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Article

Targeting malaria hotspots to reduce transmission incidence in Senegal

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Abstract: In central Senegal malaria incidences have declined from 2000 to 2010 in response to scaling-up of control measures and then remained stable, making elimination improbable. Additional control measures are needed to reduce transmission.

We simulated chemoprophylaxis interventions targeting malaria hotspots, using a meta-population mathematical model based on differential equation framework and incorporating human mobility. The model was fitted to weekly malaria incidences from 45 villages. Three approaches for selecting intervention targets were compared: a) villages with malaria cases during the low transmission season of the previous year; b) villages with highest incidences during the high transmission season of the previous year; c) villages with highest connectivity with adjacent populations.

Our modeling, considering human mobility, showed that the intervention strategies targeting hotspots would be effective in reducing malaria incidence in both targeted and untargeted areas. But whatever the intervention, pre-elimination stage (1-5 cases per 1,000 per year) would not be reached without simultaneously increasing vector control by more than 10%.

Targeted interventions allow increasing overall malaria control and elimination potential.

Keywords: Malaria elimination; Mathematical model; Human mobility; Intervention chemotherapy

1. Introduction

Malaria remains a major health burden, with a global annual incidence of 219 million new cases and 430,000 deaths in 2017, most of which occurred in sub-Saharan Africa [1]. In line with the situation in Senegal nationwide, malaria incidence has declined in the Mbour area since the 2000s, due to scaling-up of malaria control. This is primarily due to universal coverage of long-lasting insecticide-treated bednets (LLIN) [2], improved access to diagnosis (Rapid Diagnostic Tests RDT) and prompt treatment of malaria with Artemisinin-based Combination Therapy (ACT) [3,4]. Senegal is still in the control phase of the malaria program, according to the World Health Organization (WHO) classification (more than 5

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cases per 1,000 inhabitants per year), but the country has been committed to achieving the objectives of pre-elimination stage by 2020 [5].

Malaria control and elimination projections are challenging due to the complex interactions between humans, vectors, parasite genetic complexity, environmental and socioeconomic factors. Spatial heterogeneity of incidences characterizes low-transmission settings within non-endemic areas of sub-Saharan Africa and Asia [6,7]. Hotspots are often broadly defined as areas where malaria transmission exceeds an average level [8,9]. Targeting interventions to specific hotspots may be efficient in reducing malaria burden in the entire area [8,10,11]. Operational definitions of hotspots allow the evaluation of the impact of targeted interventions in dry or rainy seasons. Intervention strategies simulated in this study were:

- Focused Mass Drug Administration (MDA) consists of systematically treating individuals in a selected geographic area with antimalarial drugs, without screening for infection.
- Focused Mass Screen and Treat (MSAT) consists of malaria screening using a rapid diagnostic test and providing treatment to those with a positive test result, in a selected area.
- Seasonal Malaria Chemoprevention (SMC) consists of intermittently administrating preventive antimalarial treatment to children during the main transmission period.
- Long-Lasting Insecticide-treated Nets (LLIN) intend to avoid mosquito bites relying on physical and chemical barriers of manufactured nets.

Human mobility plays a critical role in malaria elimination strategies, leading to reintroduction and resurgence of malaria in treated areas, hampering malaria elimination efforts [12].

This study aimed to understand the impact of spatially targeted malaria interventions, considering human mobility and using a metapopulation mathematical model based on a Susceptible-Exposed-Infected-Recovered (SEIR) framework, with spatially separated populations that interact with each other via moving individuals.

2. Materials and Methods

2.1. Study area and dataset

The population data came from 45 villages in the health district of Mbour, Senegal (Figure 1) and were collected from 2008 to 2012 through a health and demographic surveillance system established in central Senegal [13]. Malaria cases at health facilities were confirmed by rapid diagnostic test and geographical coordinates of village centroids recorded using GPS (Global Positioning System) devices. Estimates of rainfall were extracted from Goddard Earth Sciences Data and Information Services Center (http://disc2.nascom.nasa.gov/). The model was implemented using R 3.1.2 free software [14] (The R Foundation for Statistical Computing), deSolve [15] and FME [16] packages for numerical solution of differential equations describing transmission. The Geosphere R package [17] was used to estimate distances between villages. Graphics were edited with Paint.NET freeware raster graphics editor (dotPDN LLC, Rick Brewster). The dataset analyzed during the current study is available as additional file.

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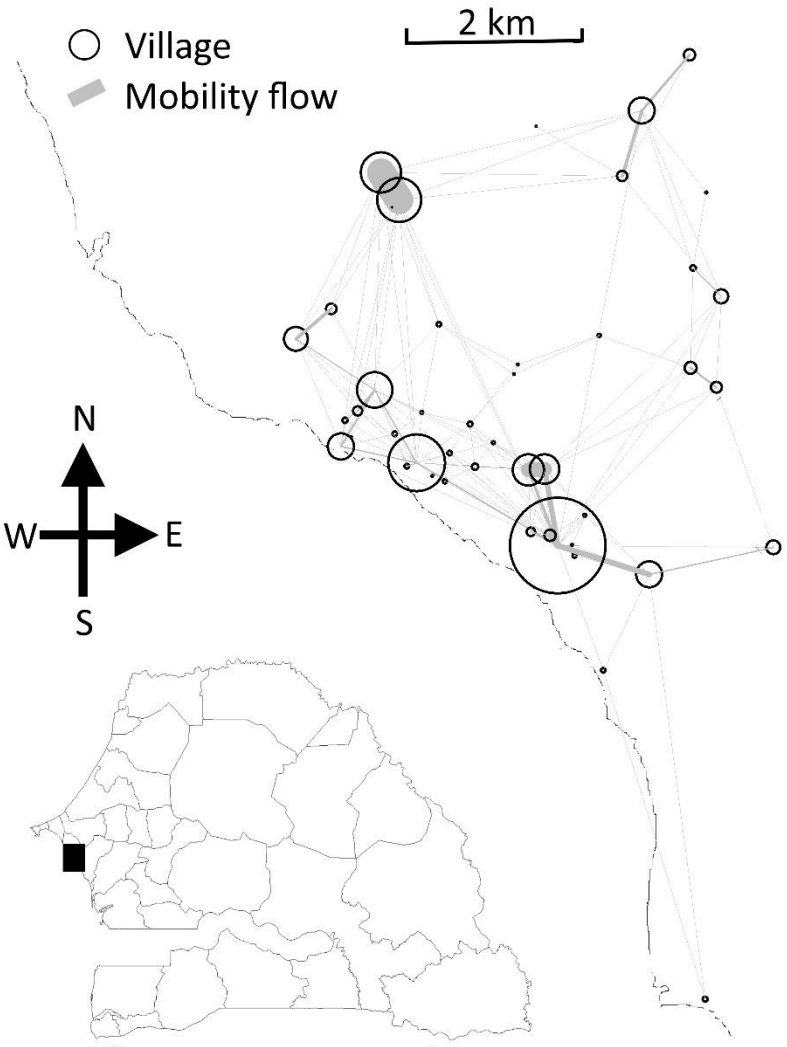

Figure 1. Mbour zone, Senegal, 2008-2012. Geographical coordinates of the 45 villages are represented by black circles and mobility flows by gray lines. The thickness of the lines reflects the number of trips.

