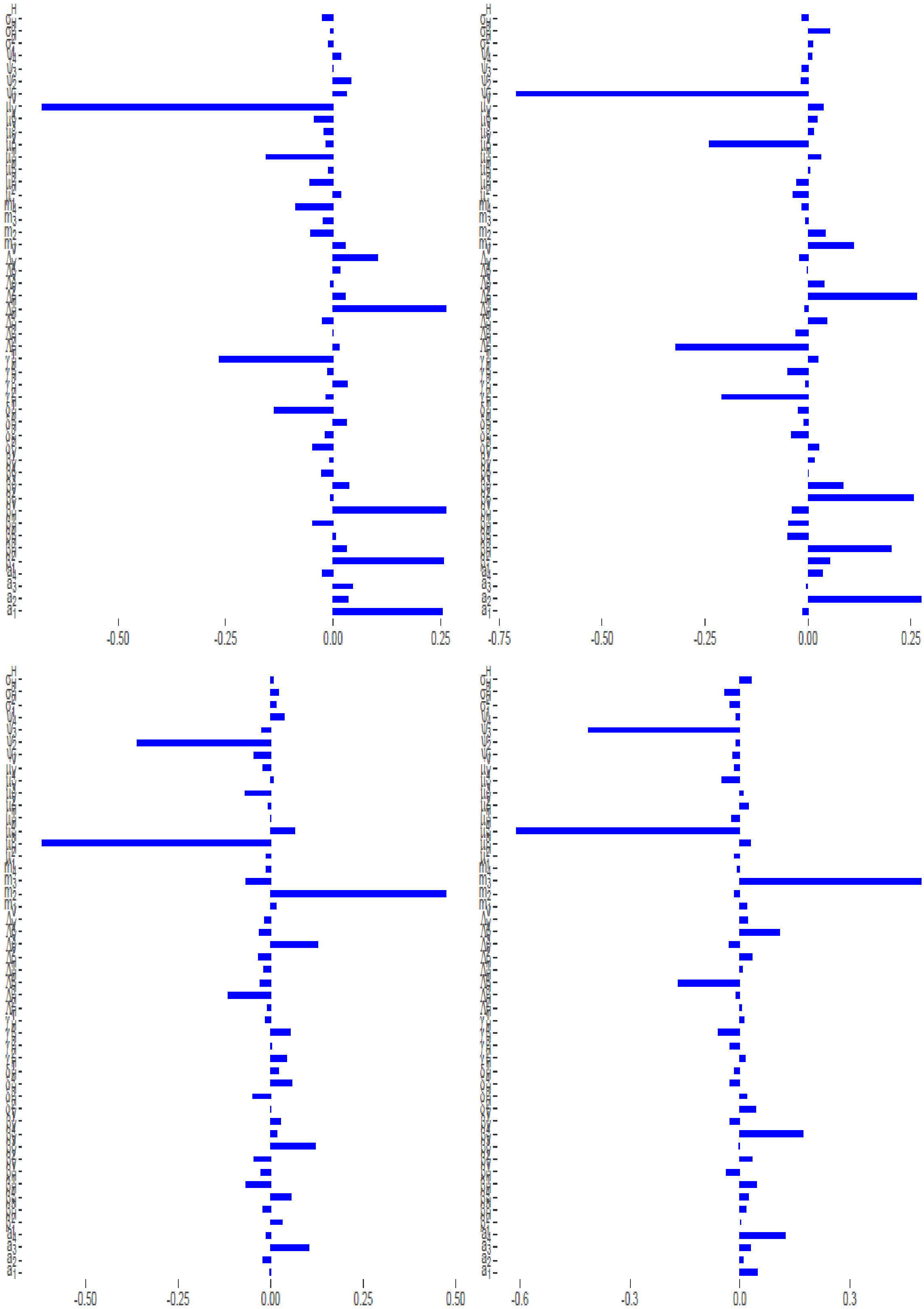
B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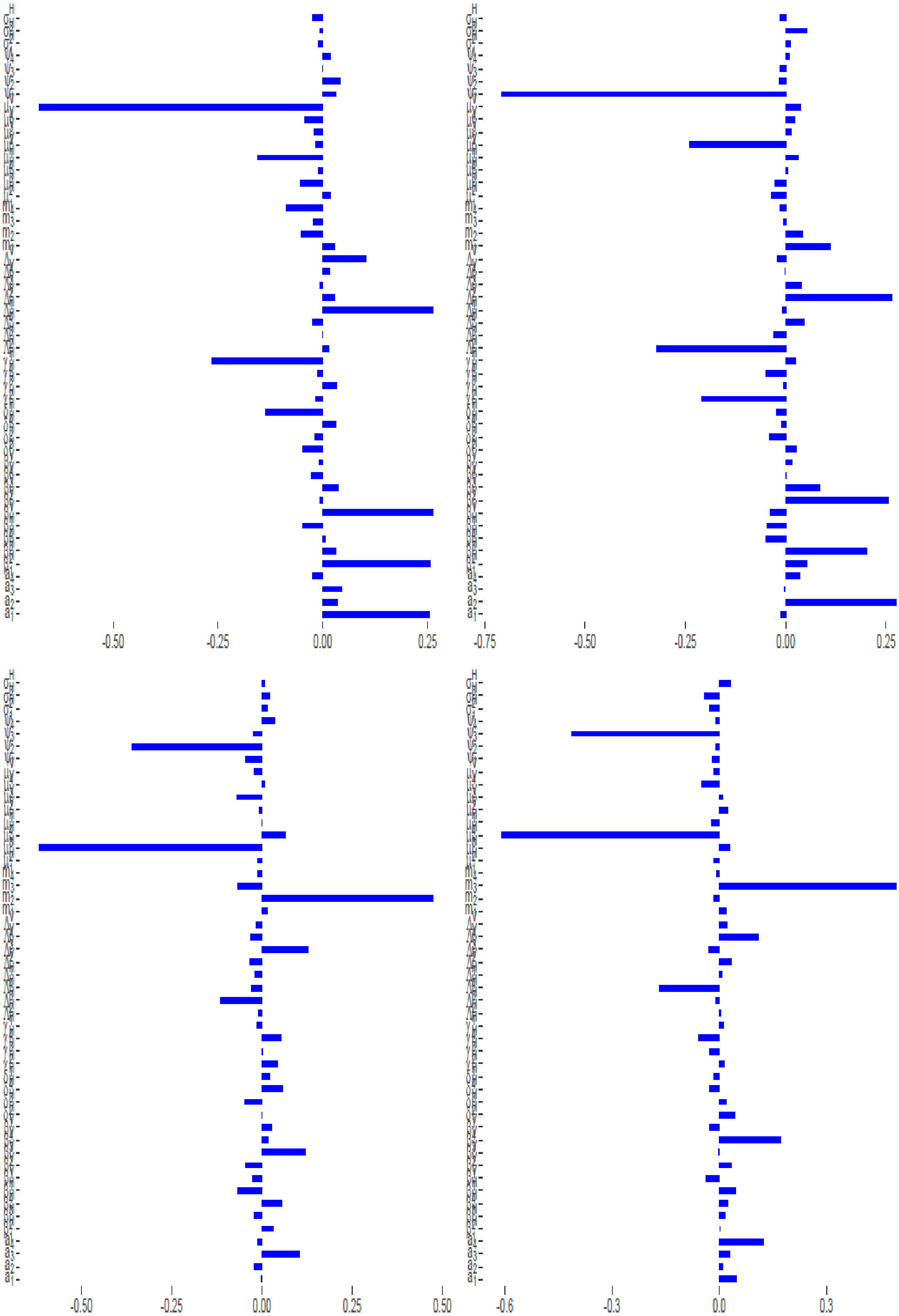
C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D

