



*Research article***Integrated malaria control and drug resistance in an age- and sex-structured model with seasonal malaria chemoprevention, mass drug administration, and routine case management****Manuela M. Nimpa^{1,2}, Franck J. Dongmo^{1,3}, Charles S. Wondji^{1,4} and Ramsès Djidjou-Demasse^{5,6,*}**¹ Centre for Research in Infectious Diseases, Yaoundé, Cameroon² Department of Mathematics, Faculty of Sciences, University of Yaoundé I, Yaoundé, Cameroon³ Department of Mathematics and Computer Science, University of Dschang, Dschang, Cameroon⁴ Department of Vector Biology, Liverpool School of Tropical Medicine, Liverpool, UK⁵ UMI 209 UMMISCO, IRD, Sorbonne University, Paris, France⁶ École Polytechnique de Thiès, Thiès, Sénégal* **Correspondence:** Email: ramses.djidjoudemasse@ird.fr.

Abstract: Malaria control is increasingly threatened by antimalarial drug resistance. We develop an age- and sex-structured malaria transmission model integrating drug-sensitive and drug-resistant parasites, routine case management, seasonal malaria chemoprevention (SMC), and mass drug administration (MDA). The main novelty is the joint representation of demographic heterogeneity and time since recovery and intervention exposure, allowing waning immunity and drug efficacy to interact with the interventions' deployment and resistance dynamics. We establish the well-posedness of the model and derive the basic reproduction number $\mathcal{R}_0$ using a next-generation operator. Global sensitivity analysis and scenario-based simulations are used to identify the key drivers of clinical burden and resistance and to compare intervention strategies. Under the constant intervention assumption used for the $\mathcal{R}_0$ analysis, neither SMC nor MDA alone reduces $\mathcal{R}_0$ below unity over the coverage ranges considered, whereas their combination can reduce $\mathcal{R}_0$ below unity. Time-dependent simulations further show that the interventions' coverage, timing, and repeated cycles shape both the clinical impact and resistance dynamics. An optimization framework determines the minimal intervention coverage required to achieve predefined reductions in clinical cases. Overall, the framework provides a mechanistic basis for investigating the epidemiological-evolutionary trade-offs of integrated malaria control strategies.

Keywords: structured model; nonlinear dynamical systems; drug resistance; MDA; SMC; routine management

Mathematics Subject Classification: 37N25, 35Q92, 92D30

1. Introduction

Despite the availability of effective preventive and therapeutic tools, malaria remains one of the leading infectious diseases worldwide. The effectiveness of current control strategies is increasingly challenged by several factors, including changes in the vectors' ecology, limited access to healthcare, insufficient intervention coverage, and, most importantly, the emergence and spread of antimalarial drug resistance [1]. Drug-resistant *Plasmodium* parasites survive therapeutic drug concentrations, reducing treatment efficacy and facilitating onward transmission [2]. Once established, resistant strains are particularly difficult to eliminate because treatment failures prolong infectiousness, increasing the likelihood that resistant parasites are transmitted to mosquitoes and subsequently spread throughout the human population [3, 4]. Resistance to several first-line antimalarials, including chloroquine, piperaquine, and sulfadoxine-pyrimethamine (SP), has already been documented in multiple endemic regions [5–7]. Preserving the efficacy of existing drugs therefore remains a major priority for malaria control.

To reduce the malaria burden in moderate- to high-transmission settings, the World Health Organization recommends seasonal malaria chemoprevention (SMC) for young children living in highly seasonal areas [8], while mass drug administration (MDA) is increasingly considered in settings where elimination remains difficult [9]. SMC consists of monthly administration of sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) during the transmission season without prior screening of asymptomatic children. By maintaining therapeutic drug concentrations, it clears existing infections and provides approximately four weeks of prophylactic protection, making the timing of successive treatment rounds crucial for maximizing efficacy while limiting resistance selection [8, 10]. In contrast, MDA administers a complete antimalarial treatment course to an entire population regardless of infection status [11]. When implemented with high coverage and effective vector control, repeated MDA campaigns can substantially reduce parasites' prevalence and suppress both drug-sensitive and drug-resistant parasites [12, 13]. However, because drug-induced protection generally persists for only one to three months, the epidemiological impact of both SMC and MDA depends critically on the timing, frequency, and the coverage of intervention rounds [13].

Mathematical models have long contributed to understanding malaria's transmission, intervention strategies, and the evolution of drug resistance. Previous studies have investigated the effects of treatment coverage [14, 15], vector control [5], resistant parasites' emergence [16], and combined intervention strategies under a variety of epidemiological settings [17]. Collectively, these studies demonstrate that interventions' effectiveness depends strongly on the transmission intensity, treatment coverage, and resistance prevalence, and that combining therapeutic and vector control interventions generally outperforms single-control strategies. Nevertheless, an important limitation remains. Existing models evaluating SMC and/or MDA are generally memoryless (Markovian), implicitly assuming exponentially distributed residence times in the corresponding protected states, e.g., [17, 18]. In practice, however, drug efficacy depends on the time elapsed since administration, as the protective effect of the drug generally wanes with time since administration. Accounting for this memory effect is therefore important for accurately representing the duration of protection and, consequently, the optimal timing of intervention rounds [19]. Ignoring such temporal dependence may overestimate an intervention's effectiveness and lead to suboptimal deployment strategies. More generally, memory effects have been shown to play an important role in capturing epidemiological dynamics that cannot

be adequately represented by memoryless formulations; see, e.g., [20–22].

To address these limitations, we develop an age-structured malaria transmission model that evaluates the combined effects of routine case management, SMC, and MDA in the presence of drug resistance. Rather than treating the host population as homogeneous, the proposed framework incorporates several biologically meaningful structured variables that directly influence both malaria's transmission and the interventions' effectiveness [22].

The first structure describes the time since recovery, accounting for the fact that naturally acquired immunity to malaria is partial and wanes after parasite clearance; consequently, susceptibility to reinfection depends not only on the recovery status but also on the time elapsed since recovery, allowing us to capture the gradual loss of immune protection. The second structure represents the time since treatment, reflecting the time-since-administration pharmacodynamic efficacy profile of SMC and MDA, whereby drug concentrations decrease continuously after administration, leading to a progressive loss of prophylactic efficacy; this formulation enables quantification of the duration of post-treatment protection and an analysis of how the timing and spacing of SMC and MDA rounds affect the population-level impact. Finally, the host population is structured by age and sex, since age determines eligibility for the intervention, where SMC targets young children while MDA covers a broader population, and because school-aged children constitute a major infectious reservoir due to frequent asymptomatic infections and high gametocyte carriage [23,24], while sex structure is included because pregnancy reduces immunity and increases susceptibility to malaria [25], and because pregnant women and women of reproductive age are often excluded from MDA campaigns, thereby affecting effective coverage.

The model further distinguishes drug-sensitive and drug-resistant parasites, symptomatic and asymptomatic infections, and treated and untreated clinical cases. Routine case management targets symptomatic individuals, whereas SMC and MDA additionally protect susceptible, recovered, and asymptomatically infected individuals through prophylactic drug action whose efficacy decreases continuously over time.

Compared with the existing literature on structured malaria transmission models (e.g., [26–28]), the main novelty of this work lies in integrating these epidemiological, demographic, pharmacodynamic, and evolutionary components within a single structured transmission framework. In particular, the model simultaneously accounts for age- and sex-dependent heterogeneity, time since recovery, time since intervention exposure, co-circulation of drug-sensitive and drug-resistant parasites, routine case management, and preventive treatment through SMC and MDA. This structure makes it possible to investigate not only the epidemiological impact of individual and combined interventions, but also their consequences for the emergence and propagation of drug resistance under waning drug protection.

From a mathematical perspective, we establish the well-posedness of the resulting nonlinear structured system and derive the basic reproduction number $\mathcal{R}_0$ using next-generation operator theory. We then combine a global sensitivity analysis and time-dependent numerical simulations to identify the principal drivers of clinical burden and resistance, compare alternative intervention schedules and coverage levels, and investigate the trade-off between short-term epidemiological impact and resistance selection.

The remainder of the paper is organized as follows. Section 2 introduces the mathematical model. Section 3 establishes its fundamental analytical properties, including its well-posedness and the derivation of the basic reproduction number. Section 4 presents the numerical parameterization

and investigates the epidemiological impact of routine case management, SMC, and MDA. Finally, Section 5 discusses the main biological and mathematical implications of our findings.

2. Model formulation

The model couples malaria transmission between humans and mosquitoes while distinguishing drug-sensitive and drug-resistant parasite strains. The human population is stratified by sex and chronological age and is divided into susceptible, asymptomatic, symptomatic, and recovered epidemiological states. Symptomatic infections are further distinguished according to routine case management status. To represent transient immunity and pharmacological protection, recovered individuals are additionally structured by time since recovery, whereas individuals receiving SMC or MDA are structured by time since intervention. SMC and MDA act on eligible non-symptomatic individuals, while routine case management acts on symptomatic infections. Figure 1 summarizes the corresponding transitions, and Table 1 provides the definitions of all state variables. Systems (2.1)–(2.5) subsequently formalize these processes.

Subscripts $\{s, r\}$ denote sensitive (s) and resistant (r) infections in humans, while $\{T, U\}$ indicate the routine case management status of clinical infections, distinguishing between treated (T) and untreated (U) individuals. Sex is denoted by $g \in \{\varphi, \sigma\}$, φ for female, and σ for male. Subscripts m and h refer to the mosquito and human populations, respectively. The mosquito population is divided into susceptible mosquitoes $S_m(t)$ and infectious mosquitoes $I_m^k(t)$ carrying either a sensitive ($k = s$) or resistant ($k = r$) parasite strain. Humans may be exposed to MDA, SMC, or remain unexposed to both interventions. At time t , unexposed humans of age a are divided into four epidemiological classes: Susceptible $S_h^g(t, a)$, asymptomatic infected $A_h^{k,g}(t, a)$, symptomatic infected (clinical cases) $I_{h,\ell}^{k,g}(t, a)$, and recovered $R_h^g(t, a, \sigma)$, where σ denotes time since recovery, $\ell \in \{T, U\}$ is treatment status, and $k \in \{s, r\}$ is the infection type. Only non-symptomatic individuals (susceptible, asymptomatic, or recovered) are eligible for MDA or SMC. Susceptible and recovered individuals exposed to SMC (respectively, MDA) are denoted by $Y_{h,SMC}^g(t, a, \sigma)$ (respectively, $Y_{h,MDA}^g(t, a, \sigma)$), while asymptomatic infected individuals exposed to SMC or MDA are denoted by $A_{h,SMC}^{k,g}(t, a, \sigma)$ and $A_{h,MDA}^{k,g}(t, a, \sigma)$, respectively, with σ denoting the time since exposure.