2.2. Model structure

Malaria transmission in each village was represented by a deterministic compartmental SEIR transmission model based on the "Bancoumana" model described by Gaudart et al. [18] (Figure 2). Infection remove susceptible individuals from the susceptible compartment $S_k(t)$. The proportion of human infection in village k, denoted $I_k(t)$ was proportional to anopheles density $\upsilon(t)$, to frequency of mosquito bites α, to human susceptibility to infection β, and to the effective proportion of infected mosquitoes $i(t)$. The latter represent a weighted sum of the local proportion of infected mosquitoes $Ai_k(t)$ and the remote proportion of infected mosquitoes $Ai_j(t)$ (equation 1). The weights depended on the proportion of people that are away at a given time (m) and also on relative probabilities Q_{kj} of travel from remote locations *j* to local village *k*.

$$i(t) = \left[(1-m)\, Ai_k + m \sum_{j \neq k} Q_{kj} Ai_j \right] \qquad (1)$$

Probabilities Q_{kj} were estimated via the radiation model of human mobility [19] (equation 1):

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$$Q_{kj} = \frac{P_k P_j}{(P_k + s_{kj})(P_k + P_j + s_{kj})} \qquad (2)$$

P_k and P_j are the populations sizes in locations *k* and *j* respectively and s_{kj} the total population inside the circle centered at *k* whose circumference touches *j*, excluding the source and destination populations (P_k and P_j). Travel was modeled as round trips of approximately one-week duration. Villages populations sizes were assumed constant over the study period to avoid complexity. Each inhabitant of a village *k* could infect or be infected at other villages *j*. In this approach, moving individuals remain residents of their home village but spend some time in neighboring villages. Long-term mobility is not incorporated.

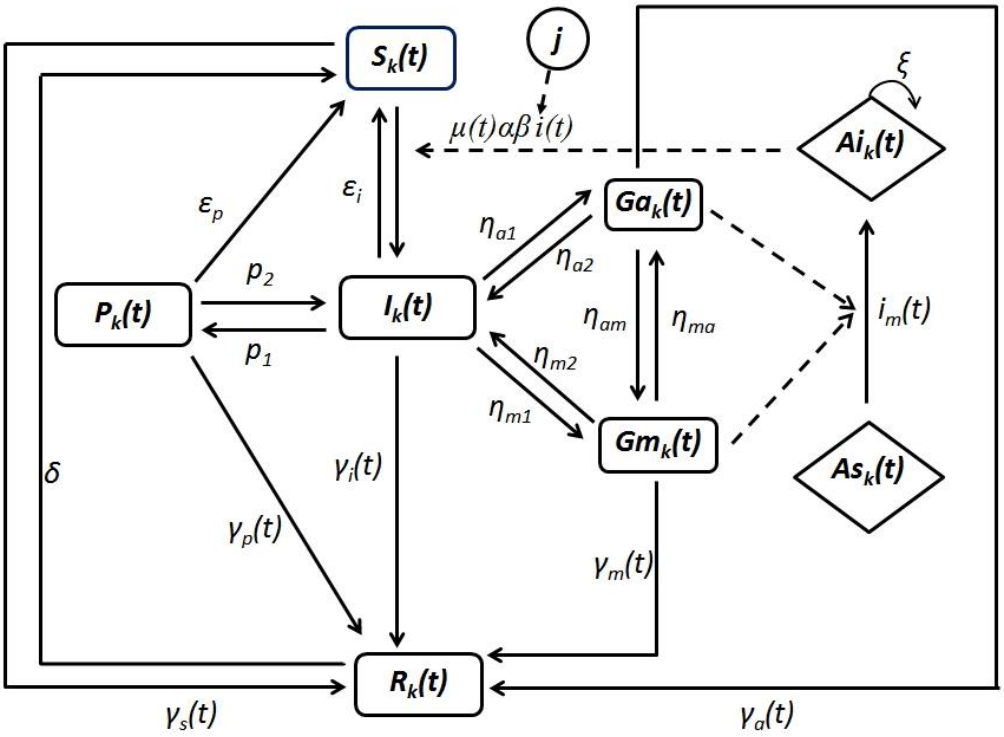

Figure 2. Malaria transmission diagram at a local village *k*. Letter j stands for remote villages. Human compartments are *Sk*: susceptible, *Pk:* premunition, *Ik*: blood stage infection, *Gak*: asymptomatic carriage of gametocytes, *Gmk*: symptomatic carriage of gametocytes, *R*: resistance due to treatment. Mosquito compartments are *Aik*: infected mosquitoes and *Ask*: susceptibles mosquitoes. The arrows represent the transition rates between compartments.

The model assumes that newly-infected individuals at village *k* $I_k(t)$ initially carry only blood stage infection. Gametocytes subsequently appear, and the individual may have malaria symptoms or be asymptomatic, leading to respective compartments Gm_k (symptomatic, infectious) and Ga_k (asymptomatic, infectious). All gametocyte carriers were assumed to contribute to transmission. Infection of mosquitoes depends on the effective proportion of human infection $i_m(t)$, represented as a weighted sum of human infection at local and neighboring villages. Gametocytes were transmitted to anopheles from gametocyte carriers that resid in the local village *k*, and by gametocyte carriers that travel from remote villages *j* to the local village *k*. It was assumed that mosquitoes are infected by feeding on human carrying gametocyte, and that blood-fed anopheles do not move from one village to another [20].

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The model assumes that adults gradually acquire partial immunity (premunition) at a rate p_1 [21], after several malaria attacks. Premunition is assumed to be lost at rate p_2 [21].

Targeted interventions were modeled as a transition of individuals to the compartment of protected. The transition rates are defined as rectangular pulse functions reflecting interventions over a limited period of time. Protection resulting from drug administration is assumed to be lost at constant rate depending on antimalarial' half-life.

Seasonal variations of anopheles density $\upsilon(t)$ were modeled assuming that anopheles density is proportional to the cumulative rainfall over the previous six weeks and oscillated between the minimum and maximum values reported in previous entomological studies for this area (0 to 12 anopheles/individual/day) [22]. The correlation lag between anopheles' densities and malaria incidences was estimated by sensitivity analysis (Figure. A1). The estimated value was about 6 weeks, 95% CI [3,8]. This value was consistent with previous studies[23,24].

The equations of the model are set out in Appendix A and a fine description of the parameters is given in Table A1.

Model calibration

The meta-population model was fitted to weekly malaria incidence data from January 1, 2008 to December 31, 2008, using an optimization approach based on Markov Chain Monte Carlo (MCMC)[25]. Initial values of model compartments were defined as conditions values at the beginning of each rainy season. Several parameter values relied on expert advice and values from the literature [26] (Table A1). The sensitivity of model parameters was assessed by varying them around the estimated value.

Hotspots definitions and interventions

Three pragmatic definitions of hotspot were investigated:

1. Low Transmission Period hotspots (LT hotspots) were defined as villages reporting at least one malaria case in the previous low transmission period (December to May).
2. High Transmission Period Hotspots (HT hostpots) were villages with the highest malaria incidences during the previous transmission season (June to November).
3. High Connectivity Hotspots (HC hotspots) were villages highly connected to neighboring villages based on human mobility potential.

   Connectivity was approximated by degree centrality score (equation 3). Degree centrality of village k (d_k) was defined as the number of travel connections from outside villages to village k which volumes were above the first decile of total volume of travels towards k [27]. Degree centrality capture infection routes from outside villages to k, and higher values indicate an increased vulnerability to malaria spread.

$$\boldsymbol{d_k = card(w_{jk} | w_{jk} \geq 0.1 w_k)} \qquad (3)$$

   in which, d_k represents the degree centrality score of village k, *card* (cardinality) represents the number of connections to village k above the threshold $L=0.1$, w_{jk} the number of trips from villages j to village k, and w_k the total volume of travels towards village k.

These definitions were kept deliberately simple to be applicable in practice and do not require neither prior serological surveys nor special clustering analysis [8,10,28].