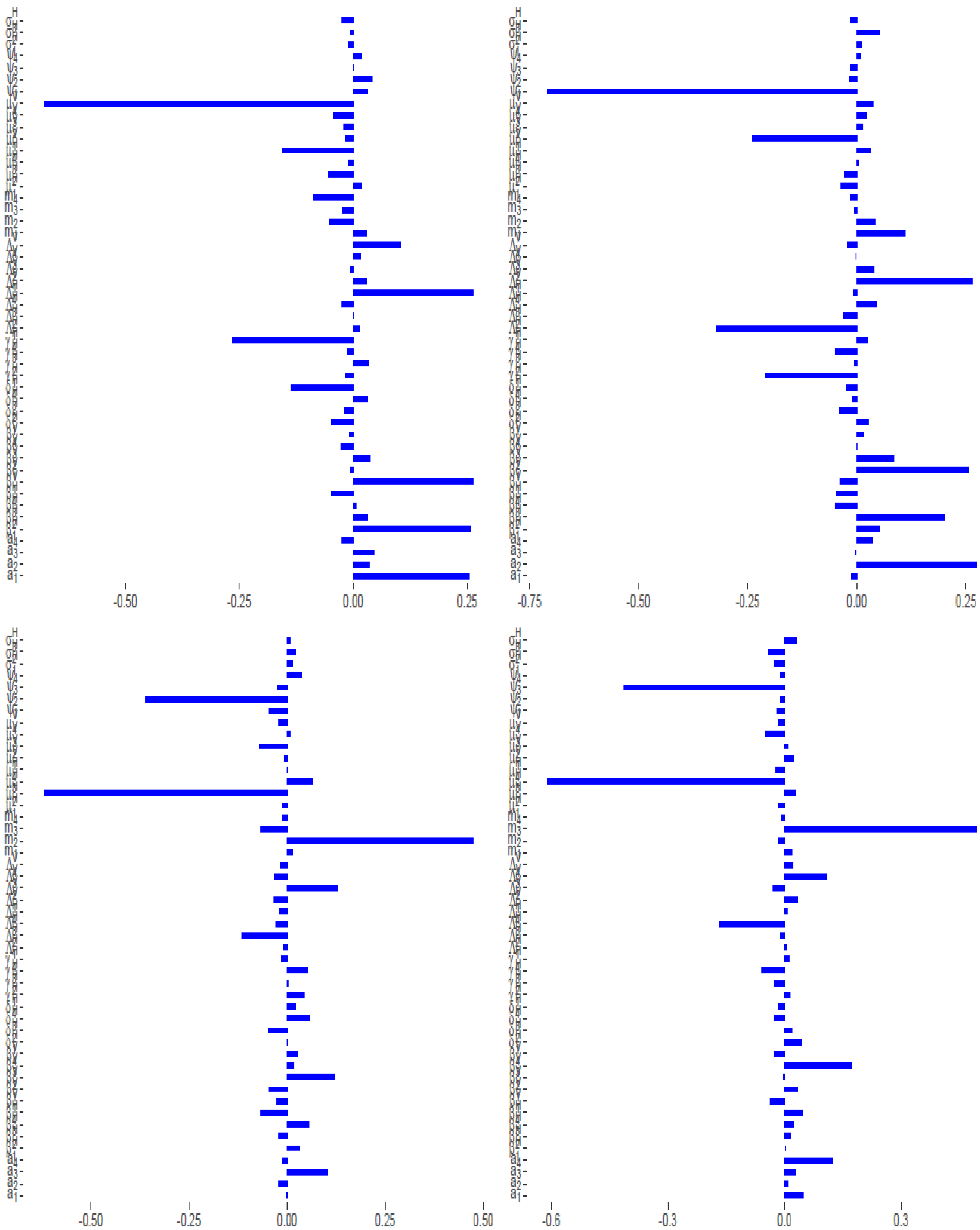

Fig.5. 3: Partial rank correlation values for the model (Eq. 5.1) using the basic reproduction number as the response function. A, B, C, and D stand for baseline, heterogeneous use, linear association between ownership and use,

and decay of ITNs scenarios.Λ_{11}^H, Λ_{12}^H, Λ_{21}^H, Λ_{22}^H recruitment rate of children, adults living in the first patch and of children and adult living in the second patch, respectively; $\mu_{11}^H, \mu_{12}^H, \mu_{21}^H, \mu_{22}^H$ death rate of children and adults in the first patch and children and adults in the second patch, respectively; $\gamma_{11}^H, \gamma_{12}^H, \gamma_{21}^H, \gamma_{22}^H$ recovery rate of children and adults in the first patch and children and adults in the second patch, respectively; $\beta_{11}^H, \beta_{12}^H, \beta_{21}^H, \beta_{22}^H$ the transmission rate from infectious human to mosquitoes of children and adults in the first patch and children and adults in the second patch, respectively; $\delta_{11}^H, \delta_{12}^H, \delta_{21}^H, \delta_{22}^H$ disease induced death of children and adults in the first patch and children and adults in the second patch, respectively;$m_{11}, m_{12},, m_{22}$ migration rate between patch of children and adults in the first patch and children and adults in the second patch, respectively; $\psi_{11}^H, \psi_{12}^H, \psi_{21}^H, \psi_{22}^H$ proportion of ITN use of children and adults in the first patch and children and adults in the second patch, respectively; μ_1^V, μ_2^V death rate of mosquitoes living in the patch 1 and 2, respectively; a_1, a_2 biting rate of mosquitoes living in the patch 1 and 2, respectively; Λ_1^V, Λ_2^V recruitment rate of mosquitoes living in the patch 1 and 2, respectively; β_1^V, β_2^V transmission rate from infected mosquitoes to humans living in the patch 1 and 2, respectively

5.4. Discussion

Ghana has made a lot of progress to control malaria over the last two decades, which lead to a significant reduction of disease-induced mortality (Awine et al. 2017). This progress was achieved using both pharmaceutical (ACT-based therapy) and non-pharmaceutical control (i.e., seasonal indoor residual spraying and high coverage of ITNs). Yet, in cities such as Accra, the non-pharmaceutical and proactive control measures are limited to the distribution of ITNs. Despite the proven benefits of ITNs in Ghana (Scates et al. 2020), there are still some pockets of reluctance to use this preventive control measure in Accra (Ahorlu et al. 2019). Our empirical study showed that contrary to popular belief, that there is no significant causal relationship between the ownership and the use of ITNs. Several earlier cross-sectional studies also reported that high ownership did not necessarily cause high uptake of ITNs in Ghana (Abotsi 2009; Nyavor et al. 2017; Kanmiki et al. 2019). Among the factors responsible for the reluctance of ITN usage, Abotsi et al. (2009) showed that in high-density households, dwellers tend not to use ITN. Although household density was not explicitly covered by our cross-sectional study, it seems to play a considerable role in the reluctance of using ITNs. To reduce the costs for rent, dwellers in the James Town and Korle-Dudor communities of Accra often live in a group of ten and more in one room of less than $12m^2$ (Danso-Wiredu 2018) which is probably insufficient space for all tenants to use ITNs. Our empirical findings showed that people are aware of the malaria risk and the benefit of using ITNs as a preventive measure. Yet, in addition to the space constraint surveyed participants described a web of reasons for their reluctance in using ITNs, where one of the most important is repurposing. Doda et al. (2018) argued that malaria risk perception becomes less of a pressing issue when confronted with clear benefits stemming from repurposing of the ITNs, especially for people living in deprived conditions. Therefore, the mass distribution of ITN alone will not lead to the effective control of malaria in Accra (Bertozzi-Villa et al. 2021).