The total number of human $N_h(t)$, and mosquitoes $N_m(t)$ are, respectively, given by

$$N_h(t) = \int_0^\infty \sum_{g \in \{\varphi, \sigma\}} \left(S_h^g(t, a) + \sum_{k \in \{s, r\}} A_h^{k,g}(t, a) + \sum_{k \in \{s, r\}, \ell \in \{T, U\}} I_{h,\ell}^{k,g}(t, a) \right) da \\ + \int_0^\infty \int_0^\infty \sum_{g \in \{\varphi, \sigma\}} \left(R_h^g(t, a, \sigma) + \sum_{\mathcal{Y} \in \{Y, A\}} \left(\mathcal{Y}_{h,SMC}^g(t, a, \sigma) + \mathcal{Y}_{h,MDA}^g(t, a, \sigma) \right) \right) d\sigma da,$$

and

$$N_m(t) = S_m(t) + \sum_{k \in \{s, r\}} I_m^k(t).$$

The schematic illustration of the model is shown in Figure 1, and all variables and parameters of the model are summarized in Tables 1 and 2, respectively.

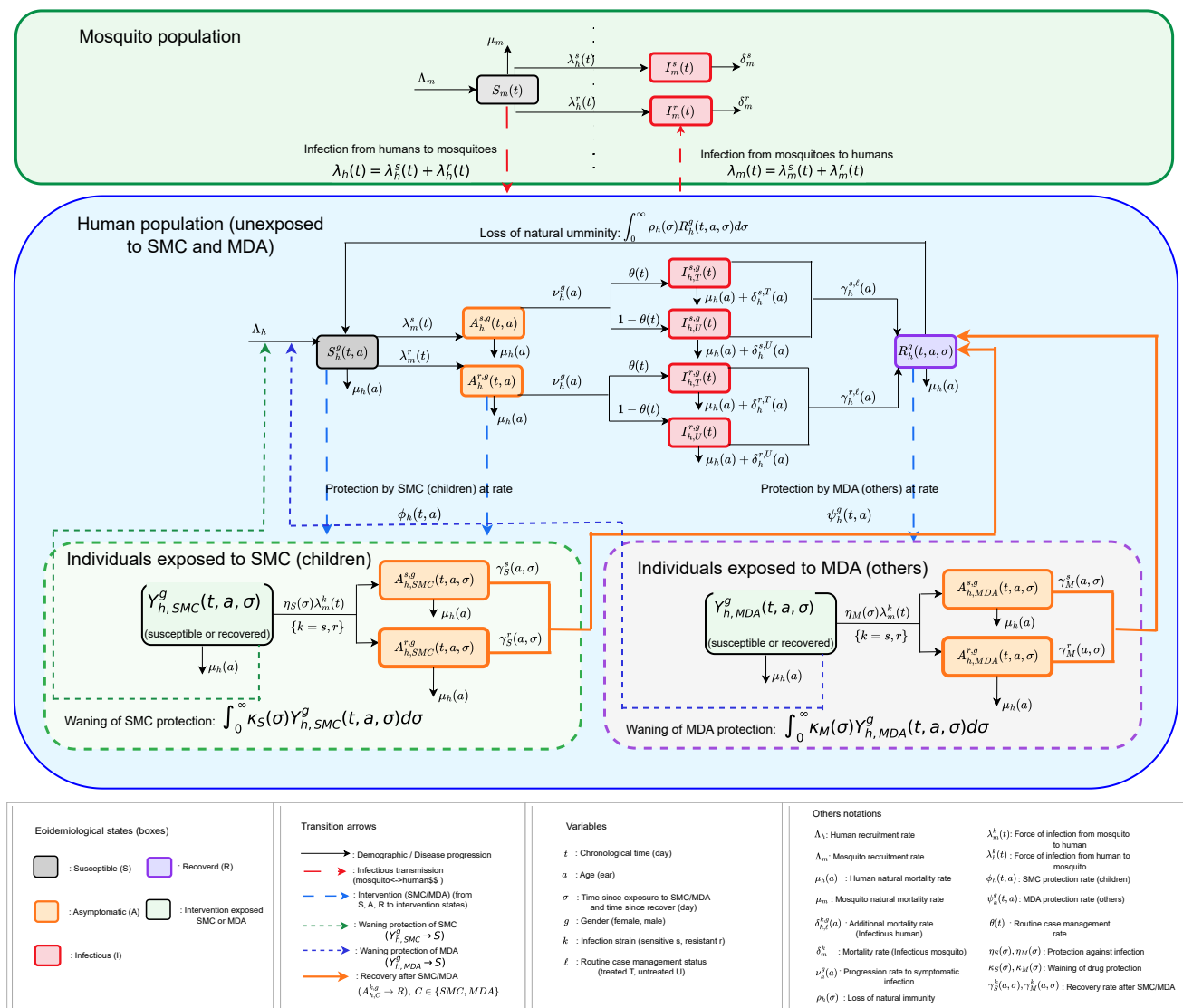


Figure 1. Schematic representation of the malaria transmission model incorporating SMC, MDA, and routine case management. The model distinguishes mosquito and human populations and tracks sensitive (s) and resistant (r) infections. Humans unexposed to SMC and MDA are structured by sex g and age a into susceptible S_h^g , asymptomatic $A_h^{k,g}$, symptomatic $I_{h,\ell}^{k,g}$, and recovered R_h^g states, with symptomatic infections further distinguished by routine case management status ℓ . SMC, applied to eligible children at a rate of $\phi_h(t, a)$, and MDA, applied to other eligible individuals at a rate of $\psi_h^g(t, a)$, target susceptible, asymptomatic, and recovered individuals and transfer them to the corresponding intervention-exposed states $Y_{h,C}^g$ and $A_{h,C}^{k,g}$, $C \in \{SMC, MDA\}$. Drug protection modifies susceptibility to mosquito-borne infection through $\eta_S(\sigma)$ and $\eta_M(\sigma)$; waning protection returns $Y_{h,C}^g$ to the unprotected susceptible state, whereas recovery of intervention-exposed asymptomatic individuals leads to R_h^g . Recovered individuals lose natural immunity and return to S_h^g . Mosquito-to-human and human-to-mosquito transmission are governed by $\lambda_m(t) = \lambda_m^s(t) + \lambda_m^r(t)$ and $\lambda_h(t) = \lambda_h^s(t) + \lambda_h^r(t)$, respectively.

Table 1. Notations of variables, their biological meaning, and unit.

Notations	Description (unit)
t	Time (day)
a	Age of human population (year)
σ	Time since exposure to SMC, MDA, and time since recovery (day)
$g \in \{\varnothing, \sigma\}$	Sex of human population (female, male)
$k \in \{s, r\}$	Strain of infection (sensitive, resistant)
$\ell \in \{T, U\}$	Routine case management status (treated, untreated)
Human unexposed to SMC and MDA	
$S_h^g(t, a)$	Sex-specific susceptible humans, aged a , unexposed to SMC and MDA
$A_h^{k,g}(t, a)$	Sex-specific asymptomatic humans, infected to k -infection, aged a , unexposed to SMC and MDA
$I_{h,\ell}^{k,g}(t, a)$	Sex-specific symptomatic humans, infected with k -infection, under routine case management status ℓ , aged a , unexposed to SMC and MDA
$R_h^g(t, a, \sigma)$	Sex-specific recovered humans, aged a , unexposed to SMC and MDA
Human exposed to SMC	
$Y_{h,SMC}^g(t, a, \sigma)$	Sex-specific susceptible and recovered humans, aged a , exposed to SMC
$A_{h,SMC}^{k,g}(t, a, \sigma)$	Sex-specific asymptomatic humans, infected to k -infection, aged a , exposed to SMC
Human exposed to MDA	
$Y_{h,MDA}^g(t, a, \sigma)$	Sex-specific susceptible and recovered humans, aged a , exposed to MDA
$A_{h,MDA}^{k,g}(t, a, \sigma)$	Sex-specific asymptomatic humans, infected to k -infection, aged a , exposed to MDA

Table 2. Parameters, their biological meaning, and value.

Variable parameters		
Parameters	Description (unit)	Value [Ref]
$\phi_h(t, a)$	Rate of exposure to SMC	$\{0.1, 0.5, 0.95\}$
$\psi_h^g(t, a)$	Sex-specific rate of exposure to MDA	$\{0.1, 0.5, 0.95\}$
$\theta(t)$	Routine treatment coverage rate of clinical cases	$\{0.1, 0.5, 0.95\}$
InitPrev	Initial resistance prevalence	$\{0.01, 0.1\}$
p_f	Proportion of pregnant female humans	$\{0.1, 0.2\}$ [29]
a_{lim}	Age to be eligible for SMC implementation (years)	$\{5, 10\}$ [30]
n_c	Number of SMC and MDA cycles	$\{3, 4, 5\}$ [8, 31]
ε_s	Probability of mutation from drug-sensitive treated infections to drug-resistant infections	$\{0.01, 0.1\}$
ε_r	Probability of mutation from drug-resistant treated infections to drug-sensitive infections	$\bar{\varepsilon}\varepsilon_s$
$\delta_h^{r,T}(a)$	Additional death rate of treated resistant infections (day^{-1})	$\bar{\delta}_h\delta_h^{s,U}$
$\gamma_h^{r,T}(a)$	Recovery rate of treated humans to resistant infection (day^{-1})	$\bar{\gamma}_h\gamma_h^{s,T}$
$\gamma_h^{r,U}(a)$	Recovery rate of untreated humans to resistant infection (day^{-1})	$\bar{\gamma}_h\gamma_h^{r,U}$
β_m^r	Human infection rate from resistant mosquitoes (day^{-1} bites $^{-1}$)	$\bar{\beta}_m\beta_m^s$
δ_m^r	Mortality rate of resistant infectious mosquitoes (day^{-1})	$\bar{\delta}_m\delta_m^s$