In silico interventions were simulated from 2010. MSAT and MDA drug interventions assumed the use of Dihydroartemisinin plus Primaquine. Coverage rate was set to 70% for each round of MDA/MSAT, meaning that 70% of the population in targeted hotspots effectively received the intervention (treatment in the case of MDA and pre-treatment screening in the case of MSAT). Two rounds of intervention, separated by one-month interval, were assumed for both MDA and MSAT with drugs provided during the first week of September and again during the first week in October (High Transmission Period simulations), or in February and March (Low Transmission Period simulations).

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The simulated SMC strategy targeted only children under 10 years old, assumed to represent 30% of the population [29]. Delivery occurred on the first 4 days of each month from September to December, in the entire study area. According to WHO recommendations, SMC should not be implemented as a geographically limited targeted strategy.

The impact of long-lasting insecticidal nets was implemented as a direct decrease in the rate of mosquito bites (α) over the intervention period.

The intervention efficacy, Δ_I was defined as the relative variation in malaria annual incidence from no intervention assumption to intervention assumption.

$$\Delta_I = 1 - \frac{I_1}{I_0} \qquad (4)$$

I_0 and I_1 were cumulative incidences of malaria respectively before and after intervention.

3. Results

3.1. Parameters estimates and sensitivity analysis

The estimated weekly mobility rate was m = 0.09 (95% CI: 0.0015, 0.2) corresponding to 2-200 individuals moving between villages per 1,000 inhabitants per week. The entomological inoculation rate (EIR) calculated from the model, varied seasonally between 0 and 2.16 infected bites per person per night.

Key parameters were varied to assess their sensitivity on malaria incidences (Figure 3). Model predictions were sensitive to the following parameters: density of anopheles (33% increase in malaria incidence while increasing parameter by about 5%), access to treatment (16% increase in malaria incidence while decreasing parameter by about 5%), loss of premunition (4.5% increase in malaria incidence for 5% parameter increase) and human mobility (1% increase in malaria incidence for 100% parameter increase).

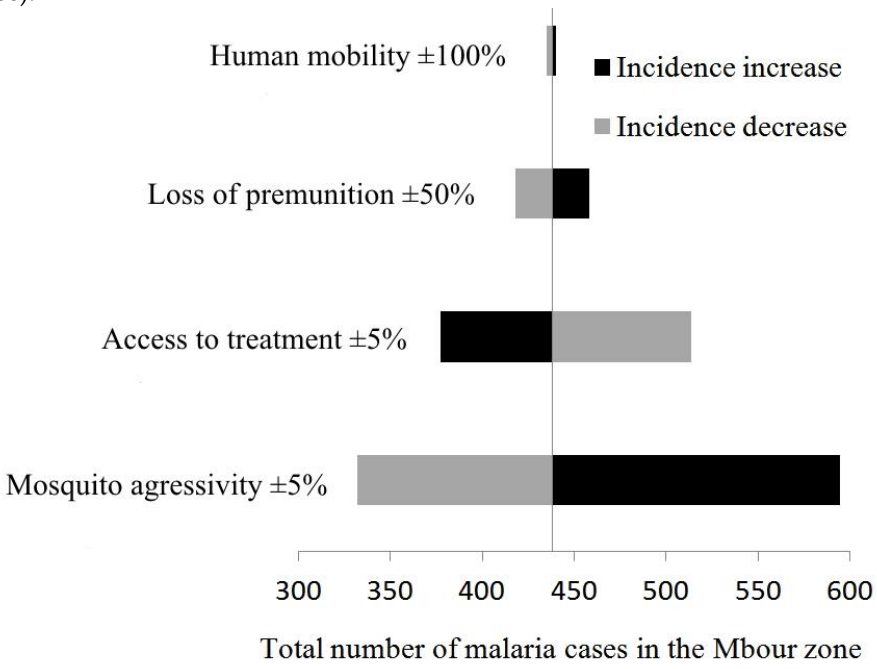

Figure 3. Sensitivity of model parameters in the malaria meta-population model, Mbour, Senegal 2008-2012. Right and left correspond to parameter increase or decrease respectively (percentages). Black and gray bars represent respectively increase and decrease in total malaria cases, subsequent to parameter variations.

3.2. Sensitivity of hotspot definitions

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LT hotspots showed temporal instability. Their locations changed from one year to another (Cohen's Kappa coefficient 0.21, 95% CI: (0.16, 0.33) versus 0.6, 95% CI: (0.36, 0.85) for HT hotspots). HC hotspots were static in time because this definition relied mobility estimates based on population densities which were assumed stable over years.

HT hotspots were less populated than LT hotspots (average population per HT hotspot 510 inhabitants versus 1,703 inhabitants in LT hotspot, Wilcoxon test P=0.13), suggesting that small population groups had higher incidence rates during the transmission season.

HC hotspots were slightly more populated than LT hotspots (average population per HT hotspot, 1,876 inhabitants versus 1,703 inhabitants in LT hotspot, Wilcoxon test P=0.6) and demonstrated lower malaria incidences than LT hotspots (Wilcoxon test P=0.03).

3.3. Intervention simulations

Variations in annual incidences after a unique intervention and after yearly repeated interventions on LT hotspots are shown on Figure 4, for the overall study area.

Percentage of villages defined as LT hotspots in 2011 and 2012 were 35% and 31% respectively. As LT hotspots were not predictable beyond data limit, we assumed its proportion to remain 31%, in order to allow forecasting. Repeating MDA and MSAT interventions in LT hotspots, once a year, during the rainy seasons, after five consecutive years, yielded a decrease in malaria incidence of 34% and 28% respectively. As interventions stopped, the efficacy reverted and stabilized at 25%. Delivering SMC sequentially in dry seasons, efficacy reached only 10% after 5 years. Effects are higher with SMC sequentially delivered in rainy seasons (20% after 5 years). Monthly uninterrupted SMC would reach 50% incidence decrease after 5 years delivery.

When targeting the equivalent proportion of HT hotspots, repeated interventions stabilized at 56% efficacy when delivered during the dry season. When delivered during the rainy seasons they yielded, respectively, 67% and 56% long term efficacy (Figure A2).

Targeting equivalent proportion of villages according to HC hotspot definitions, five years repeated interventions during the rainy seasons yielded 74% and 64% efficacy respectively for MDA and MSAT, which decreased and stabilized both at 57% at cessation of interventions. MDA and MSAT targeting HC hotspots in dry season yielded similar long-term results (Figure. A3).