We showed that the odds of ITN use increased in the households where a member had visited a healthcare facility the week before our cross-sectional survey. In a qualitative study, Ahorlu et al.(2019) observed that falling ill to malaria improved ITN uptake. Along the same lines in our analysis, a visit to a healthcare facility most likely improved the awareness of household members of the dangers of malaria and hence increased their willingness to use ITNs. In a cluster-randomized trial, Kilian et al. (2015) demonstrated additionally that increasing awareness of participants on ITNs through a regular one-on-one discussion increased their usage significantly. The same was observed in rural Ethiopia where another cluster-randomized control trial, the uptake of ITNs increased when the head of the household was knowledgeable about malaria (Deribew et al. 2012). Similarly, the uptake increased when pregnant women were malaria-educated (Amoran et al. 2012) and when the education was followed by an incentive (Krezanoski et al. 2010).

Our model provided evidence to support that with a homogenous use of ITN at 60%, the epidemics will end. However, when the spatial heterogeneity is included in the parameterization of our multi-patch mechanistic model we found that malaria becomes persistent in Accra. Thus, our findings support the previously already articulated need to consider spatial heterogeneity in malaria transmission (Frank et al. 2016). Moreover, our study results showed that policy-makers and modelers tend to underestimate malaria transmission when the behavior and attitude of communities visà-vis ITNs are not considered in the model. Like in Ebola (Castillo-Chavez et al. 2015, 2016) group and individual behavior impact the transmission of infectious diseases like malaria. However, few frameworks embody host behavior into a mechanistic model (Fenichela et al. 2011). Yet, it is important to stress that our model does not consider an adaptive behavioral change despite its impact on the pattern of infectious diseases but instead considers a static behavior. Yet, our study clearly revealed how important is to consider human behavior in the mechanistic models testing the efficacy of ITNs.

Our sensitivity analysis showed that the human mobility between the ecological patches significantly impacts malaria transmission and therefore supports previous evidence from previous patch models (Auger et al. 2008; Gao and Ruan 2012; Agusto 2014; Gao et al. 2014; Bichara and Iggidr 2018b). Hence a thorough understanding of human mobility can substantially improve the control of malaria.

5.2 Conclusion

Our study provided empirical evidence of the heterogeneous uptake of ITNs in Accra. We could also show that the uptake or the absence of it is influenced by human behavior that is spatially heterogeneous. Although the surveyed communities in Jame Town and Korle-Dudor (Accra) acknowledge the benefits of using ITNs to control malaria, their uptake is hampered by the often perceived rapid decay of nets. Hence ITNs should be distributed at shorter intervals than the currently used 3 years cycle. Moreover, our model emphasized the usefulness of integrating human behavior in the ordinary differential framework to quantify the effectiveness of ITNs. More specifically, we found that the integration of this layer of heterogeneity in the compartmental model allowed us to better estimate the infectiousness of malaria which turned out to be two-fold higher than estimated by simple SIR models. In addition, we found that a one-on-one discussion could increase the odds of uptake. Therefore, we suggest that the ITN distribution in communities should go hand in hand with regular malaria education programs, coupled with follow-up on ITN use for instance by youth volunteers from the neighborhoods. As the most affected societal segment by malaria burden remain poor city dwellers, addressing their living conditions probably will significantly reduce the overall malaria disease level in cities, thereby contributing to a progressive elimination of the disease. The efficacy and impact of other preventive and curative measures used by the surveyed communities as well as future interventions like malaria vaccine remain to be investigated in cities across Africa.

6. GENERAL CONCLUSIONS

6.1. Malaria, urbanization, and sources of heterogeneity

Although in ten years from 2005 to 2015 malaria incidence in Ghana has been reduced by 15%, the disease is still a major public health concern (Shretta et al. 2020). The steady reduction in malaria transmission is, however, hampered by the transition of Ghana from a low to a middle-income country (World Bank 2019). One consequence of this economic transition was a considerable drop in foreign aid received for combatting malaria (Aregawi et al. 2017). Given the situation, more strategic control of malaria in Ghana would require a better understanding of both the transmission dynamics of the disease and the presently applied non-pharmaceutical control measures. Throughout this thesis, it could be demonstrated that the transmission of malaria was spatially and temporarily heterogeneous in Ghana and particularly in urban areas where a constellation of drivers represents the key sources of heterogeneity. Moreover, it was proven that when key sources of heterogeneity are not embedded in the model, the efficacy of ITNs is overestimated.

The findings showed that space, season, and age represented important sources of heterogeneity. However, contrary to the common thought that malaria is primarily a rural disease, the findings showed that the malaria burden can be also high in urban areas. The findings further suggested that in big cities such as Accra and Kumasi, the disease incidence increase with the density of the population. Besides, the study showed that there is a diffusion in the epidemics, suggesting the existence of healthcare catchment areas and the mobility of populations towards the centre of the cities.

Moreover, it could be revealed that 45 determinants related to different intervention sectors interacted to maintain the transmission of malaria in cities (chapter 4). It was additionally observed that trust in physicians can reduce the transmission but patients' noncompliance can exacerbate the disease transmission, potentially fueling drug resistance of the parasite. Thus, communities' behaviors were spotted as a key source of heterogeneity.

Integrating communities' behavior into an ordinary differential model allowed us to demonstrate that the infectiousness of the disease is often underestimated (chapter 5). Moreover, it could be shown that reducing the movement of communities can help to reduce malaria transmission in cities. On the other hand, the empirical data analyses revealed that the uptake of ITNs is mostly triggered by a visit to a healthcare facility that can be interpreted as a reminding effect. Several reasons explain the reluctance of ITN use namely, the lack of space, the itchiness of nets, the perceived difficulty to breathe properly when under the nets, the physical/ chemical decay of the nets, and the repurposing.

Overall, the study illustrated the complex nature of malaria transmission and control in highly heterogeneous urban settings in Ghana. Spotting the sources of heterogeneity and accounting for them in malaria control will improve targeted interventions and further contribute to the elimination of the disease.

6.2. Strengths and limitations

The detailed analyses of the empirical data using statistical modeling revealed that the relationship between urbanization and malaria is contextual. Most specifically, evidence could be provided that in big cities such as Accra and Kumasi, the incidence follows a diffusion process that could be explained by the mobility patterns of city dwellers. Therefore, it can be hypothesized that monitoring mobility can contribute to more effective control of malaria in urban environments. Most importantly, results from this study showed that the link between urbanization and malaria incidence is nonlinear and multifactorial. Therefore, defining the prevailing conditions of a given association between malaria and urbanization united the large body of literature that documents this association. It could be particularly demonstrated that malaria incidence is highly heterogeneous and that its dynamic in cities depends on the density of the population and the vegetation cover.