Continued on the next page

Fixed parameters		
Parameters	Description (unit)	Value [Ref]
$\bar{\gamma}_h$	Relative recovery factor for humans under resistant infection	0.7 [assumed]
$\bar{\delta}_h$	Relative disease-induced mortality factor for humans under resistant infection	1.5 [assumed]
$\bar{\epsilon}$	Scale factor defining the relative probability of infection for resistant strains compared with sensitive ones	0.5 [assumed]
$\bar{\beta}_m$	Relative transmission weight for the infection of humans by mosquitoes carrying resistant parasites	0.5 [assumed]
$\bar{\delta}_m$	Relative mortality factor for mosquitoes under resistant infection	0.95 [assumed]
$\gamma_h^{s,U}(a)$	Untreated recovery from sensitive infection (day^{-1})	0.0035 [32]
$\gamma_h^{s,T}(a)$	Treated recovery from sensitive infection (day^{-1})	3×0.0035 [33]
$\gamma_M^k(a, \sigma)$	Recovery rate of humans due to MDA treatment (day^{-1})	Eq (4.7)
$\gamma_S^k(a, \sigma)$	Recovery rate of humans due to SMC treatment (day^{-1})	Eq (4.7)
$\beta_h^s(a)$	Mosquito infection rate from sensitive humans ($\text{day}^{-1} \text{ bites}^{-1}$)	Eq (4.2)
$\beta_h^r(a)$	Mosquito infection rate from resistant humans ($\text{day}^{-1} \text{ bites}^{-1}$)	Eq (4.2)
$\bar{\beta}_{h,S}^s(a, \sigma)$	Sensitive infection rate in mosquitoes from humans under SMC	Eq (4.1)
$\bar{\beta}_{h,S}^r(a, \sigma)$	Resistant infection rate in mosquitoes from humans under SMC	Eq (4.1)
$\bar{\beta}_{h,M}^s(a, \sigma)$	Sensitive infection rate of mosquitoes by infected humans exposed to MDA	Eq (4.1)
$\bar{\beta}_{h,M}^r(a, \sigma)$	Resistant infection rate of mosquitoes by infected humans exposed to MDA	Eq (4.1)
β_m^s	Human infection rate from sensitive mosquitoes ($\text{day}^{-1} \text{ bites}^{-1}$)	0.022 [32]
$\delta_h^{s,T}(a)$	Additional death of treated sensitive infections (day^{-1})	0 [Assumed]
$\delta_h^{s,U}(a)$	Additional death of untreated sensitive infections (day^{-1})	Defined in [22]
$\delta_h^{r,U}(a)$	Additional death of untreated resistant infections (day^{-1})	Defined in [32]
Λ_h	Susceptible human recruitment rate ($\text{day}^{-1} \text{ humans}$)	3.075×10^4 [22]
Λ_m	Susceptible mosquitoes recruitment rate ($\text{day}^{-1} \text{ mosquitoes}$)	Variable
$\mu_h(a)$	Natural mortality rate of humans (day^{-1})	Defined in [22]
μ_m	Natural mortality rate of mosquitoes (day^{-1})	0.13 [42]
δ_m^s	Mortality rate of sensitive infectious mosquitoes (day^{-1})	0.033 [32]
$\rho_h(\sigma)$	Loss of immunity rate of recovered humans (day^{-1})	5.5×10^{-4} [32]
$\nu_h^g(a)$	Transition rate from asymptomatic to infectious (day^{-1})	Eq (4.3)
$\eta_M(\sigma), \eta_S(\sigma)$	Relative reduction in infection risk due to MDA or SMC	Eq (4.6)
$\kappa_M(\sigma), \kappa_S(\sigma)$	Loss of effectiveness of MDA or SMC	Eq (4.5)
p	The proportion of females	0.52 [22]

2.1. The transmission process

The k -infection is transmitted to susceptible humans through bites from mosquitoes carrying the k -parasite strain, with the transmission rate

$$\lambda_m^k(t) = \frac{1}{N_h(t)} \beta_m^k I_m^k(t), \quad k \in \{s, r\},$$

for individuals unexposed to SMC or MDA, where β_m^k is the mosquito-to-human transmission probability. Individuals exposed to SMC or MDA acquire an infection at a reduced rate $\eta_i(\sigma) \lambda_m^k(t)$,

where $\eta_i(\sigma)$ denotes the relative protection depending on time since exposure σ .

Sensitive infections are transmitted to mosquitoes feeding on asymptomatic or infectious humans carrying the sensitive strain, with reduced likelihood when biting individuals protected by SMC or MDA. This force of infection is given by

$$\begin{aligned} \lambda_h^s(t) = & \frac{1}{N_h(t)} \int_0^\infty \sum_{g \in \{\varnothing, \sigma\}} \beta_h^s(a) (A_h^{s,g}(t, a) + I_{h,U}^{s,g}(t, a) + \varepsilon_r I_{h,T}^{r,g}(t, a) + (1 - \varepsilon_s) I_{h,T}^{s,g}(t, a)) da \\ & + \frac{1}{N_h(t)} \int_0^\infty \sum_{g \in \{\varnothing, \sigma\}} \int_0^\infty (\bar{\beta}_{h,S}^s(a, \sigma) A_{h,SMC}^{s,g}(t, a, \sigma) + \bar{\beta}_{h,M}^s(a, \sigma) A_{h,MDA}^{s,g}(t, a, \sigma)) d\sigma da, \end{aligned}$$

where $\beta_h^s(a)$ and $\bar{\beta}_{h,S}^s(a, \sigma), \bar{\beta}_{h,M}^s(a, \sigma)$ are the transmission probabilities as defined in Table 2.

Analogously, resistant infections are transmitted to mosquitoes feeding on asymptomatic or infectious individuals with the resistant strain, with a reduced risk from those exposed to SMC or MDA, yielding the force of infection

$$\begin{aligned} \lambda_h^r(t) = & \frac{1}{N_h(t)} \int_0^\infty \sum_{g \in \{\varnothing, \sigma\}} \beta_h^r(a) (A_h^{r,g}(t, a) + I_{h,U}^{r,g}(t, a) + \varepsilon_s I_{h,T}^{s,g}(t, a) + (1 - \varepsilon_r) I_{h,T}^{r,g}(t, a)) da \\ & + \frac{1}{N_h(t)} \int_0^\infty \sum_{g \in \{\varnothing, \sigma\}} \int_0^\infty (\bar{\beta}_{h,S}^r(a, \sigma) A_{h,SMC}^{r,g}(t, a, \sigma) + \bar{\beta}_{h,M}^r(a, \sigma) A_{h,MDA}^{r,g}(t, a, \sigma)) d\sigma da, \end{aligned}$$

with the transmission probabilities $\beta_h^r(a)$ and $\bar{\beta}_{h,S}^r(a, \sigma), \bar{\beta}_{h,M}^r(a, \sigma)$ defined in Table 2, and where ε_r and ε_s denote the mutation probabilities between treated resistant and sensitive infections.

2.2. Human-mosquito population dynamics

For $g \in \{\varnothing, \sigma\}, k \in \{s, r\}, \ell \in \{T, U\}$,

$$\left\{ \begin{aligned} S_h^{\varnothing}(t, 0) &= p\Lambda_h, \quad S_h^{\sigma}(t, 0) = (1 - p)\Lambda_h, \\ U_1(t, a = 0) &= 0_{L^1}, \quad \text{for } U_1 = \{A_h^{k,g}, I_{h,\ell}^{k,g}\}, \\ U_2(t, a = 0, \cdot) &= 0_{L^1}, \quad \text{for } U_2 \in \{R_h^g, Y_{h,SMC}^g, Y_{h,MDA}^g, A_{h,SMC}^{k,g}, A_{h,MDA}^{k,g}\}, \\ R_h^g(t, a, 0) &= \sum_{k \in \{s,r\}, \ell \in \{T,U\}} \gamma_h^{k,\ell}(a) I_{h,\ell}^{k,g}(t, a) \\ &\quad + \int_0^\infty \sum_{k \in \{s,r\}} \gamma_M^k(a, \sigma) A_{h,MDA}^{k,g}(t, a, \sigma) d\sigma \\ &\quad + \int_0^\infty \sum_{k \in \{s,r\}} \gamma_S^k(a, \sigma) A_{h,SMC}^{k,g}(t, a, \sigma) d\sigma, \\ Y_{h,SMC}^g(t, a, 0) &= \phi_h(t, a) \left(S_h^g(t, a) + \int_0^\infty R_h^g(t, a, \sigma) d\sigma \right), \\ A_{h,SMC}^{k,g}(t, a, 0) &= \phi_h(t, a) A_h^{k,g}(t, a), \\ Y_{h,MDA}^g(t, a, 0) &= \psi_h^g(t, a) \left(S_h^g(t, a) + \int_0^\infty R_h^g(t, a, \sigma) d\sigma \right), \\ A_{h,MDA}^{k,g}(t, a, 0) &= \psi_h^g(t, a) A_h^{k,g}(t, a). \end{aligned} \right. \quad (2.1)$$

In System (2.1), all newborns enter the human population as susceptible individuals with no prior exposure to SMC or MDA, classified by sex, where p denotes the proportion of females and Λ_h is the recruitment rate. Clinical and asymptomatic individuals exposed to SMC and MDA recover at the rates $\gamma_h^{k,\ell}(a)$, $\gamma_S^k(a, \sigma)$, and $\gamma_M^k(a, \sigma)$, respectively. A time- and age-dependent proportion $\phi_h(t, a)$ of eligible non symptomatic individuals is targeted by SMC, while a proportion $\psi_h^g(t, a)$ is targeted by MDA. Eligibility for SMC is restricted to non symptomatic individuals aged $a \leq a_{\text{lim}}$, whereas MDA targets non symptomatic individuals older than a_{lim} .

Furthermore, for $g \in \{\varnothing, \sigma\}$ and $k \in \{s, r\}$, the population dynamics of humans without exposure to SMC or MDA are given by the following system:

$$\left\{ \begin{array}{l} (\partial_t + \partial_a)S_h^g(t, a) = \int_0^\infty \rho_h(\sigma)R_h^g(t, a, \sigma) d\sigma - (\mu_h(a) + \lambda_m^s(t) + \lambda_m^r(t) + \phi_h(t, a) + \psi_h^g(t, a))S_h^g(t, a) \\ \quad + \int_0^\infty \kappa_S(\sigma)Y_{h,\text{SMC}}^g(t, a, \sigma) d\sigma + \int_0^\infty \kappa_M(\sigma)Y_{h,\text{MDA}}^g(t, a, \sigma) d\sigma, \\ (\partial_t + \partial_a)A_h^{k,g}(t, a) = \lambda_m^k(t)S_h^g(t, a) - (\mu_h(a) + \nu_h^g(a) + \phi_h(t, a) + \psi_h^g(t, a))A_h^{k,g}(t, a), \\ (\partial_t + \partial_a)I_{h,T}^{k,g}(t, a) = \theta(t)\nu_h^g(a)A_h^{k,g}(t, a) - (\mu_h(a) + \delta_h^{k,T}(a) + \gamma_h^{k,T}(a))I_{h,T}^{k,g}(t, a), \\ (\partial_t + \partial_a)I_{h,U}^{k,g}(t, a) = (1 - \theta(t))\nu_h^g(a)A_h^{k,g}(t, a) - (\mu_h(a) + \delta_h^{k,U}(a) + \gamma_h^{k,U}(a))I_{h,U}^{k,g}(t, a), \\ (\partial_t + \partial_a + \partial_\sigma)R_h^g(t, a, \sigma) = -(\mu_h(a) + \phi_h(t, a) + \psi_h^g(t, a))R_h^g(t, a, \sigma) - \rho_h(\sigma)R_h^g(t, a, \sigma). \end{array} \right. \quad (2.2)$$

In System (2.2), $\delta_h^{k,\ell}(a)$ denotes disease-induced mortality among clinical cases, while asymptomatic individuals progress to symptomatic infection at a rate of $\nu_h^g(a)$, with a proportion $\theta(t)$ receiving routine case management. Protection conferred by SMC and MDA wanes at rates $\kappa_S(\sigma)$ and $\kappa_M(\sigma)$, respectively. Although individuals under SMC or MDA remain susceptible to mosquito infection, their risk is reduced by $\eta_S(\sigma)$ and $\eta_M(\sigma)$, which depend on the time since exposure σ . Natural human mortality occurs at a rate of $\mu_h(a)$, and recovered individuals lose immunity at a rate of $\rho_h(\sigma)$.