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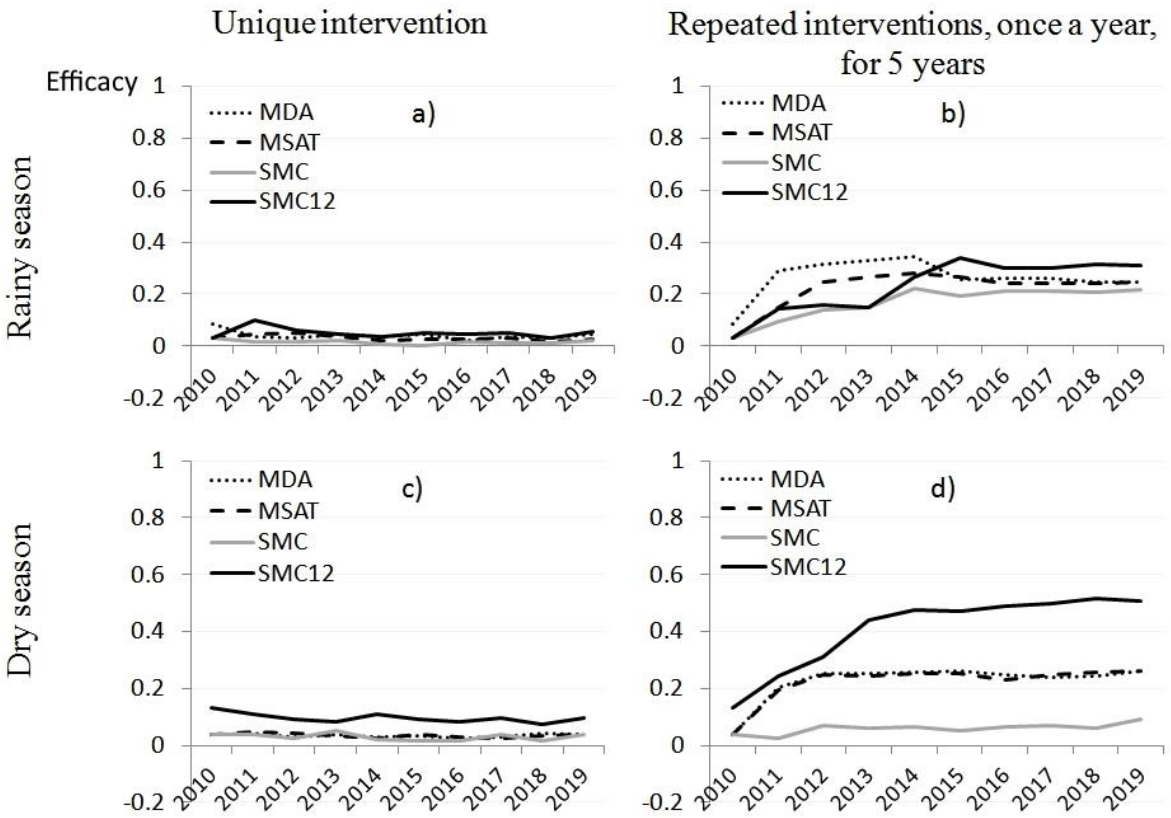

Figure 4. Decrease in malaria incidence while targeting Low Transmission period hotspots (LT hotspots), Mbour, Senegal 2008-2012. Y-axis represents the percentage of decrease in malaria incidence for the overall area (45 villages). a) Unique one-year intervention in rainy season, b) Repeated interventions over five consecutive rainy seasons, once a year, c) Unique one-year intervention in dry season, d) Repeated interventions over five consecutive dry seasons, once a year. SMC12 corresponds to a theoretical schedule of uninterrupted monthly administration of SMC over 12 months

3.4. Pre-elimination / elimination stage

MDA simulated over one single year, targeting LT hotspots led to the pre-elimination stage (1-5 cases per 1,000 per year) provided that mosquito bites were simultaneously reduced by 10% or more (Figure 5). The elimination stage (less than 1 case per 1,000 per year) would be theoretically expectable by combining 70% vector decrease and MDA in LT hotspots. Targeting HT or HC hotspots, more than 10% simultaneous decrease in mosquito bites would be needed to reach pre-elimination, whatever the MDA coverage.

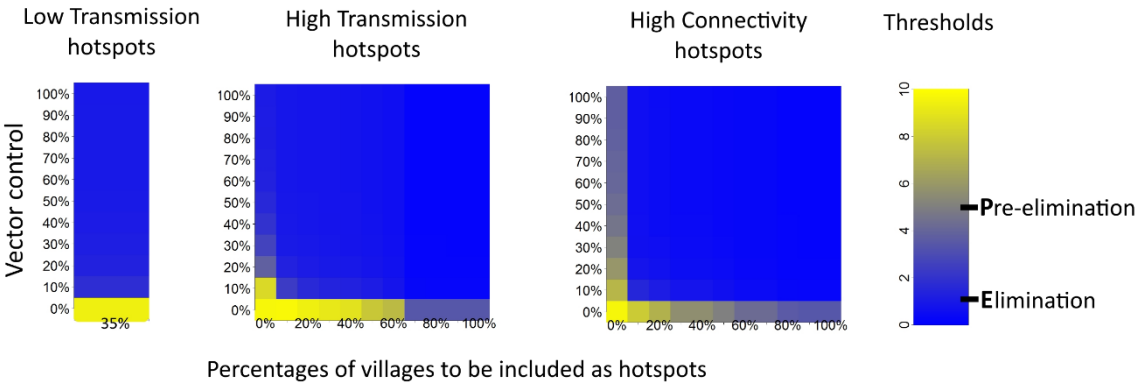

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Figure 5. Malaria incidences in the year following simulated combined interventions of Mass Drug Administration associated with Vector Control. Various definitions of hotspots are tested. X-axis represents the percentage of villages included as hotspots. Y-axis represents the assumed decrease in mosquito bites from baseline.

3.5. Rebound effects due to human mobility

An incidence rebound was noticed at the cessation of repeated MDA/MSAT interventions. Rebounds occurred only if mobility was considered not null. While targeting one third of HC hotspots for five consecutive rainy seasons, rebound (incidence increase after interventions ended) was about 17% for the overall area and 43% in targeted villages. This may be a worst-case scenario as we assumed an average proportion of 20% travelers moving between villages.

4. Discussion

This study investigated the use of a spatially explicit malaria meta-population model, fitted to weekly malaria incidence in rural villages in central Senegal.
A final decrease in the incidence of malaria of more than 25% was reached in the overall area with both MDA and MSAT simulated interventions repeated for five years on LT hotspots and 57% on HT or HC hotspots. Monthly uninterrupted SMC simulated on the 45 villages over five years showed similar results (50% decrease in the incidence of malaria). Reaching the pre-elimination stage (1-5 cases per 1,000 per year) was expectable only when simultaneously decreasing mosquito bites by more than 10%. We highlighted the foreseeable interest of spatially targeted interventions and promising SMC opportunities.

Obviously, the reservoir of parasites is not limited to hotspots. The asymptomatic reservoir in untargeted areas may trigger transmission especially when mosquito bites increased at the beginning of a new rainy season. This would explain why targeting LT hotspots (31-35% of villages, supposed to be the bottleneck in dry season), was not enough to reach the elimination stage, despite the important impact of this strategy. Targeting LT hotspots in the dry season was intended to quickly clear the parasite reservoir when its level was low. But if a widespread asymptomatic parasite carriage is assumed, high coverage and repeated interventions would be needed to reach elimination. Asymptomatic and sub-microscopic parasite carriage should be investigated to display geographical patterns of the reservoir [31,32]. Further research is needed on the relationship between sub-microscopic parasitemia and clinical malaria hotspot definition [33]. It has been argued that clinical malaria incidences should not be used in hotspot definitions without considering asymptomatic malaria patterns [8,34] and clustering of asexual parasite carriage using serological tools to detect malaria-specific immune responses [8].
Human mobility had usually been identified as a threat to malaria-free areas [35,36]. In our study, malaria incidence decreased in untargeted areas due to the decrease in malaria importation. Some studies assumed this could be related to less infected mosquitoes moving from targeted areas [37] but mosquito mobility modeling was not relevant in our patterns. More than 80% of villages were more than 3 km far from the nearest. Real human mobility data may be more accurate than estimations from the radiation model. But concerns about geographical scale prevented us from using proxies as Anonymized Call Details Records [38] to estimate mobility. Systematic studies are needed to inform mobility patterns in rural and semirural malaria areas in Senegal.
In the past, MDA interventions have contributed to eliminate malaria from islands and remote areas where population movements were closely controlled and gametocytocidal drugs have been used [39,40]. No resistance to Dihydroartemisinin-Primaquine was previously reported in our study area by 2017 and therefore this was not modeled.