To document the other sources of urban malaria heterogeneity a participatory system modeling and network analysis revealed that the behavior of communities plays a key role in the transmission and the persistence of malaria in Accra. These findings enabled the development of a mathematical framework to strengthen the uptake of existing malaria-related public health recommendations and stimulate the co-learning of participants. Besides, the study results displayed the complex character of the transmission and persistence of malaria in Accra while disclosing the web of interacting sources of heterogeneity.

Rooting on the above-mentioned sources of heterogeneity, and more specifically those related to human behavior, the magnitude of the bias in disease infectiousness was quantified by means of mathematical modeling. While increasing the realism of the mathematical framework through the integration of i) spatial heterogeneity, ii) demographic heterogeneity, and iii) behavior of both modelers and communities, it could be shown that the mobility pattern within urban areas can hamper malaria control and thus jeopardizes the envisaged malaria elimination in Accra and other urban areas of Ghana.

Nonetheless, this research has some limitations that need to be mentioned. Due to the lack of documented traveling history of patients, it was impossible to figure out the direction of the diffusion process. This could be particularly important in the cities such as Accra, which are in the malaria pre-elimination stage.

Moreover, to document the additional sources of heterogeneity, a qualitative system approach was used to map both the complexity and the interplay between causal drivers of the transmission and the persistence of malaria in Accra. As the study is perception-based, it leaves room to question the causality and the interplay between the drivers.

The mathematical model embedding communities' behavior fails to consider human behavior as a systematic factor, i.e., as an additional compartment of the model, but rather embodies human behavior as a parameter that affects the contact with mosquitoes. This approach lacked to consider group dynamics in communities, e.g. competition and influence. Yet, taking into account the group dynamic can help to target the type of malaria education/awareness to provide and the persons who need to be trained to increase the uptake of ITNs.

6.3. Implications of the thesis and policy recommendations

In this research, several sources of heterogeneity in the urban malaria epidemic were identified. Data-driven sources of heterogeneity (chapter 3) allowed us to emphasize the importance of environmental factors in epidemics. Therefore, surveillance of environmental factors and vectors can most help to reduce the risk of malaria in cities. Such surveillance is more crucial in a context where the recently introduced *An stephensi* may be a new threat in African cities (Sinka et al. 2020). This species, contrary to *An. gambiae* can feed on both animals and humans and thrives more in an urban environment. Moreover, the three clusters of malaria detected indicated that there is a need for a differential implementation of policy recommendations. In addition, the sources of heterogeneity in malaria epidemics involved different sectors with often-conflicting policies (chapter 4). For instance, there is an inherent conflict between the uses of pyrethroid-based insecticides in urban agriculture and for malaria control as it may lead to resistance development in mosquitoes. Therefore, a one-health multi-sectoral collaboration can be used to resolve policy conflicts. Besides, the three main loops (Chapter 4) give a hint on the three potential domains of policy recommendation. They are related to i) the urbanization-related transmission and acquired resistance of Anopheles to insecticides, (ii) the human's infection-prone behavior, and (iii) the healthcare efficiency and Plasmodium resistance. Moreover, it can be shown that the mobility pattern of communities affects the infectiousness of malaria in urban Ghana (chapter 5). Such findings indicated that there is a need to monitor mobility for better control of malaria. This calls for monitoring of communities movement as well as an improvement of communities' awareness for better control.

6.4. Future directions

Several future research directions can be foreseen as a result of this study. Results of this research are specific to the city of Accra and some extent also on Kumasi. Yet, heterogeneity in cities development vary. Therefore, findings from this study should be corroborated from other municipalities in Ghana and beyond. A better understanding of the dynamics of malaria based on those of urbanization can help develop pro-active control measures with a view to malaria elimination in Africa.

The inability to disentangle the direction of the observed diffusion in malaria transmission in bigger cites requires further studies, for instance, those that account for the travel history of malaria patients. Such data could be overlaid with the disease pattern to ascertain that the respective cities represent the malaria healthcare catchment areas. Besides, such sites would help to not only clarify the direction of the diffusion process but also identify the places of infection that are often confused with the places where the disease has been reported.

The causal links identified (chapter 4) were done by the means of a semi-quantitative approach leaving room for the accuracy of the causal associations. Therefore, conducting empirical studies on the causal links in form of random-clinical trials could help to ascertain the reliability of the causal link suggested in this study.

As the behavior of communities plays an important role in the chain of transmission in cities, it was integrated into a mathematical framework as a parameter. Such an approach does not consider larger communities' behavior such as collaboration and influence of peers in the uptake of ITNs. Therefore, developing a compartmental model with a compartment dedicated specifically to group behavior should be envisaged. To account for the randomness in human behavior, such a model can be a stochastic model and simulations can be done using the Monte Carlo process.

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APPENDICES

Appendix 1: Chapter 2

Table 1. Distribution of malaria incidence from 2015-2018 per region in Ghana

Region	Median	Mean	Standard deviation
Ashanti	12.952	22.489	28.188
Brong Ahafo	20.359	36.111	44.424
Central	17.663	28.034	29.580
Eastern	17.042	27.519	28.847
Greater Accra	9.477	16.272	21.100
Northern	6.318	14.735	24.912
Upper East	18.746	39.661	58.977
Upper West	12.525	22.694	28.685
Volta	10.598	17.703	19.330
Western	20.359	36.342	44.399