Similarly, the dynamics of the human population subjected to SMC or MDA are described by the following system:

$$\left\{ \begin{array}{l} (\partial_t + \partial_a + \partial_\sigma)Y_{h,\text{SMC}}^g(t, a, \sigma) = -(\mu_h(a) + \eta_S(\sigma)(\lambda_m^s(t) + \lambda_m^r(t)) + \kappa_S(\sigma))Y_{h,\text{SMC}}^g(t, a, \sigma), \\ (\partial_t + \partial_a + \partial_\sigma)A_{h,\text{SMC}}^{k,g}(t, a, \sigma) = \eta_S(\sigma)\lambda_m^k(t)Y_{h,\text{SMC}}^g(t, a, \sigma) - (\mu_h(a) + \gamma_S^k(a, \sigma))A_{h,\text{SMC}}^{k,g}(t, a, \sigma), \\ (\partial_t + \partial_a + \partial_\sigma)Y_{h,\text{MDA}}^g(t, a, \sigma) = -(\mu_h(a) + \eta_M(\sigma)(\lambda_m^s(t) + \lambda_m^r(t)) + \kappa_M(\sigma))Y_{h,\text{MDA}}^g(t, a, \sigma), \\ (\partial_t + \partial_a + \partial_\sigma)A_{h,\text{MDA}}^{k,g}(t, a, \sigma) = \eta_M(\sigma)\lambda_m^k(t)Y_{h,\text{MDA}}^g(t, a, \sigma) - (\mu_h(a) + \gamma_M^k(a, \sigma))A_{h,\text{MDA}}^{k,g}(t, a, \sigma), \end{array} \right. \quad (2.3)$$

and the ones governing the mosquito population are expressed as

$$\left\{ \begin{array}{l} \dot{S}_m(t) = \Lambda_m - \mu_m S_m(t) - (\lambda_h^s(t) + \lambda_h^r(t))S_m(t), \\ \dot{I}_m^k(t) = \lambda_h^k(t)S_m(t) - \delta_m^k I_m^k(t), \quad k \in \{s, r\}, \end{array} \right. \quad (2.4)$$

where Λ_m denotes the recruitment rate of new mosquitoes. Susceptible and infectious mosquitoes die at a rate of μ_m and δ_m^k , respectively.

For tractability, mosquito infection is represented here using an (susceptible infectious) SI formulation, so that the parasites' extrinsic incubation period is not explicitly modelled. Accordingly, newly infected mosquitoes enter the infectious class directly. This simplification allows the present analysis to focus on the human demographics, intervention, and resistance structures.

Finally, Systems (2.2)–(2.4) are supplemented with the following initial conditions:

$$\begin{cases} S_h^g(0, a) = S_{h0}^g(a), & A_h^{k,g}(0, a) = A_{h0}^{k,g}(a), & I_{h,\ell}^{k,g}(0, a) = I_{h0,\ell}^{k,g}(a), \\ R_h^g(0, a, \sigma) = R_{h0}^g(a, \sigma), & Y_{h,\text{SMC}}^g(0, a, \sigma) = Y_{h0,\text{SMC}}^g(a, \sigma), & Y_{h,\text{MDA}}^g(0, a, \sigma) = Y_{h0,\text{MDA}}^g(a, \sigma), \\ A_{h,\text{SMC}}^{k,g}(0, a, \sigma) = A_{h0,\text{SMC}}^{k,g}(a, \sigma), & A_{h,\text{MDA}}^{k,g}(0, a, \sigma) = A_{h0,\text{MDA}}^{k,g}(a, \sigma), \\ S_m(0) = S_{m0}, & \text{and} & I_m^k(0) = I_{m0}^k. \end{cases} \quad (2.5)$$

3. Preliminary analytical results

Systems (2.1)–(2.5) are considered under the following assumptions.

Assumption 3.1.

- (1) The parameters $\Lambda_m, \Lambda_h, \mu_m, \delta_m^k, \varepsilon_k, p$, and θ are positive constants, $\forall k \in \{s, r\}$.
- (2) Natural mortality $\mu_h \in L_+^\infty(\mathbb{R}_+)$ and disease-induced mortality $\delta_h^{k,\ell} \in L_+^\infty(\mathbb{R}_+)$, are such that there are μ_{h0}, δ_{h0} positive real numbers such that

$$\forall \zeta \in \mathbb{R}_+, \quad \mu_h(\zeta) \geq \mu_{h0} \quad \text{and} \quad \delta_h^{k,\ell}(\zeta) \geq \delta_{h0}, \quad \forall k \in \{s, r\}, \ell \in \{T, U\}.$$

- (3) The parameters $\nu_h, \eta_i, \kappa_i, \rho_h, \gamma_h^{k,\ell} \in L_+^\infty(\mathbb{R}_+)$, $\gamma_i^k \in L_+^\infty(\mathbb{R}_+^2)$; $\nu_{h0}, \eta_{i0}, \kappa_{i0}, \gamma_{\kappa_0}, \rho_{h0}, \gamma_{M_0}, \gamma_{S_0}$, and γ_{h0} exist such that

$$\begin{aligned} \nu_h(\zeta) &\geq \nu_{h0}, & \eta_i(\zeta) &\geq \eta_{i0}, & \kappa_i(\zeta) &\geq \kappa_{i0}, & \rho_h(\zeta) &\geq \rho_{h0}, \\ \gamma_h^{k,\ell}(\zeta) &\geq \gamma_{h0}, & \gamma_M^k(\zeta, \epsilon) &\geq \gamma_{M_0}, & \gamma_S^k(\zeta, \epsilon) &\geq \gamma_{S_0}, \\ \forall \zeta, \epsilon &\in \mathbb{R}_+, & \forall k &\in \{s, r\}, & \ell &\in \{T, U\}, & i &\in \{S, M\}. \end{aligned}$$

- (4) The initial human conditions are such that

$$S_{h0}^g \in L_+^1(\mathbb{R}_+, \mathbb{R}_+), \quad A_{h0}^{k,g} \in L_+^1(\mathbb{R}_+, \mathbb{R}_+), \quad I_{h0,\ell}^{k,g} \in L_+^1(\mathbb{R}_+, \mathbb{R}_+), \quad \text{and} \quad R_{h0}^g \in L_+^1(\mathbb{R}_+^2, \mathbb{R}_+).$$

Furthermore, $z \in L_+^1(\mathbb{R}_+^2, \mathbb{R}_+)$, for all

$$z \in \{Y_{h0,\text{SMC}}^g, Y_{h0,\text{MDA}}^g, A_{h0,\text{SMC}}^{k,g}, A_{h0,\text{MDA}}^{k,g}\}, \quad k \in \{s, r\}, \ell \in \{T, U\}, g \in \{\varphi, \sigma\}.$$

- (5) The mosquitoes' initial conditions S_{m0} and I_{m0} are assumed to be positive.

3.1. The existence of a global solution

The first result concerns the global well-posedness of Systems (2.1)–(2.5). Let

$$X = L^1(\mathbb{R}_+, \mathbb{R}^{12}) \times L^1(\mathbb{R}_+^2, \mathbb{R}^{14}) \times \mathbb{R}^3$$

associated with the product norm $\|\cdot\|$, as well as

$$X_+ = L_+^1(\mathbb{R}_+, \mathbb{R}^{12}) \times L_+^1(\mathbb{R}_+^2, \mathbb{R}^{14}) \times \mathbb{R}_+^3$$

as its positive cone, and, for any $\epsilon \geq 0$, we define the space $\Omega_\epsilon = \{w \in X : \|w\| \geq \epsilon\}$.

Theorem 3.2. Suppose that Assumption 3.1 holds. Let

$$\epsilon \in \left(0, \frac{\Lambda_h}{4(\|\mu_h\|_{L^\infty} + \|\phi_h\|_{L^\infty} + \psi_h + \eta + \kappa + \bar{\gamma}_M + \bar{\gamma}_S + \nu_h + \bar{\delta}_h + \bar{\gamma}_h + \|\rho_h\|_{L^\infty})}\right), \quad (3.1)$$

with

$$\begin{aligned} \eta &= \max_{i \in \{S, M\}} \|\eta_i\|_{L^\infty}, & \bar{\delta}_h &= \max_{k \in \{s, r\}, \ell \in \{T, U\}} \|\delta_h^{k, \ell}\|_{L^\infty}, \\ \kappa &= \max_{i \in \{S, M\}} \|\kappa_i\|_{L^\infty}, & \bar{\gamma}_h &= \max_{k \in \{s, r\}, \ell \in \{T, U\}} \|\gamma_h^{k, \ell}\|_{L^\infty}, \\ \nu_h &= \max_{g \in \{\varphi, \sigma\}} \|\nu_h^g\|_{L^\infty}, & \bar{\gamma}_M &= \max_{k \in \{s, r\}} \|\gamma_M^k\|_{L^\infty}, \\ \psi_h &= \max_{g \in \{\varphi, \sigma\}} \|\psi_h^g\|_{L^\infty}, & \bar{\gamma}_S &= \max_{k \in \{s, r\}} \|\gamma_S^k\|_{L^\infty}. \end{aligned}$$

Then Systems (2.1)–(2.5) generates a globally defined strongly continuous semiflow $\{\mathcal{W}(t, \cdot)\}_{t \geq 0}$ on $X_+ \cap \Omega_\epsilon$ such that for any $w_0 \in X_+ \cap \Omega_\epsilon$, we have

$$\mathcal{W}(t, w_0) = \left(\left(S_h^g, A_h^g, \left(I_{h, \ell}^{k, g} \right)_{k \in \{s, r\}}^{\ell \in \{T, U\}}, R_h^g, Y_{h, \text{SMC}}^g, Y_{h, \text{MDA}}^g, \left(A_{h, \text{SMC}}^{k, g}, A_{h, \text{MDA}}^{k, g} \right)_{k \in \{s, r\}} \right)_{g \in \{\varphi, \sigma\}}, S_m, I_m^s, I_m^r \right)(t),$$

and

$$\begin{aligned} N_h(t) &\leq N_h(0)e^{-\mu_{h0}t} + \frac{\Lambda_h}{\mu_{h0}} (1 - e^{-\mu_{h0}t}), \\ N_m(t) &\leq N_m(0)e^{-\min(\mu_m, \delta_m^*)t} + \frac{\Lambda_h}{\min(\mu_m, \delta_m^*)} (1 - e^{-\min(\mu_m, \delta_m^*)t}), \end{aligned}$$

where $\delta_m^* = \min_{k \in \{s, r\}} (\delta_m^k)$.