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In practice, coverage and efficacy of drug interventions would also depend on the cooperation, involvement and education of local communities alongside with good communication and support from local authorities [41].

5. Conclusions

Our meta-population model specifically and explicitly considered human mobility at village scale, analyzing malaria transmission and interventions efficacy in Senegal. Whatever the intervention, pre-elimination stage (1-5 cases per 1,000 per year) could not be reached without simultaneously increasing vector control by more than 10%. Compartmental modeling remains an interesting tool to specifically guide malaria strategies and policies. Nevertheless, this quite deterministic approach needs to be cautiously interpreted. Unexpected changes in climatic, biological and socio-environmental factors could generate high inaccuracies in predictions.

Author Contributions: K.S. and J.G. designed the study, performed data processing, the statistical analysis and interpretation, and wrote the first draft of the article; R.G and M.P. contributed to the statistical analysis. E-H.B. and B.C. coordinated the data collection and validation; R.P. contributed to the interpretation of the results. All authors have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: none reported

Appendix A: model description and parameters

Model Description

In each village *k*, malaria transmission was described by a set of equations describing variations in human and mosquito compartments. The terms of the equations are defined below.

$S_k(t)$: Proportion of humans susceptible to malaria infection

$I_k(t)$: Proportion of blood-stage-infected humans, with few gametocytes, not immune and positive to Rapid Diagnostic Test (RDT)

$P(t)$: Proportion of humans with partial immunity (premunition). Individuals could remain in this state for many years but could lose their immunity if pregnant or on cessation of exposure. They were assumed to be RDT positive and own few gametocytes.

$Ga_k(t)$: Proportion of infected, gametocyte-positive, asymptomatic humans.

$Gm_k(t)$: Proportion of infected, gametocyte-positive, symptomatic humans.

$R_k(t)$: Proportion of humans who were temporarily not susceptible to new infection as a result of prophylactic effect of treatment for a malaria episode.

$Ai_k(t)$: Proportion of female mosquitoes that carry sporozoites in their salivary glands

$As_k(t)$: Proportion of female mosquitoes that have survived the cycle and were free from malaria sporozoites

m: Proportion of people that are away at a given time in the overall population (visiting other villages than their own village *k*)

$\upsilon(t)$: Anopheles density (ratio of the number of female mosquitoes to the number of humans at time *t*)

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α : Number of bites per female mosquito per night

β : Probability that a person bitten by an infectious mosquito becomes infected

$\gamma_s(t)$, $\gamma_i(t)$, $\gamma_p(t)$ and $\gamma_a(t)$ are rectangular pulse functions $\gamma(t) = K$ = -log(1-c)/Δ where c represents coverage and Δ the intervention duration in weeks

$\gamma_s(t)$: Rate at which susceptible individuals treated, turn to resistant compartment

$\gamma_i(t)$: Rate at which blood stage infected individuals, treated, turn to resistant compartment

$\gamma_p(t)$: Rate at which naturally immune individuals treated, turn to resistant compartment. Naturally immune individuals are assumed RDT positive. At the contrary, susceptible individuals are RDT negative.

$\gamma_a(t)$: Rate at which asymptomatic gametocyte carriers treated, turn to resistant compartment. Asymptomatic gametocyte carriers are assumed RDT positive.

$\gamma_m(t)$: Rate at which symptomatic gametocyte carriers treated, turn to resistant compartment. This corresponds to access to care in periods of no intervention.

η_{a1} : Transition rate from blood stage infection to asymptomatic gametocyte carriage

η_{a2} : Transition rate from asymptomatic gametocyte carriage to blood stage infection

η_{m1} : Transition rate from blood stage infection to symptomatic gametocyte carriage

η_{m2} : Transition rate from symptomatic gametocyte carriage to blood stage infection

η_{am} : Transition rate from asymptomatic gametocyte carriage to symptomatic gametocyte carriage

η_{ma} : Transition rate from symptomatic gametocyte carriage to asymptomatic gametocyte carriage

ε_i : Spontaneous recovery rate from blood stage infection

ε_p : Transition rate from premunition to susceptible

p_1 : Transition rate from blood stage infection to premunition

p_2 : Transition rate from premunition to blood stage infection (lost of premunition)

δ : Transition rate from resistant to susceptible (lost of treatment protection)

ζ_m : Probability that a mosquito biting a symptomatic gametocyte carrier got infected by plasmodium

ζ_a : Probability that a mosquito biting an asymptomatic gametocyte carrier got infected by plasmodium

ξ : Mortality rate of mosquitoes

Q_{kj} : Relative probabilities of travel from remote locations *j* to local village *k*.

$r(t)$: Rainfall at week *t*

Differential Equations describing malaria transmission inside a village *k* are listed below. *j* stands for remote villages.

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$$\begin{cases} \dfrac{dS}{dt} = -\upsilon(t)\times\alpha\beta S(t)i(t) + \delta R(t) + \varepsilon_i I(t) - \gamma_s(t)S(t) + \varepsilon_p P(t) \qquad (A1) \\ \dfrac{dI}{dt} = \upsilon(t)\times\alpha\beta S(t)i(t) + \eta_{a2}Ga(t) + \eta_{m2}Gm(t) - \left(\eta_{a1} + \eta_{m1} + \gamma_i + \varepsilon_i + p_1\right)I(t) + p_2\ P(t) \qquad (A2) \\ \dfrac{dP}{dt} = p_1 I(t) - (p_2 + \gamma_p + \varepsilon_p)P(t) \qquad (A3) \\ \dfrac{dGa}{dt} = \eta_{a1}I(t) + \eta_{ma}Gm(t) - (\eta_{a2} + \eta_{am} + \gamma_a)Ga(t) \qquad (A4) \\ \dfrac{dGm}{dt} = \eta_{m1}I(t) + \eta_{am}Ga(t) - (\eta_{m2} + \eta_{ma} + \gamma_m)Gm(t) \qquad (A5) \end{cases}$$

$$\frac{dR}{dt} = \gamma_m Gm(t) + \gamma_a Ga(t) + \gamma_i I(t) + \gamma_p P(t) + \gamma_s S(t) - \delta R(t) \qquad (A6)$$

$$\frac{dAi}{dt} = \alpha\left(1\text{-}Ai(t)\right)i_m(t) - \xi Ai(t) \qquad (A7)$$

$$i(t) = \left(1-m\right)Ai_k(t) + m\sum_{j\neq k} Q_{kj}Ai_j(t) \qquad (A8)$$

$$i_m(t) = \left(1-m\right)\left(\zeta_a Ga_k(t) + \zeta_m Gm_k(t)\right) + m\sum_{j\neq k} Q_{jk}\left(\zeta_a Ga_j(t) + \zeta_m Gm_j(t)\right) \qquad (A9)$$

$$\upsilon(t) \propto \sum_{t-lag}^{t} r(t) \qquad (A10)$$

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Model parameters

Table A1. Descriptions, sources and values of parameters used in the malaria transmission meta-population model, Mbour zone, Senegal, 2008-2012