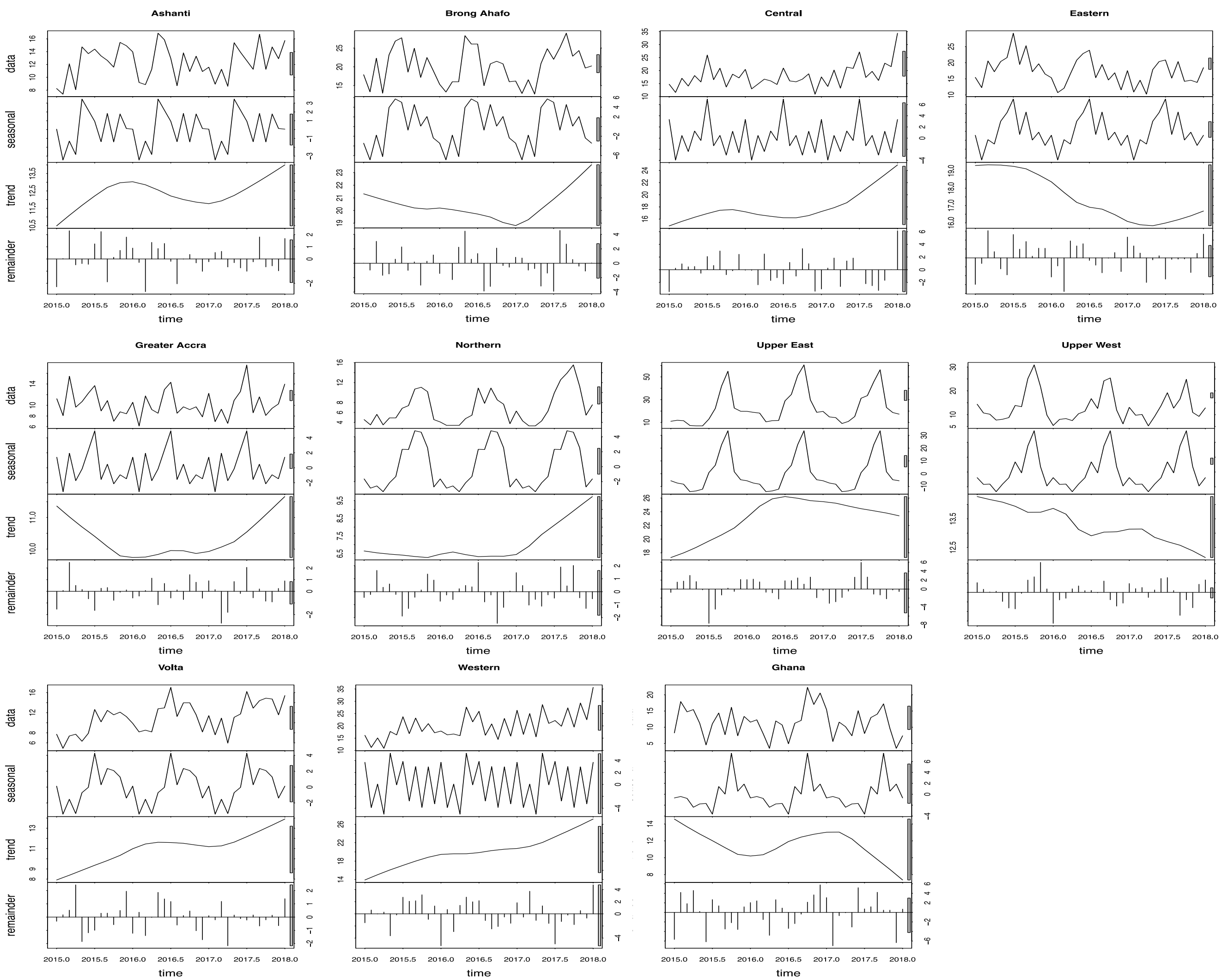

Fig 1. Incidence decomposition showing the seasonality and the trend in each region and the overall country

The STL decomposition showed dominance in the overall country incidence around September but this dominant pick is not observed in the same month when regions are considered.

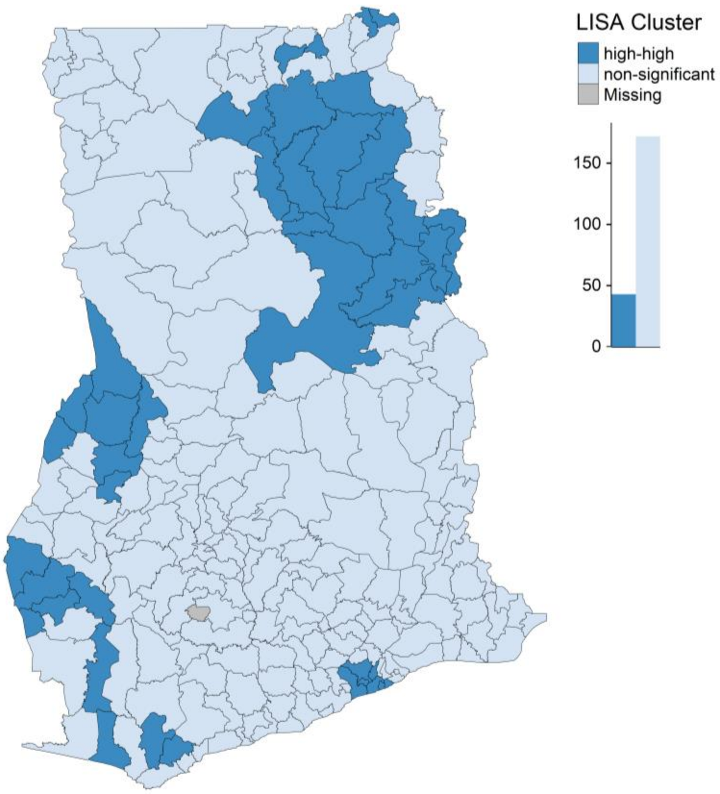

Fig. 2: Local Indicator of the spatial association cluster map

The following map (Fig. 4) projects the spatial location of the urban areas in Ghana. Based on the proxy of urbanization used the location of urban areas varied.