The proof of Theorem 3.2 can be established using an integrated semigroup approach (see [34, 35]). In particular, the analysis can follow the framework in [27], which addresses the well-posedness of epidemiological models with multiple continuous structures. The main ideas underlying the proof of Theorem 3.2 are outlined in Section A.

3.2. The reproduction number

Let Assumption 3.1 hold. For the purpose of deriving a time-independent disease-free equilibrium and the associated basic reproduction number, here, we consider an autonomous version of the model in which the intervention functions ϕ_h and ψ_h^g are constant with respect to the calendar time t , while retaining their dependence on the demographic variables. This assumption is introduced specifically for the analytical characterization of $\mathcal{R}_0$ and should therefore be distinguished from the time-dependent implementation of SMC and MDA considered in Section 4, where intervention campaigns are delivered intermittently through the modulation functions $\bar{\phi}_h(t)$ and $\bar{\psi}_h(t)$.

The disease-free equilibrium, denoted $\bar{E}$, consists solely of susceptible individuals, who may be either covered by SMC, denoted $\bar{Y}_{h, \text{SMC}}^g$, covered by MDA, denoted $\bar{Y}_{h, \text{MDA}}^g$, or not covered by either intervention, denoted $\bar{S}_h^g$. These quantities satisfy

$$\bar{S}_h^g(a) = \bar{S}_h^g(0)e^{-\int_0^a (\mu_h(u) + \phi_h(u) + \psi_h^g(u))du} + \int_0^a \int_s^a e^{-\int_\eta^a (\mu_h(u) + \phi_h(u) + \psi_h^g(u))du} \chi_h^g(\eta, s) \bar{S}_h^g(\eta - s) d\eta ds,$$

$$\bar{Y}_{h,\text{SMC}}^g(a, \sigma) = \mathbf{1}_{a>\sigma}(a, \sigma) \phi_h(a - \sigma) e^{-\left(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_S(\eta) d\eta\right)} \bar{S}_h^g(a - \sigma),$$

$$\bar{Y}_{h,\text{MDA}}^g(a, \sigma) = \mathbf{1}_{a>\sigma}(a, \sigma) \psi_h^g(a - \sigma) e^{-\left(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_M(\eta) d\eta\right)} \bar{S}_h^g(a - \sigma),$$

with

$$\bar{S}_h^{\varnothing}(0) = p \Lambda_h, \quad \bar{S}_h^{\sigma}(0) = (1 - p) \Lambda_h,$$

and

$$\chi_h^g(a, \sigma) = \kappa_S(\sigma) \phi_h(a - \sigma) e^{-\left(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_S(\eta) d\eta\right)} + \kappa_M(\sigma) \psi_h^g(a - \sigma) e^{-\left(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_M(\eta) d\eta\right)},$$

$$\bar{N}_h = \int_0^\infty \left(\bar{S}_h^g(a) + \int_0^\infty \bar{Y}_{h,\text{SMC}}^g(a, \sigma) d\sigma + \int_0^\infty \bar{Y}_{h,\text{MDA}}^g(a, \sigma) d\sigma \right) da.$$

Note that $\chi_h^g(a, \sigma) \bar{S}_h^g(a - \sigma)$ quantifies the number of susceptible individuals who have been exposed to SMC or MDA for a duration σ , and who were at age $a - \sigma$ at the time of exposure.

Furthermore, by linearizing Systems (2.2)–(2.4) at the equilibrium $\bar{E}$, we find that

$$\begin{aligned} \lambda_h^s(t) &= \sum_{g \in \{\varnothing, \sigma\}} \int_0^t \lambda_m^s(t - \tau) K_g^{s \rightarrow s}(\tau) d\tau + \sum_{g \in \{\varnothing, \sigma\}} \int_0^t \lambda_m^r(t - \tau) K_g^{r \rightarrow s}(\tau) d\tau, \\ \lambda_h^r(t) &= \sum_{g \in \{\varnothing, \sigma\}} \int_0^t \lambda_m^r(t - \tau) K_g^{r \rightarrow r}(\tau) d\tau + \sum_{g \in \{\varnothing, \sigma\}} \int_0^t \lambda_m^s(t - \tau) K_g^{s \rightarrow r}(\tau) d\tau, \end{aligned} \quad (3.2)$$

$$\lambda_m^k(t) = \int_0^t \lambda_h^k(t - \tau) K_m^k(t - \tau) d\tau, \quad k \in \{s, r\},$$

with

$$\begin{aligned} K_g^{s \rightarrow s}(\tau) &= \frac{1}{\bar{N}_h} \left[\int_\tau^\infty \beta_h^s(a) \bar{S}_h^g(\tau) \left(\vartheta_h^g(\tau, a) \right) da \right. \\ &\quad + \int_\tau^\infty \beta_h^s(a) \bar{S}_h^g(\tau) \left(\int_\tau^a \nu_h^g(\eta) \vartheta_h^g(\tau, \eta) \left[(1 - \theta) \xi_{h,U}^s(\eta, a) + (1 - \varepsilon_s) \theta \xi_{h,T}^s(\eta, a) \right] d\eta \right) da \\ &\quad + \int_0^\infty \int_\tau^\infty \bar{\beta}_{h,S}^s(a, \sigma) \left[\bar{S}_h^g(\tau) \vartheta_h^g(\tau, a - \sigma) \phi_h(a - \sigma) \pi_{h,S}(a, \sigma) \right. \\ &\quad \quad \left. + \mathbf{1}_{\sigma>\tau}(\sigma, \tau) \eta_S(\tau) \bar{Y}_{h,\text{SMC}}^g(a - \tau, \sigma - \tau) \pi_{h,S}(a, \tau) \right] da d\sigma \\ &\quad + \int_0^\infty \int_\tau^\infty \bar{\beta}_{h,M}^s(a, \sigma) \left[\bar{S}_h^g(\tau) \vartheta_h^g(\tau, a - \sigma) \psi_h^g(a - \sigma) \pi_{h,M}(a, \sigma) \right. \\ &\quad \quad \left. + \mathbf{1}_{\sigma>\tau}(\sigma, \tau) \eta_M(\tau) \bar{Y}_{h,\text{MDA}}^g(a\tau, \sigma - \tau) \pi_{h,M}(a, \tau) \right] da d\sigma \Big], \end{aligned}$$

$$K_g^{r \rightarrow s}(\tau) = \frac{1}{\bar{N}_h} \int_\tau^\infty \beta_h^s(a) \bar{S}_h^g(\tau) \left(\varepsilon_r \theta \int_\tau^a \nu_h^g(\eta) \vartheta_h^g(\tau, \eta) \xi_{h,T}^r(\eta, a) d\eta \right) da,$$

$$K_g^{r \rightarrow r}(\tau) = \frac{1}{\bar{N}_h} \left[\int_\tau^\infty \beta_h^r(a) \bar{S}_h^g(\tau) \left(\vartheta_h^g(\tau, a) \right) da \right.$$

$$\begin{aligned}
& + \int_{\tau}^{\infty} \beta_h^r(a) \bar{S}_h^g(\tau) \left(\int_{\tau}^a v_h^g(\eta) \vartheta_h^g(\tau, \eta) \left[(1 - \theta) \xi_{h,U}^r(\eta, a) + (1 - \varepsilon_r) \theta \xi_{h,T}^r(\eta, a) \right] d\eta \right) da \\
& + \int_0^{\infty} \int_{\tau}^{\infty} \bar{\beta}_{h,S}^r(a, \sigma) \left[\bar{S}_h^g(\tau) \vartheta_h^g(\tau, a - \sigma) \phi_h(a - \sigma) \pi_{h,S}(a, \sigma) \right. \\
& \quad \left. + \mathbf{1}_{\sigma > \tau}(\sigma, \tau) \eta_S(\tau) \bar{Y}_{h,SMC}^g(a - \tau, \sigma - \tau) \pi_{h,S}(a, \tau) \right] da d\sigma \\
& + \int_0^{\infty} \int_{\tau}^{\infty} \bar{\beta}_{h,M}^r(a, \sigma) \left[\bar{S}_h^g(\tau) \vartheta_h^g(\tau, a - \sigma) \psi_h^g(a - \sigma) \pi_{h,M}(a, \sigma) \right. \\
& \quad \left. + \mathbf{1}_{\sigma > \tau}(\sigma, \tau) \eta_M(\tau) \bar{Y}_{h,MDA}^g(a - \tau, \sigma - \tau) \pi_{h,M}(a, \tau) \right] da d\sigma \Big],
\end{aligned}$$

$$K_g^{s \rightarrow r}(\tau) = \frac{1}{N_h} \int_{\tau}^{\infty} \beta_h^r(a) \bar{S}_h^g(\tau) \left(\varepsilon_s \theta \int_{\tau}^a v_h^g(\eta) \vartheta_h^g(\tau, \eta) \xi_{h,T}^s(\eta, a) d\eta \right) da,$$

$$K_m^k(\tau) = \frac{1}{N_h} \beta_m^k \bar{S}_m e^{-\tau \delta_m^k},$$

and where

$$\begin{aligned}
\vartheta_h^g(\eta, a) &= e^{-\int_{\eta}^a (\mu_h + v_h^g + \phi_h + \psi_h^g) du}, \\
\xi_{h,\ell}^k(\eta, a) &= e^{-\int_{\eta}^a (\mu_h + \delta_h^{k,\ell} + \gamma_h^{k,\ell}) du}, \\
\pi_{h,S}(a, \sigma) &= e^{-\int_0^{\sigma} (\mu_h(a-r) + \kappa_S(r)) dr}, \\
\pi_{h,M}(a, \sigma) &= e^{-\int_0^{\sigma} (\mu_h(a-r) + \kappa_M(r)) dr}.
\end{aligned}$$

Note that $\mathcal{K}_g^{k \rightarrow k'}$ accounts for all human-to-mosquito transmission pathways of type $k \rightarrow k'$, including asymptomatic (A), treated infectious (I_T), untreated infectious (I_U), and individuals under SMC or MDA, while $\mathcal{K}_m^k$ accounts for all mosquito-to-human transmission pathways of type k .