	Parameter description	References	Parameter values	95% C.I.
$\upsilon(t)$	Anopheles density in relation to hosts	0 to 12 mosquitoes per human [1,2]	0-12	
α	Mosquito biting rate, per night	0.08 to 0.46 [3]	0.46 bite/anopheles/night	
β	Human susceptibility to infection	0.3 [3]	0.3	
EIR	Entomological Inoculation Rate	0 to 17.6 [4]	0 to 2.16 /per person/ year	
ζ_m	Mosquito susceptibility to infection from symptomatic humans	0.80 [3]	0.80	
ζ_a	Mosquito susceptibility to infection from asymptomatic humans	expert opinion $\zeta_a = 0.1\zeta_m$	0.08	
η_{m1}	Transition rate from blood stage parasitemia to symptomatic infection with gametocytemia	0.05 to 0.2 [5]	0.1 days^{-1}	
η_{m2}	Transition rate from symptomatic infection with gametocytemia to blood stage parasitemia	expert opinion	0	
η_{a1}	Transition rate from blood stage parasitemia to asymptomatic infection with gametocytemia	0.05 to 0.2 [5]	0.1 days^{-1}	
η_{a2}	Transition rate from symptomatic infection with gametocytemia to blood stage parasitemia	expert opinion	0	
η_{am}	Transition rate from asymptomatic infection with gametocytemia to symptomatic infection with gametocytemia	expert opinion	0	
η_{ma}	Transition rate from symptomatic infection with gametocytemia to asymptomatic infection with gametocytemia	expert opinion	0	
δ	Transition rate from post-treatment protection to susceptible	0.032 [6,7]	0.032 days^{-1}	
ξ	Daily Mosquito mortality rate	0.18 [3]	0.18	
p_1	Rate of the acquisition of premunition	fitted	0.0002 days^{-1}	0.0001, 0.00035 days^{-1}
p_2	Rate of the loss of premunition	fitted	0.0002 days^{-1}	0.0001, 0.00035 days^{-1}
γ_m	Usual recovery rate by access to care, not related to specific interventions	fitted	0.37 days^{-1}	0.20, 0.51 days^{-1}

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m	Proportion of people who are away from their home village at a given time	fitted	0.01	0.09, 0.2
ε_i	Spontaneous recovery rate from blood stage infection	expert opinion	0	
ε_p	Transition rate from premunition to susceptible	expert opinion	0	

[1] Ndiath, M. O. et al. Low and seasonal malaria transmission in the middle Senegal River basin: identification and characteristics of Anopheles vectors. Parasites & vectors 5, 21, doi:10.1186/1756-3305-5-21 (2012). [2] Ndiath, M. O. et al. Methods to collect Anopheles mosquitoes and evaluate malaria transmission: a comparative study in two villages in Senegal. Malaria journal 10, 270, doi:10.1186/1475-2875-10-270 (2011). [3] Ermert, V., Fink, A. H., Jones, A. E. & Morse, A. P. Development of a new version of the Liverpool Malaria Model. I. Refining the parameter settings and mathematical formulation of basic processes based on a literature review. Malaria journal 10, 35, doi:10.1186/1475-2875-10-35 (2011). [4] Gadiaga, L. et al. Conditions of malaria transmission in Dakar from 2007 to 2010. Malaria journal 10, 312, doi:10.1186/1475-2875-10-312 (2011). [5] Baker, D. A. Malaria gametocytogenesis. Molecular and biochemical parasitology 172, 57-65, doi:10.1016/j.molbiopara.2010.03.019 (2010). [6] Henriques, G. et al. Artemisinin resistance in rodent malaria - mutation in the AP2 adaptor μ-chain suggests involvement of endocytosis and membrane protein trafficking. Malaria journal 12, 118, doi:10.1186/1475-2875-12-118 (2013). [7] Bretscher, M. T. et al. A comparison of the duration of post-treatment protection of artemether-lumefantrine, dihydroartemisinin-piperaquine and artesunate-amodiaquine for the treatment of uncomplicated malaria. Malaria journal 13, P19-P19, doi:10.1186/1475-2875-13-S1-P19 (2014).

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Equation A1 describes variations in the proportion of susceptible individuals $S(t)$

In each village *k*, individuals leave the susceptible compartment by getting infected. Human infection rate was the product of the anopheles density $\upsilon(t)$, the frequency of mosquito bites α, the human susceptibility to infection β and the effective proportion of infected mosquitoes affecting village *k* and represented by

$$i(t)=\left[(1-m)Ai_k+m\sum_{j\neq k}Q_{kj}Ai_j\right]$$

The effective proportion of infected mosquitoes affecting village *k* was a weighted average of local proportion of infected mosquitoes Ai_k and remote proportions of infected mosquitoes Ai_j. The weights depended on the proportion of human mobility (m) and also on the relative probabilities of travel from remote locations *j* to local village *k* (Q_{kj}).

The proportion of susceptible individuals in village *k* was increased by individuals losing their protection from resistant compartment (δR), who were no longer under treatment effect. These individuals turned back to the susceptible compartment, at the rate δ. In case of mass intervention, the proportion of susceptible individuals in village *k* was decreased by the fraction of treated individuals ($-\gamma_s(t)\times S$).

Spontaneous recovery was assumed unlikely ($\varepsilon_i=\varepsilon_p=0$) and population sizes remained stable since travels are supposed to be round trips. Birth and death rates were supposed to balance each other.

Equation 2 *(A2)* describes variations in the proportion of blood stage infection (*I*)

New infections increased the compartment (I) by $\upsilon(t)\times\alpha\beta S\times i(t)$.

At the opposite, compartment I was decreased by:

- Spontaneous recovery from blood stage infection ($-\varepsilon_i I$)
- Gametocyte production ($-\left(\eta_{a1}+\eta_{m1}\right)I$)
- Acquisition of premunition ($-p_1 I$)

Theoretically, compartment I could be increased by receiving gametocyte carriers who had lost their gametocytes ($+\eta_{a2}Ga+\eta_{m2}Gm$). In this study, this phenomenon was assumed unlikely.

Equation 3 *(A3)* describes variations in the proportion of preimmune (P)

The compartment increased by receiving individuals acquiring premunition after several blood stage infections ($+p_1 I$). The compartment decreased when infection was reactivated by loss of immunity ($-p_2 P$) or by interventional treatment ($-\gamma_p(t)P$). Spontaneous recovery towards compartment of susceptible ($-\varepsilon_p P$) was considered unlikely ($\varepsilon_p=0$).

Equations 4 *(A4)* and 5 *(A5)* describe variations in compartments of gametocyte carriers

Compartments of gametocyte carriers increased by receiving individuals from blood stage infection ($+\eta_{a1}I$ or $+\eta_{m1}I$) and from each other ($+\eta_{ma}Gm$ or $+\eta_{am}Ga$). These compartments could decrease by spontaneous end of gametocytogenesis ($+\eta_{a2}Ga$ or $+\eta_{m2}Gm$) or transition to resistant compartment because of treatment ($-\gamma_a(t)\times Ga$, $-\gamma_m(t)\times Gm$).

Equation 6 *(A6)* describes variations in the proportion of individuals which became resistant to malaria due to treatment effects

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The compartment was filled by individuals under treatment effects (usual malaria therapies or interventional drugs), coming from all compartments where an effective malaria treatment had been delivered. Compartment was depleted by the loss of protection ($-\delta R$), beyond drug half-life. Long-acting drugs as DHA-PQ and SPAQ were supposed used for MDA/MSAT and SMC respectively, all yielding protection for about 4 weeks duration.

Equation 7 *(A7)* describes variations in the proportion of infective mosquitoes

The proportion of infective mosquitoes was the product of the frequency of mosquito bites α, by the effective proportion of infected humans affecting location k, denoted $i_m(t)$.

$$i_m(t) = (1-m)\left(\zeta_a Ga_k + \zeta_m Gm_k\right) + m\sum_{j\neq k} Q_{kj}\left(\zeta_a Ga_j + \zeta_m Gm_j\right)$$

This quantity is a weighted average of the local proportion of infected humans $\left(\zeta_a Ga_k + \zeta_m Gm_k\right)$ and remote proportions of infected humans $\sum_{j\neq k} Q_{kj}\left(\zeta_a Ga_j + \zeta_m Gm_j\right)$. The weights depended on the proportion of human mobility (m) and on the relative probabilities of travel from remote locations j to local village k (Q_{kj}). The susceptibility of mosquitoes to infection from human (ζ_m) was assumed ten times higher from symptomatic than from asymptomatic (ζ_a) (expert opinion).