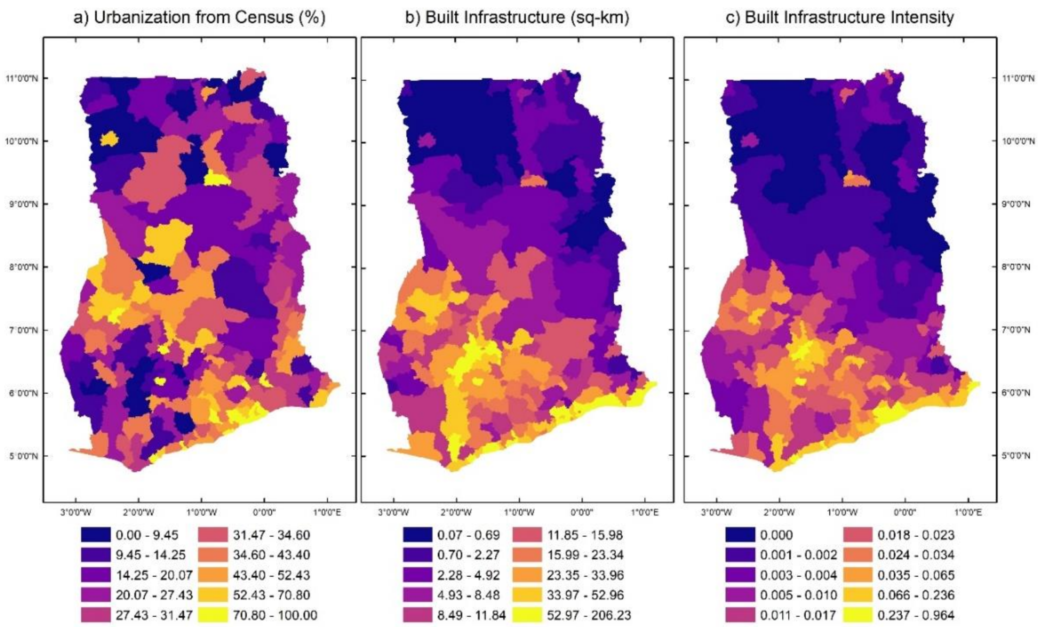

Fig. 3: Spatial repartition of urban areas according to the three definitions

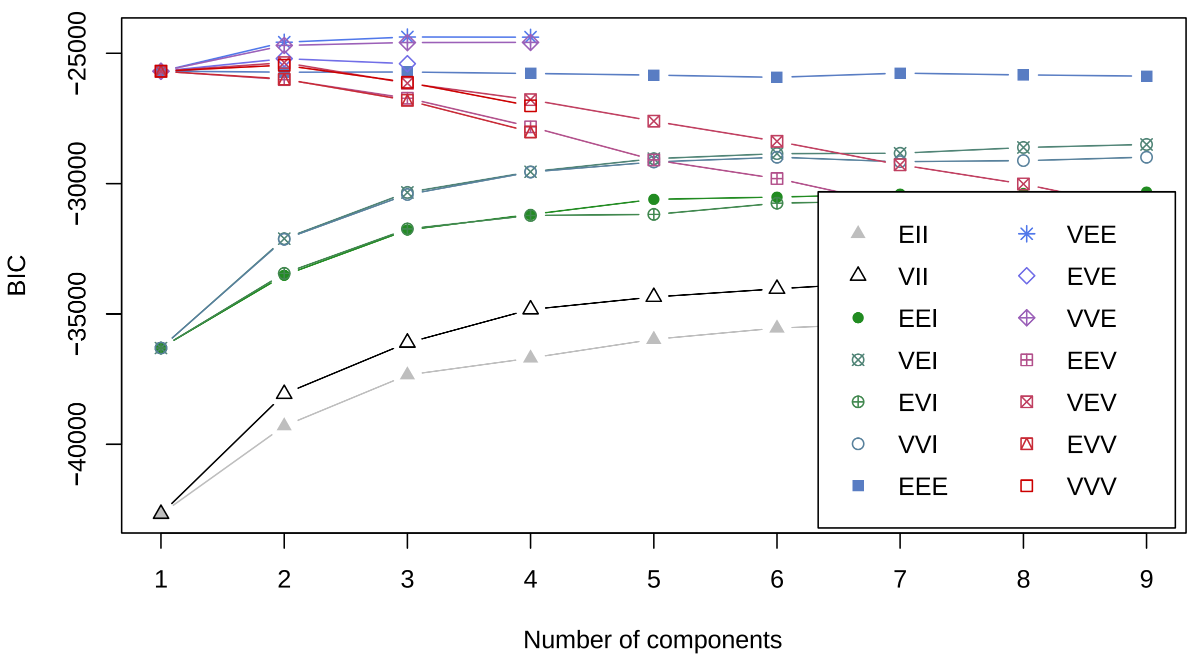

Figure 4: Bayesian information criterion (BIC) values from k-means clustering for different numbers of components/clusters and for different multivariate mixture models of clustering. Legend reference:- "EII" spherical, equal volume; "VII" spherical, unequal volume; "EEI" diagonal, equal volume and shape; "VEI" diagonal, varying

volume, equal shape; "EVI" diagonal, equal volume, varying shape; "VVI" diagonal, varying volume and shape; "EEE" ellipsoidal, equal volume, shape, and orientation; "EVE" ellipsoidal, equal volume and orientation; "VEE" ellipsoidal, equal shape and orientation; "VVE" ellipsoidal, equal orientation; "EEV" ellipsoidal, equal volume and equal shape; "VEV" ellipsoidal, equal shape; "EVV" ellipsoidal, equal volume; and "VVV" ellipsoidal, varying volume, shape, and orientation. Among these models, VEE model with 3 components/clusters performed the best.

Appendix 2: Chap 3

Table 1: Composition of the group building sessions

Institutions	Field of expertise	Number of participants
Ghana National Malaria Program	Entomology surveillance	1
Malaria Initiative/ USAID	Prevention campaign and ITN distribution	1
World Health Organization	Prevention and control	1
Ghana Health Service	Public awareness	1
Plant Protection and Regulatory Services/ Ministry of Food and Agriculture	Pest management	1
Noguchi Memorial Institute for Medical Research	Genetic	1
VectorWork	ITN distribution	1
Korle Bu Teaching Hospital	Physician	1
Dodowa Health Research Center	Research	1
School of Public Health Ghana	Medical geography and malaria expert	1
Greater Accra Municipal Assemblies	Community service	1
Ghana National Malaria Program	Prevention and control	1

Table 2: Operationalization of the determinants

	Label	Operationalization
1	Existence and enforcement of city planning and regulation	Legal dispositions regulating the construction and renovation of buildings in cities. e.g., laws preventing mosquito breeding sites in building/renovation activities. It also includes disposition on urban planning.
2	Adequate housing construction	House building after the recommendations of the city planning offices
3	Convenient waste and sewage management	Regular waste collection and disposal, and existence and maintenance of drain and gutters for sewage evacuation
4	Urban agriculture	Farming activities carried out nearby urban housings. Usually associated with the use of pesticides, digging of wells, and also hosting conditions
5	Wells excavation	For irrigation purposes, which also offer sites for mosquito egg-laying
6	Number of breeding sites	Temporary or permanent pits and ponds that can offer breeding conditions for mosquitoes
7	More rainfall	Between 800-1200 millimeters a year, optimal for mosquitoes mating and reproduction
8	Householders' awareness and decision-making on malaria infection risk	People information and empowerment of measures leading to prevent the infection and properly treat malaria
9	Hygiene and sanitation of households' compound	To prevent mosquito breeding sites

10	Household income	Financial/monetary income of the household, correlated to higher capabilities to acquire medicines, look for medical treatment, etc.
11	Temperature between 26 and 33°C	Ideal temperature or mating and the eggs-laying of mosquitoes
12	Higher reproduction rate of female Anopheles	As female mosquitoes are the ones that transmit malaria, their relative increase relates to mating, egg-laying, and blood-sucking activities. A mosquito carried the parasites bite a human and inject into him the parasites. Through multiplication firstly in the leaver and then in the bloodstream, the parasite creates a series of symptoms. These symptoms can be expressed as fever, chill, sweating in that the person is symptomatic. In some cases, the person carrying alongside the parasite may not express any symptom and this person is denoted as asymptomatic.
13	Number of female Anopheles	Related to 12
14	Surviving of female Anopheles	Related to 12
15	Use of insecticide in household	Specific insecticide is used in the household to kill mosquitoes, which in the long run these tend to increase their tolerance and eventually resistance
16	Insecticide resistant Anopheles strain	Eventually, mosquitoes mutate and get adapted to chemical compounds that are supposed to kill them
17	Pest management with pyrethroid-based insecticide in urban agriculture	Inadequate use and disposal of insecticide and pesticide-based pyrethroid pollutes the environment and drives the resistance of mosquitoes to insecticides.
18	Disinfection of healthcare facilities	Residuals of the pesticides applied remain in the environment and by their low doses augment mosquito resistance
19	Mosquito bites	Infection means, not all stings are infectious
20	Use of insecticide-treated bed-nets (ITN)	Used to repel mosquitoes and prevent infectious contacts with humans
21	Perceived-inconvenience of ITN	Acceptability of the ITN. Some populations allude as causes to reject them: increase in temperature, the itchiness of compound contains in the ITNs, the impossibility to breath, etc.
22	Frequency and duration of nighttime activities	Duration of the activities overnight can increase the exposure risk
23	Use of door and windows mesh	Indoor and windows to prevent mosquitoes entry
24	Infectious mosquito bites	Bite with a high likelihood of transmitting Plasmodium parasite to the human. Not all of the bites are infectious.
25	Population receiving infected bites	The fraction of the population that gets the infectious bite
26	Malaria positive cases	Population carrying Plasmodium parasite. This fraction of the population contains symptomatic and asymptomatic cases.
27	Human migration	Mobility of the population, which may imply the arrival of infected individuals
28	Human age category	The infectiousness is age-related, for example, children are more vulnerable to getting infected than adults
29	Immune state of human host	Natural protection good health safeguard
30	Asymptomatic cases	The fraction of the population carrying the parasite but not expressing any symptoms of the disease
31	Symptomatic cases	Malaria clinical cases, so showing symptoms
32	Health literacy	Peoples level of information on how to prevent malaria infection and what to do in case been infected
33	Visit a healthcare facility	Check-up for diagnosis or treatment