By the renewal of System (3.2), the next-generation matrix $\mathcal{G}$ reads

$$\mathcal{G} = \begin{pmatrix} 0_{2 \times 2} & \mathcal{G}_h \\ \mathcal{G}_m & 0_{2 \times 2} \end{pmatrix},$$

where $\mathcal{G}_h = (\mathcal{K}_g^{j \rightarrow i})_{i,j \in \{s,r\}}$ and $\mathcal{G}_m = \text{diag}(\mathcal{K}_m^s, \mathcal{K}_m^r)$, with

$$\begin{aligned}
\mathcal{K}_g^{j \rightarrow i} &= \sum_{g \in \{\bar{\mathcal{Q}}, \bar{\mathcal{Q}}^{\mathfrak{A}}\}} \int_0^{\infty} K_g^{j \rightarrow i}(\tau) d\tau, \\
\mathcal{K}_m^k &= \int_0^{\infty} K_m^k(\tau) d\tau.
\end{aligned}$$

From this, we deduce that the basic reproduction number $\mathcal{R}_0$ is computed as $\sqrt{r(\mathcal{G}^2)}$, where $r(\cdot)$ denotes the spectral radius, i.e.,

$$\mathcal{R}_0^2 = \frac{1}{2} \left(\mathcal{T}_0^s + \mathcal{T}_0^r + \sqrt{(\mathcal{T}_0^s - \mathcal{T}_0^r)^2 + 4Q^{s,r}} \right), \quad (3.3)$$

with

$$\mathcal{T}_0^k = \mathcal{K}_m^k \mathcal{K}^{k \rightarrow k}, \quad Q^{s,r} = \mathcal{K}_m^s \mathcal{K}_m^r \mathcal{K}^{s \rightarrow r} \mathcal{K}^{r \rightarrow s}.$$

Here, $\mathcal{T}_0^k$ denotes the contribution of the k -infection to the basic reproduction number, while $Q^{s,r}$ quantifies the cross-coupling between the two infection types, capturing the impact of r -infections on the fitness of s -infections (and vice versa). In other words, $Q^{s,r}$ reflects the interaction, competition, and potential for coexistence between s - and r -strains. When $Q^{s,r} = 0$, we have

$$\mathcal{R}_0 = \max(\mathcal{T}_0^s, \mathcal{T}_0^r),$$

highlighting the potential for exclusion between the s - and r -strains.

The detailed computation of the disease-free equilibrium and the basic reproduction number is provided in Section B.

4. Applications

This section illustrates how the general modeling framework introduced in (2.1)–(2.5) provides a quantitative foundation for analyzing the system's dynamics and evaluating intervention strategies that combine routine case management with preventive approaches, such as MDA and SMC. The numerical investigations presented below are intended as scenario-based explorations of the epidemiological and evolutionary mechanisms generated by the model rather than quantitative predictions for a particular malaria-endemic population. Although several demographic, epidemiological, and pharmacological parameters are informed by published studies, the complete model has not been calibrated against longitudinal data from a specific setting. Consequently, quantitative values of the interventions' impact should be interpreted within the parameter scenarios considered here, whereas greater emphasis should be placed on the qualitative relationships among intervention coverage, timing, routine case management, and drug resistance dynamics.

4.1. Parameter specification and epidemiological outputs

We assume that the model parameters satisfy the following scaling assumptions:

$$\left\{ \begin{array}{ll} \varepsilon_r = \bar{\varepsilon} \varepsilon_s, & \delta_h^{r,T} = \bar{\delta}_h \delta_h^{s,U}, \\ \gamma_h^{r,T} = \bar{\gamma}_h \gamma_h^{s,T}, & \gamma_h^{r,U} = \bar{\gamma}_h \gamma_h^{r,U}, \\ \bar{\beta}_{h,S}^s = \beta_h^s (1 - \text{Eff}_S), & \bar{\beta}_{h,M}^s = \beta_h^s (1 - \text{Eff}_M), \\ \bar{\beta}_{h,S}^r = \bar{\beta}_h \bar{\beta}_{h,S}^s, & \bar{\beta}_{h,M}^r = \bar{\beta}_h \bar{\beta}_{h,M}^s, \\ \beta_m^r = \bar{\beta}_m \beta_m^s, & \delta_m^r = \bar{\delta}_m \delta_m^s, \end{array} \right. \quad (4.1)$$

where $\text{Eff}_i(\sigma)$ is the efficacy of i -treatment defined later by (4.4), and the corresponding scaling parameters $\bar{x}$ is summarized in Table 2.

Moreover, the transmission rate from infected humans to susceptible mosquitoes $\beta_h(a)$ is influenced by the parasite load in the human host [36]. We model it as age-dependent, assuming equal rates for sensitive and resistant infections ($\beta_h^s(a) = \beta_h^r(a) = \beta_h(a)$), given their comparable transmission potential

and lack of evidence for differential infectivity. The function $\beta_h(a)$ is expressed as

$$\beta_h(a) = \varphi_0 \alpha_1 [\varphi_1 a e^{-a\varphi_2}]^{\alpha_2}. \quad (4.2)$$

The parameter φ_0 is the mosquitoes' biting rate which is within $[0.33, 1/2]$ [37]. φ_1 and φ_2 are estimated as 22.7 [17, 32] and 0.0934 [0.08, 0.11] [22], respectively, under a negative binomial framework that addresses the strong individual-level variation in gametocyte density. Parameters α_1 and α_2 are, respectively, equal to 0.071[0.023, 0.175] and 0.302 [0.16, 0.475] [22].

Research has demonstrated the role of climate variability in driving malaria transmission, reflecting the dynamic and evolving character of the disease (high season and low season) [38]. The seasonality is driven by the mosquito population's dynamics (more breeding sites during rains) and climatic conditions that are favorable to parasite development. In our study, it has been taken into account by the parameter φ_0 . It is shown in the literature that SMC and MDA are deployed ahead of the transmission season to reduce the parasite burden before transmission peaks [39–41]. To address malaria's seasonality, our study considers scenarios representing different transmission intensities: High and low transmission periods (see [21, 32]).

The progression rate $\nu_h^g(a)$ from asymptomatic to infectious humans is age-dependent and sex-specific. Children progress faster due to weaker immunity, while older individuals progress more slowly. Pregnancy further reduces immunity, increasing the risk of progression and highlighting pregnant women's vulnerability. Evidence shows that pregnant women have a heightened vulnerability to malaria and are more prone to severe manifestations of the disease [25]. Modeling $\nu_h^g(a)$ as age-dependent captures the key transmission heterogeneities for targeted control. Formally, this can be expressed for women and men, respectively, as follows:

$$\nu_h^{\square}(a) = \begin{cases} \nu_{h_0}, & 0 \leq a \leq 5, \\ p_f \nu_{h_0} + (1 - p_f) \nu_{h_1}, & 15 < a \leq 45, \\ \nu_{h_1}, & \text{elsewhere,} \end{cases} \quad \text{and} \quad \nu_h^{\sigma}(a) = \begin{cases} \nu_{h_0}, & 0 \leq a \leq 5, \\ \nu_{h_1}, & \text{elsewhere,} \end{cases} \quad (4.3)$$

where ν_{h_0} and $\nu_{h_1} \in [0.067, 0.2]$ (see [21, 42]) while p_f is defined in Table 2.

SMC's implementation is governed by age- and time-dependent parameters that determine who receives treatment and how long they remain protected. This treatment is applied to young children aged under a_{lim} (with the value given in Table 2) and is given as follows:

$$\phi_h(t, a) = \begin{cases} \frac{\text{PropSMC}}{D_s} \bar{\phi}(t), & a \leq a_{\text{lim}}, \\ 0, & \text{elsewhere,} \end{cases}$$

where PropSMC is the proportion of human exposed to SMC, a_{lim} is the age to be eligible for SMC, and D_s is the delay of the SMC cycle. Although SMC targets children under five years (standard SMC), the disease burden in older children may warrant extending the age range up to 10 years (extended SMC) [30].

The MDA implementation rate $\psi_h^g(t, a)$ is also defined as a function of time, age, and sex, allowing for stratified coverage by demographic group and targeted timing of drug delivery. The rate incorporates eligibility criteria and campaign scheduling, enabling a realistic representation of

intervention coverage across the population. This treatment concerns human aged older than a_{lim} , but pregnant women were often left out of previous MDA campaigns because of possible teratogenic risks from the drugs used [43]. We therefore adopt the simplifying assumption excluding all women of reproductive age from MDA campaigns, as pregnancy tests are not generally performed to confirm pregnancy. For budgetary reasons and to lower the risk of drug overexposure, MDA is applied only to the remaining population not treated with SMC. The value of $\psi_h^s(t, a)$ differs between men and women. More precisely, we have

$$\psi_h^{\circ}(t, a) = \begin{cases} \frac{\text{PropMDA}}{D_M} \bar{\psi}_h(t), & a_{\text{lim}} < a \leq 15; 45 \leq a \leq 90, \\ 0, & \text{elsewhere,} \end{cases} \quad \text{for women,}$$

and

$$\psi_h^{\sigma}(t, a) = \begin{cases} \frac{\text{PropMDA}}{D_M} \bar{\psi}_h(t), & a > a_{\text{lim}}, \\ 0, & \text{elsewhere,} \end{cases} \quad \text{for men,}$$

where PropMDA is the proportion of humans exposed to MDA, p is the proportion of females, and D_M is the delay of the MDA cycle. The functions $\bar{\psi}_h(t)$ (respectively, $\bar{\phi}_h(t)$) act as a modulation term that models the temporal pattern of the MDA (respectively, SMC). It accounts for both the campaigns duration and the time intervals between campaigns. Once a campaign concludes, MDA (respectively, SMC) exposure is interrupted until the next scheduled round, determined by the accumulated durations and inter campaign gaps. This design enables $\bar{\psi}_h(t)$ (respectively, $\bar{\phi}_h(t)$) to realistically reflect the periodic delivery of MDA (respectively, SMC), while allowing flexibility in campaign spacing to match real-world implementation patterns.