The proportion of infective mosquitoes was decreased by deaths in mosquito population ($-\xi Ai_k$).

Equation 8 *(A8)* details the effective proportion of infective mosquitoes in a location *k* taking account of human mobility

Equation 9 *(A9)* details the effective proportion of infected humans in a location *k* taking account of human mobility

Equation 10 *(A10)* represents variations in anopheles' density with respect to rainfall.

Anopheles density depends on deterministic environmental factors. Among these factors, accumulated rainfall on previous weeks was the most important. *lag* was the duration (in weeks) between rainfall and mosquito bites. Optimal lag was estimated on sensitivity analysis as the one minimizing the gap between model estimations and observations (Figure A1)

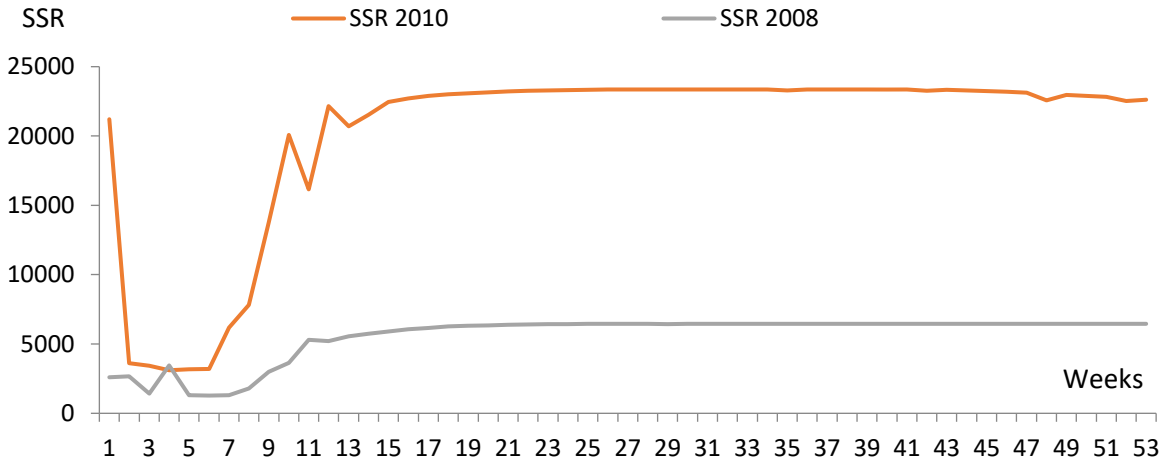

Figure A1. Goodness of fit of malaria meta-population model according to the assumed lag between rainfall and mosquito bites. Calibrations were undertaken on 2008 and 2010 transmission seasons. Optimization function computing the sum of squared residuals (SSR) were minimized for 6 weeks lag.

A3. Initial conditions

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Table A2. Initial conditions

Compartment	Assigned value	Reference
I_0	$I_0 \approx 0$. Proportion of plasmodium falciparum infection in humans in dry season	[1,3]
P_0	P_0 =0.2, Proportion of preimmune individuals	0.16 [4] 0.27 [5] 0.23-0.32 [2]
Gm_0	Proportion of symptomatic malaria in dry season. Average dry season incidence estimated from all the dataset (5years data)	[6]
Ga_0	Proportion of asymptomatic gametocyte carriers were assumed 10 times lower than symptomatic (expert advice)	Deduced from Gm_0
R_0	$R_0 \approx Gm_0$. Continuous access to treatment for symptomatic malaria.	[7] Deducted from Gm_0
Ai_0	$Ai_0 \approx 0$	[1,3]
S_0	$S_0 = 1 - Gm_0 - Ga_0 - R_0 - P_0$	Calculated

[1] Ndiath, M. O. *et al.* Low and seasonal malaria transmission in the middle Senegal River basin: identification and characteristics of Anopheles vectors. *Parasites & vectors* **5**, 21, doi:10.1186/1756-3305-5-21 (2012). [2] Males, S., Gaye, O. & Garcia, A. Long-term asymptomatic carriage of Plasmodium falciparum protects from malaria attacks: A prospective study among Senegalese children. Clinical Infectious Diseases 46, 516-522, doi:Doi 10.1086/526529 (2008). [3] -Sagna, A. B. et al. Plasmodium falciparum infection during dry season: IgG responses to Anopheles gambiae salivary gSG6-P1 peptide as sensitive biomarker for malaria risk in Northern Senegal. Malaria journal 12, 301, doi:10.1186/1475-2875-12-301 (2013). [4] Diallo, A. et al. Asymptomatic carriage of plasmodium in urban Dakar: the risk of malaria should not be underestimated. PloS one 7, e31100, doi:10.1371/journal.pone.0031100 (2012). [5] Le Port, A. et al. Relation between Plasmodium falciparum asymptomatic infection and malaria attacks in a cohort of Senegalese children. Malaria journal 7, 193, doi:10.1186/1475-2875-7-193 (2008). [6] Townes, L. R., Mwandama, D., Mathanga, D. P. & Wilson, M. L. Elevated dry-season malaria prevalence associated with fine-scale spatial patterns of environmental risk: a case-control study of children in rural Malawi. Malaria journal 12, 407, doi:10.1186/1475-2875-12-407 (2013). [7] Thiam, S. et al. Scale-up of home-based management of malaria based on rapid diagnostic tests and artemisinin-based combination therapy in a resource-poor country: results in Senegal. Malaria journal 11, 334, doi:10.1186/1475-2875-11-334 (2012).

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Appendix B: Further results from simulations