34	Enough and well trained healthcare-workers	Personnel well-trained implies better and earlier malaria diagnostic and more timely and efficient treatment
35	Adherence to prescription protocol	The patient adherence to the prescribed treatments is related to a prompt and more comprehensive recovery
36	Diagnosis (anamnesis and blood analysis)	Proper and effective diagnosis, imply an adequate medicine prescription, often measures to optimize it: anamnesis and blood screening, are poorly implemented or absent
37	Drug prescription	Prescription of malaria drug by health personnel
38	Compliance with the treatment	Patient strict observance of the posology and prescribed doses of the prescribed medicines. Also, neglection is frequent
39	Satisfaction with the treatment	Patient recovery with the received treatment
40	Trust in the healthcare system	Reaction to the effectiveness of the healthcare system
41	Inadequate utilization of the medication	Misuse of drugs, which tends to weaken its efficiency
42	Increase in Plasmodium resistance to drug	By the inadequate treatment, non-compliance of treatment, etc. resistance of the parasite to the given medicine
43	Alternative medicine	All the alternatives used to prevent and treat malaria, often traditional medicines like phytotherapy
44	Subsidy and availability on the preventive and curative malaria measures	There is an old tradition to subsidize malaria drugs and make them freely (no-prescription needed) available to the population
45	Self-medication	Use of medication without a formal prescription, quite strong in the case of anti-malaria drugs

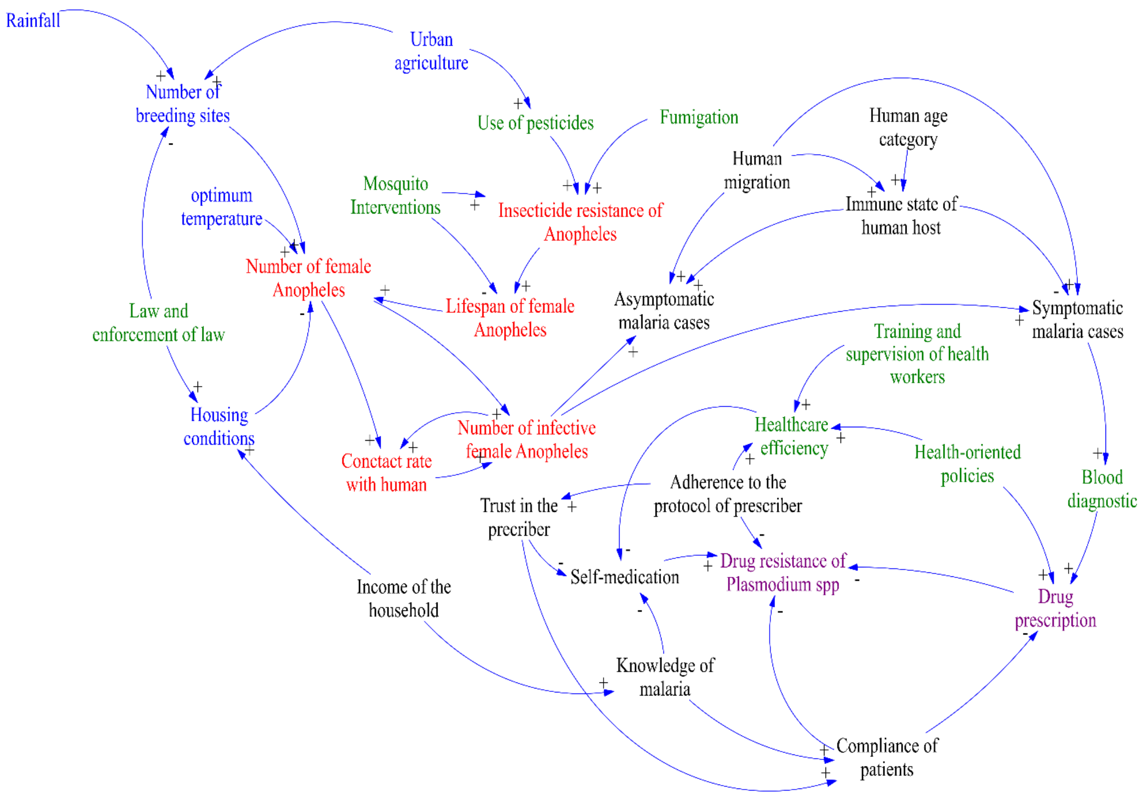

Fig.1: Earlier system depicting the complexity of malaria in urban settings.