The efficacy of i -treatment since the time of administration σ , denoted $\text{Eff}_i(\sigma)$, is given by the following formula:

$$\text{Eff}_i(\sigma) = \frac{D}{1 + \left(\frac{\sigma}{\sigma_{50}^i}\right)^{\alpha_i}}, \quad i \in \{\text{SMC}, \text{MDA}\}, \quad (4.4)$$

where $\alpha_i = [0.5, 33.6]$ [44] is the shape of i -treatment, $D = 95\%$ is the upper efficacy, and σ_{50}^i is the median effective dose of the treatment, which is 28 days for SMC [45, 46] and 35 days for MDA [47]. The probability of remaining protected throughout the duration σ by treatment i is given by

$$\frac{\text{Eff}_i(\sigma)}{D} = \exp\left(-\int_0^\sigma \kappa_i(\xi) d\xi\right).$$

It follows that the instantaneous rate of efficacy loss of treatment i , denoted κ_i , is expressed as:

$$\kappa_i(\sigma) = \frac{d}{d\sigma} \left(-\log\left(\frac{\text{Eff}_i(\sigma)}{D}\right) \right). \quad (4.5)$$

The relative reduction in the probability of infection attributable to treatment i is formulated as follows:

$$\eta_i(\sigma) = 1 - \text{Eff}_i(\sigma), \quad i \in \{\text{SMC}, \text{MDA}\}. \quad (4.6)$$

The recovery rate of the human population under SMC or MDA is defined as follows:

$$\gamma_{h,i}^k(a, \sigma) = \gamma_h^{k,U}(a) + (\gamma_h^{k,T}(a) - \gamma_h^{k,U}(a))\text{Eff}_i(\sigma), \quad i \in \{\text{SMC}, \text{MDA}\}. \quad (4.7)$$

The initial susceptible human population, as well as the asymptomatic infected, infectious, and recovered humans unprotected by SMC and MDA used for baseline simulations are those introduced in [22, 48]. The model was initialized with age-dependent initial conditions based on epidemiological parameters, including the initial prevalence of antimalarial resistance InitPrev . Specifically, the initial prevalence of malaria infection was assumed to be $\text{Prev} = 0.4\%$, with clinical infections accounting for $\text{PrevI} = 25\%$ of this prevalence.

Moreover, the time-dependent proportion of clinical cases averted by implementing the routine case management, SMC, and MDA strategies, denoted $\mathcal{S} = (\theta, \phi_h, \psi_h^{\sigma}, \psi_h^{\tau})$ and written $\Delta_{\text{gain}}(t, \mathcal{S})$, is defined as the relative reduction in the number of clinical cases compared with the baseline (absence of intervention). That is

$$\Delta_{\text{gain}}(t, \mathcal{S}) = 1 - \frac{\overbrace{\left| \int_0^\infty \sum_{g \in \{\varnothing, \sigma\}} \sum_{\ell \in \{T, U\}} (I_{h,\ell}^{s,g}(t, a) + I_{h,\ell}^{r,g}(t, a)) da \right|_{\mathcal{S} \neq 0}}^{\text{Clinical cases observed during the intervention strategy}}}{\underbrace{\left| \int_0^\infty \sum_{g \in \{\varnothing, \sigma\}} \sum_{\ell \in \{T, U\}} (I_{h,\ell}^{s,g}(t, a) + I_{h,\ell}^{r,g}(t, a)) da \right|_{\mathcal{S}=0}}_{\text{Baseline clinical cases in the absence of intervention}}}.$$

For example, if $\Delta_{\text{gain}}(t, \mathcal{S}) = 0.1$ at a given time point, this indicates a 10% reduction in clinical cases due to the intervention strategy. Furthermore, the time-dependent difference in performance between two strategies $\mathcal{S}_1$ and $\mathcal{S}_2$ is given by $\Delta_{\text{gain}}(t, \mathcal{S}_1) - \Delta_{\text{gain}}(t, \mathcal{S}_2)$, corresponding to the difference in their impact.

The time-dependent prevalence of resistant clinical cases observed across scenarios, denoted $P_{\text{revR}}(t)$, is defined as the proportion of resistant infections among all clinical infections.

In subsequent scenarios, SMC is administered to children ($\leq a_{\text{lim}}$), while MDA targets the remaining population ($> a_{\text{lim}}$), excluding women of childbearing age. The time-since-administration pharmacodynamic efficacy profile is parameterized by the median effective dose via the dose-response function (4.4), and illustrated in Supplementary Figure S1. Routine case management is applied concurrently to symptomatic cases.

4.2. Sensitivity analysis

Sensitivity analyses were performed to assess the relative importance of the model parameters on the number of clinical cases averted, Δ_{gain} , and the prevalence of drug resistance, P_{revR} . Eight parameters were considered: The proportion of humans receiving MDA (ψ_h), the proportion receiving SMC (ϕ_h), the routine treatment rate (θ), the age limit for SMC eligibility (a_{lim}), the number of SMC/MDA cycles (n_c), the proportion of pregnant women (p_f), the initial prevalence of resistance (InitPrev), and the mutation rate from drug-sensitive to drug-resistant infections (ε_s). Sensitivity indices were estimated using an analysis of variance (ANOVA) based on simulations from a full factorial design comprising 1,296 parameter combinations. The fitted ANOVA model, including interaction terms up to the third order, explained more than 99% of the observed variance ($R^2 \approx 0.995$). The ranges of variation

for the eight parameters are summarized in Table 2. It should be noted that the relative scaling factors relating sensitive and resistant strain parameters (Table 2) are held fixed in this analysis. Accordingly, the sensitivity results are conditional on these assumed relative relationships. In particular, although $\bar{\varepsilon}$ is fixed, $\varepsilon_r = \bar{\varepsilon}\varepsilon_s$ varies together with ε_s across the parameter space.

The proportion of humans receiving MDA (ψ_h), the routine treatment rate (θ), the proportion receiving SMC (ϕ_h), and the number of SMC/MDA cycles (n_c) were identified as the main determinants of the number of clinical cases averted. Collectively, these four parameters explained 97% of the total variance, with ψ_h , θ , ϕ_h , and n_c accounting for 48%, 37%, 7%, and 4% of the variance, respectively (Figure 2A). By contrast, the mutation rate from drug-sensitive to drug-resistant infections (ε_s) and the routine treatment rate (θ) were the principal determinants of the prevalence of resistant infections. Together, these two parameters explained 98% of the total variance when interactions were taken into account, with their main effects accounting for 47% and 30% of the variance, respectively (Figure 2B). In contrast, the initial prevalence of resistance, the proportion of pregnant women, and the age limit for SMC eligibility all explained only a small fraction of the variance in both the prevalence of resistant infections and the number of clinical cases averted (Figure 2).

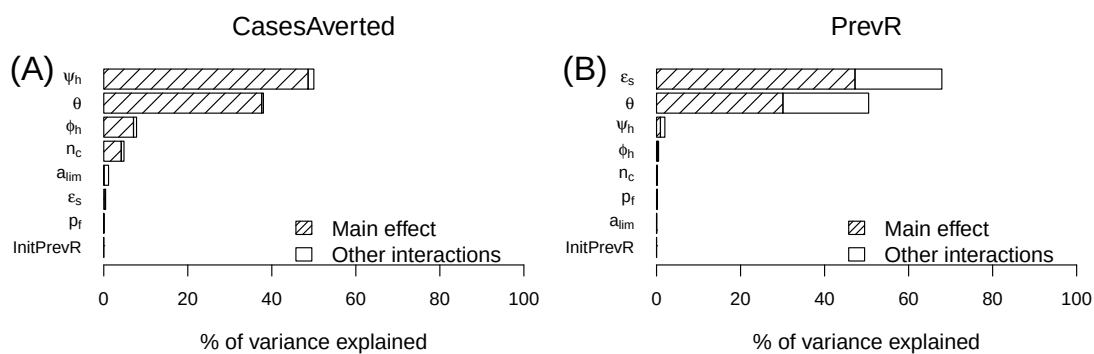


Figure 2. Sensitivity analysis for clinical cases averted (A) and resistant cases, which consists of resistant asymptomatic and symptomatic humans (B). Shaded areas show main effects, and total bar heights reflect overall influence, including interactions.

This difference reflects the distinct nature of the two model outputs. The number of clinical cases averted measures changes in the overall clinical burden, irrespective of whether infections are caused by sensitive or resistant parasites. Variation in the mutation rates primarily affects the distribution of infections between the sensitive and resistant strains and therefore has comparatively little influence on the total number of clinical infections prevented over the considered time horizon. In contrast, P_{revR} is defined as the proportion of resistant infections among all clinical infections and is therefore directly sensitive to processes governing the generation and subsequent propagation of resistant parasites. Consequently, variation in the mutation rates can produce substantial changes in the composition of the infected population without producing a comparable change in the total clinical burden.

4.3. Effect of key parameters on $\mathcal{R}_0$

The aim of this section is to investigate the influence of key parameters on the basic reproduction number $\mathcal{R}_0$. To this end, we build on the sensitivity analysis presented above, which identifies the

most influential parameters as the proportion of individuals receiving MDA (ψ_h^s), the proportion treated through routine case management (θ), and the proportion of the target population covered by SMC (ϕ_h).

Figure 3 investigates the effect of SMC, MDA, and routine case management on $\mathcal{R}_0$ under the autonomous constant intervention assumption introduced in Section 3.2. Within this analytical setting, neither SMC nor MDA, even when each is combined with routine case management, achieves sufficient coverage over the ranges considered to reduce $\mathcal{R}_0$ below one. In contrast, combining SMC and MDA can bring $\mathcal{R}_0$ below the threshold, provided that SMC coverage is sufficiently high and MDA coverage is moderate, even when routine case management coverage is as low as 10%. Moreover, increasing routine case management coverage enlarges the region of the parameter space for which $\mathcal{R}_0 < 1$, indicating that improved case management reduces the intervention coverage required for control.