Simulation of interventions targeting hotspots from various definitions

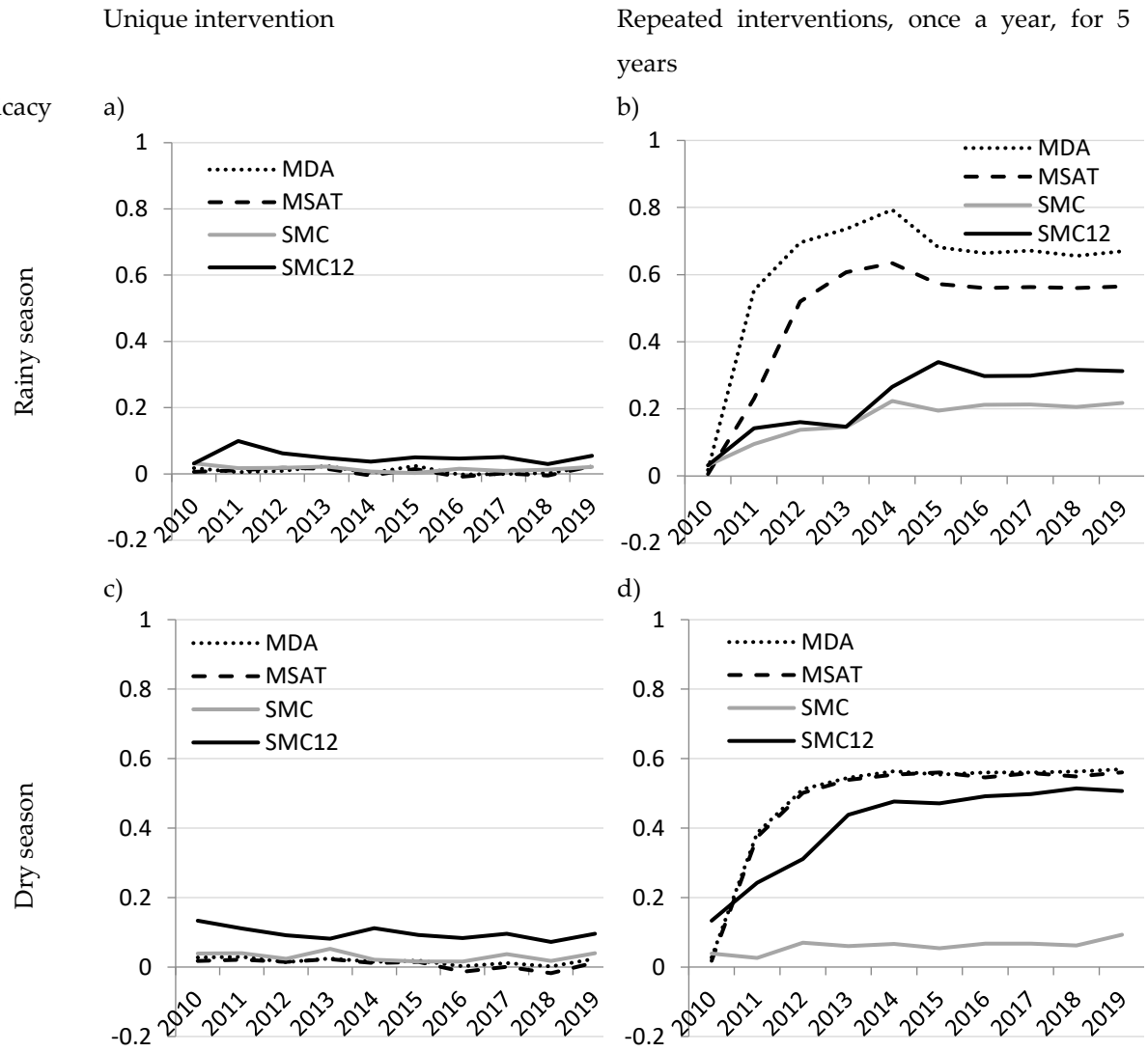

Figure. A2. Decrease in malaria incidence while simulations interventions targeting one third of HT hotspots, Mbour, Senegal 2008-2012. Y-axis represents intervention efficacy (proportionate decrease in overall malaria incidence). a) Unique one-year intervention during rainy season, b) Repeated interventions on five consecutive rainy seasons, once a year, c) Unique one-year intervention during dry season, d) Repeated interventions on five consecutive dry seasons, once a year.

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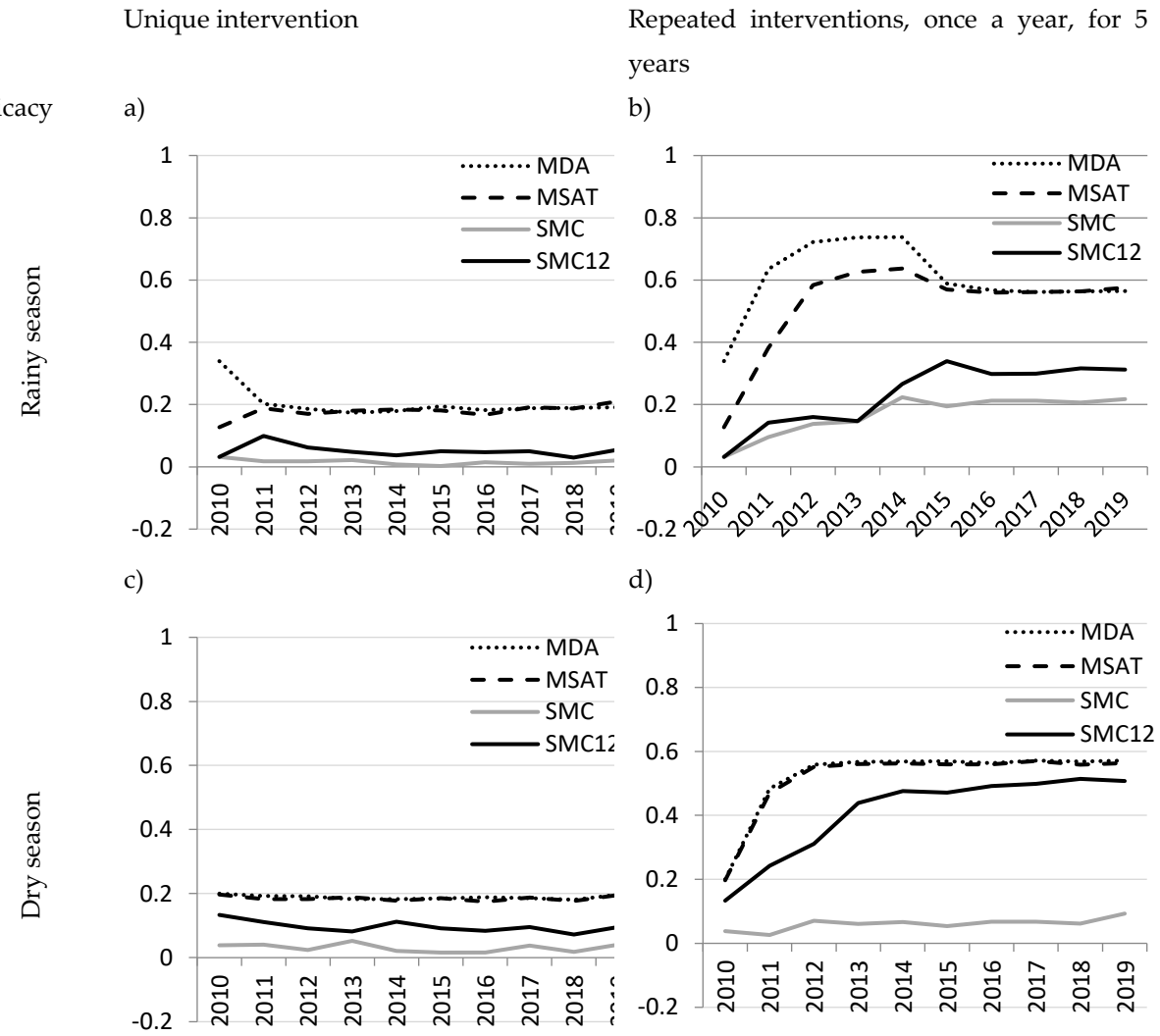

Figure. A3. Decrease in malaria incidence while targeting one third of HC hotspots, Mbour, Senegal 2008-2012. Y-axis represents the percentage of decrease in overall malaria incidence. a) Unique one-year intervention during rainy season, b) Repeated interventions on five consecutive rainy seasons, once a year, c) Unique one-year intervention during dry season, d) Repeated interventions on five consecutive dry seasons, once a year.

List of abbreviations

LLIN: long-lasting insecticide-treated bed nets
RDT: Rapid Diagnostic Tests
ACT: Artemisinin-based Combination Therapy
WHO: World Health Organization
MDA: Mass Drug Administration
MSAT: Mass Screen and Treat
SMC: Seasonal Malaria Chemoprevention
SEIR: Susceptible-Exposed-Infected-Recovered

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GPS: Global Positioning System
MCMC: Markov Chain Monte Carlo
LT Hotspots: Low Transmission Period hotspots
HT hotspots: High Transmission Period Hotspots
HC hotspots: High Connectivity Hotspots
HTP: high transmission period
LTP: low transmission period
EIR: entomological inoculation rate
IRS: Indoor Residual Spraying

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