Appendix 3: chap 4

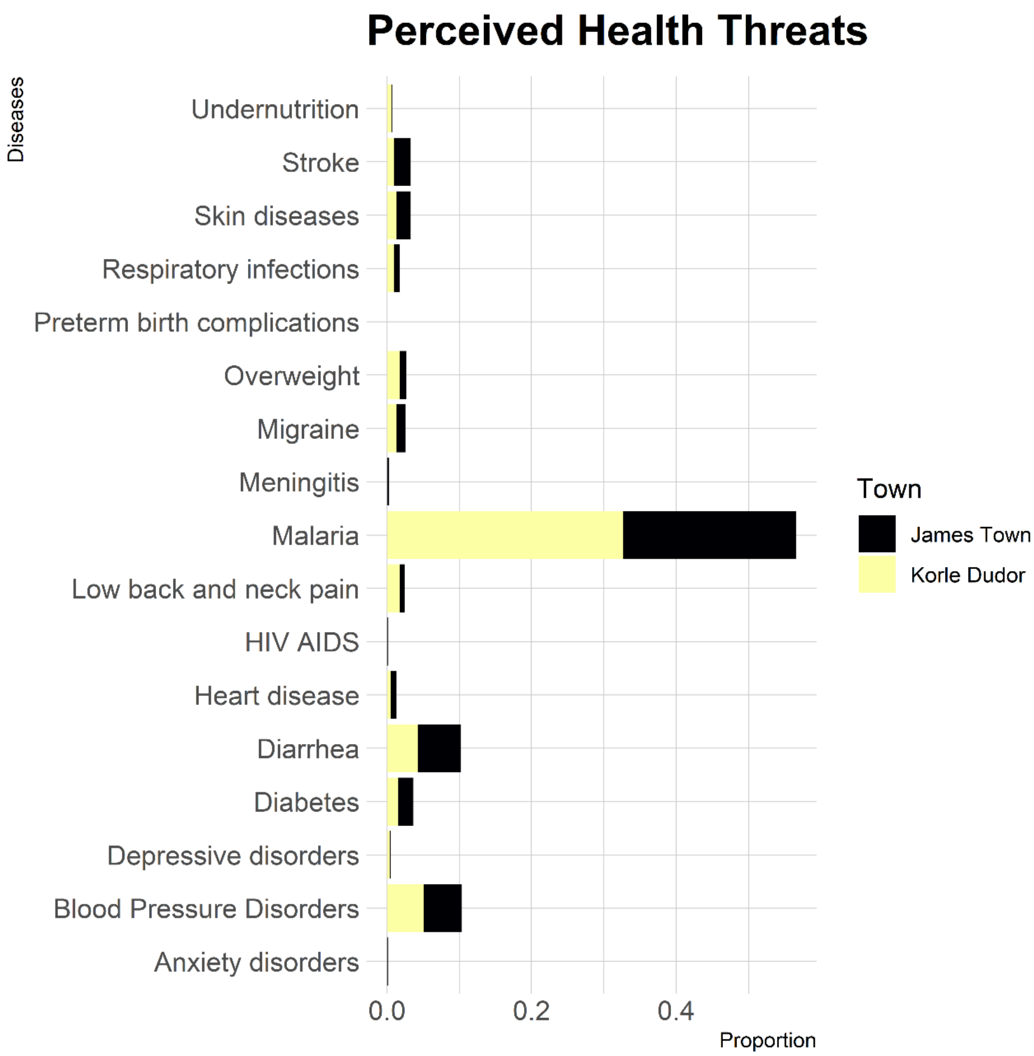

Fig. 1 Identification of the major health threats in the communities

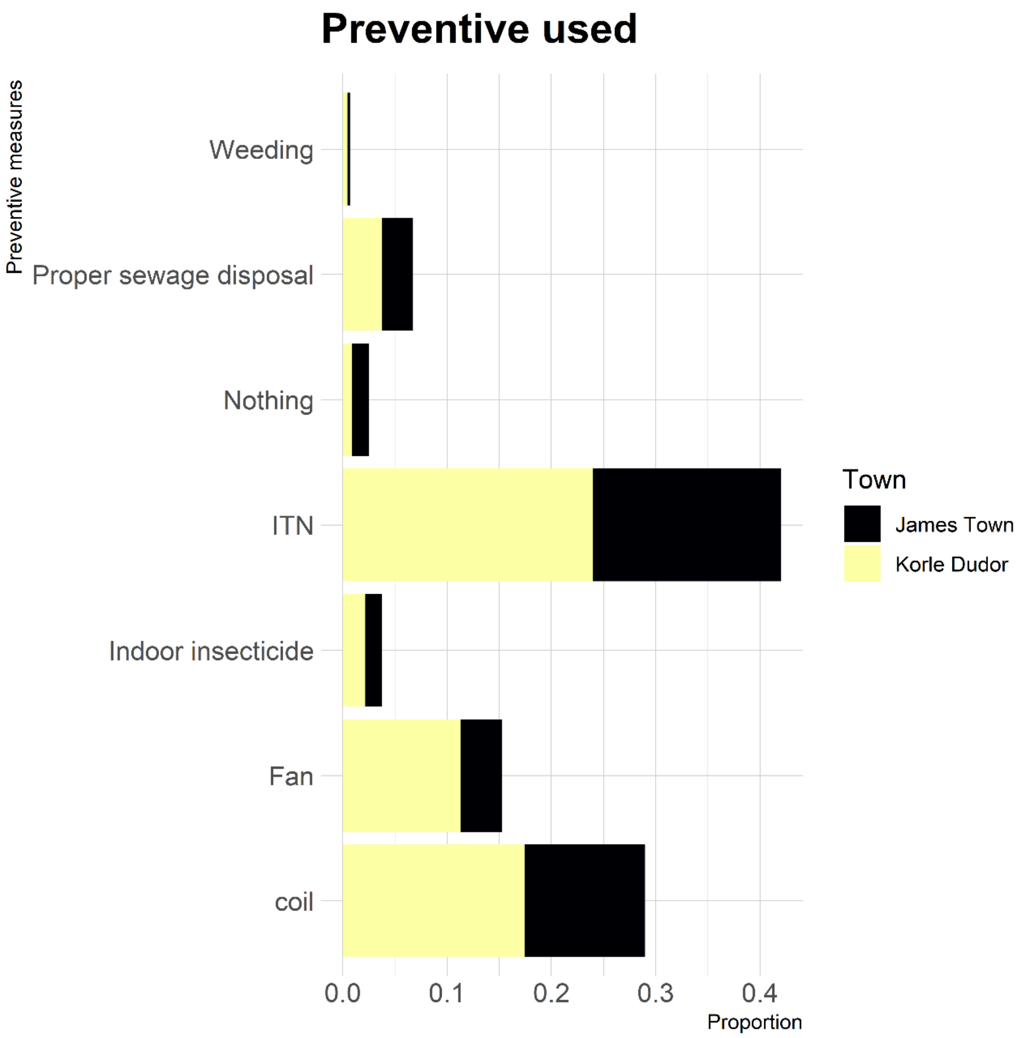

Fig. 2: Prevention measures used by the surveyed communities

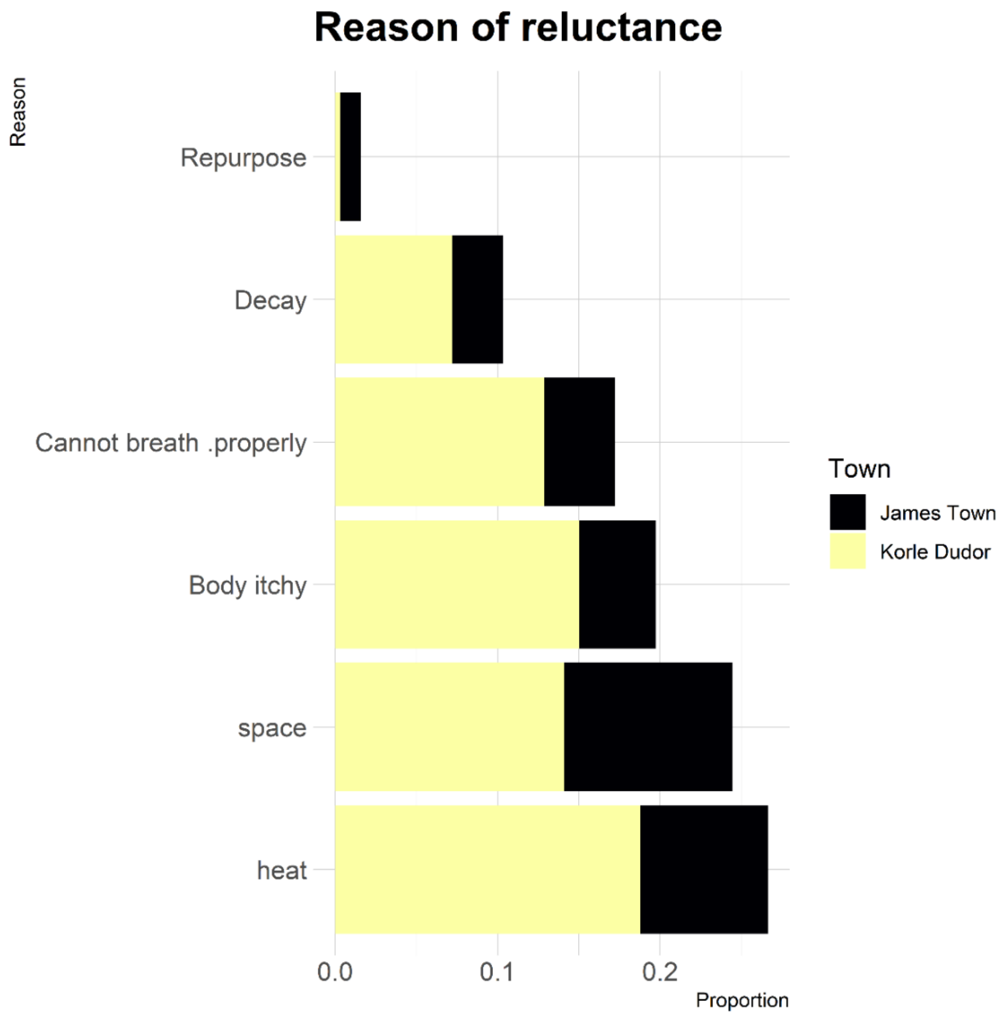

Fig.3: Reasons for nonuse of ITN

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