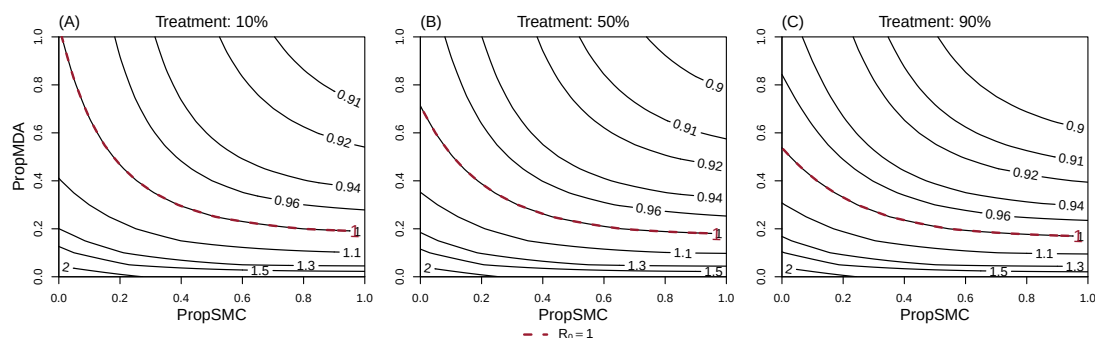


Figure 3. The effect of standard SMC, MDA, and routine case management on $\mathcal{R}_0$. The red dotted line in each panel represents the curve threshold where $\mathcal{R}_0 = 1$. The proportion of routine treatment varies across columns and the mutation rate $\varepsilon_s = 0.1$.

These threshold results apply specifically to the constant intervention approximation used to define $\mathcal{R}_0$ and should not be interpreted as threshold conditions for intermittent SMC or MDA campaigns. The impact of realistic time-dependent intervention schedules, including campaign timing, duration, and repeated rounds, is instead investigated through the non autonomous numerical simulations presented below.

4.4. Typical model-derived dynamics

The framework is age- and sex-structured to capture heterogeneity in vulnerability and infectiousness, as well as group-specific intervention criteria, while the model outputs are evaluated at the population level. Figure 4A illustrates the typical evolution of the effectively protected human population under waning efficacy over two years, for four intervention campaigns and a representative SMC and MDA coverage level of 70% within the respective target populations. The combined strategies protect up to approximately 40% of the total population against infection. This level of protection gradually declines over time due to waning efficacy, but is partially restored with successive intervention cycles, thereby sustaining protection over time. Figure 4B illustrates how the force of infection $\lambda_h(t)$ decreases over time when four intervention cycles of MDA, standard SMC, and a combined strategy (standard SMC + MDA) are administered, starting at Month 4 in the first year and Month 16 in the second, to coincide with the peak transmission season lasting 4 months. MDA alone brings about a sharp reduction of 40 – 45% which remains across successive intervention cycles, SMC

produces a moderate reduction of about 10%, and their combination results in the most pronounced reduction, nearly 50%. Moreover, as shown in Figure 4C, the interventions have a similar impact on the proportion of clinical cases averted $\Delta_{\text{gain}}(\cdot, \mathcal{S})$ over two years. Here, the proportion of resistant clinical cases among all infections yields zero because there is no routine case management and MDA has tiny effect on it.

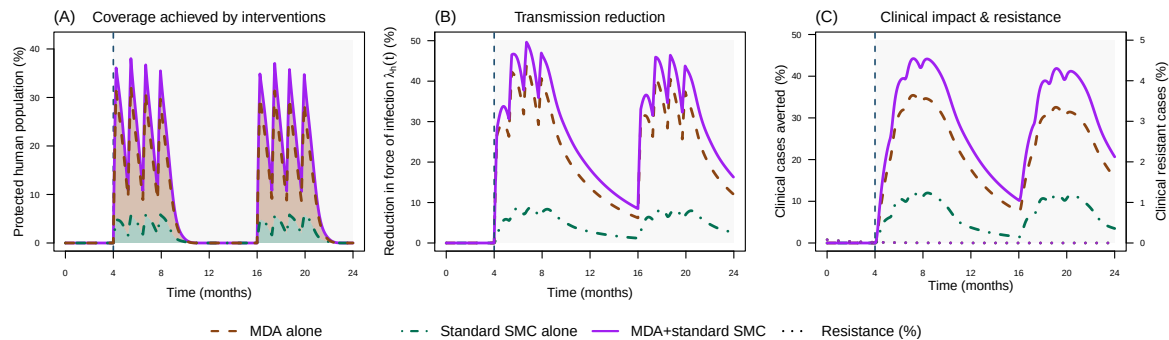


Figure 4. The effect of standard SMC and MDA on the transmission dynamic, clinical cases averted, and resistant clinical cases. (A) The typical representation of a protected human. (B) The typical representation of the reduction of the force of infection from human to mosquito, and (C) the typical representation of the proportion clinical cases averted and the proportion of resistant clinical cases, with the number of cycles for MDA and standard SMC $n_c = 4$. In this case, the coverage of SMC and MDA is 70% of the target population, there is no routine case management, and the mutation rate is $\varepsilon_s = 0.1$. The vertical dotted line represents the beginning of the seasonal period and also the administration of MDA and standard SMC.

Figure 5 presents how resistant and preventable clinical cases evolve when systematically varying three key parameters: The proportion of individuals covered by MDA and standard SMC, the routine treatment coverage (case management), and the mutation rate from drug-sensitive to drug-resistant parasite strains (ε_s). Our results demonstrate a clear relationship between the mutation rate and resistant cases' emergence. When the mutation rate is elevated (i.e., $\varepsilon_s = 0.1$), there is a substantial increase in resistant clinical cases compared with lower mutation rates, underscoring the critical role of parasites genetic plasticity in driving resistance. However, the mutation rate produces only a modest difference in clinical cases averted when comparing moderate (50%) versus high (90%) routine treatment coverage (Figure 5, Columns 2 and 3), suggesting that preventable case reduction is more strongly influenced by coverage intensity than by mutation dynamics. Expanding routine case management's coverage reveals a dual effect. Broader treatment access elevates the proportion of resistant clinical cases as increased drug exposure intensifies the selection pressure, favoring resistant strains. However, it also substantially increases the overall proportion of clinical cases averted (Figure 5, Columns 1–3). Each incremental increase in routine coverage yields both slightly more resistant cases and greater overall clinical cases averted, creating a trade-off between immediate therapeutic benefit and long-term resistance management. In contrast, mass chemoprevention strategies (MDA and SMC) exhibit a distinctly favorable profile. These interventions show strong positive effects on clinical cases averted, with higher coverage leading to proportionally greater prevention of cases (Figure 5, Rows 1–3). Critically, the coverage of MDA and SMC exert only a minimal influence on resistant clinical cases.

This resistance-sparing profile likely reflects the time-limited nature of these interventions and their deployment during specific transmission windows, reducing the overall selection pressure. This makes mass chemoprevention particularly attractive for large-scale implementation, as it provides substantial disease reduction without significantly accelerating the emergence of resistance, a key consideration for programs' sustainability.

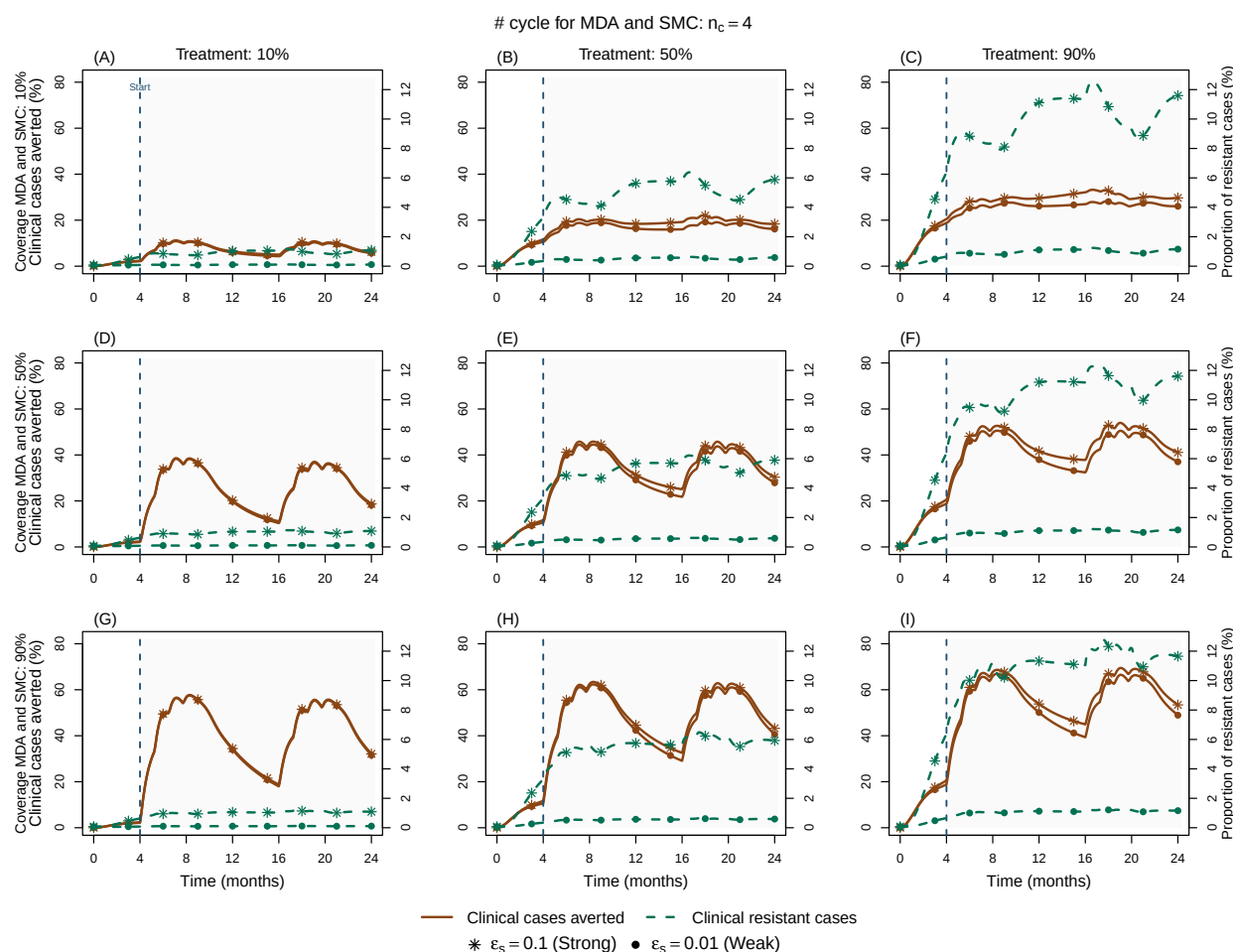


Figure 5. Dynamic of clinical cases averted and proportion of resistant clinical cases over two years when the number of cycles for MDA and SMC is 4, with the coverage of MDA and SMC varying by row and the routine case management varying by column, for the same starting campaign.

Figure 6 demonstrates the sustained impact of individual and combined control strategies using standard SMC, MDA, and routine case management over a one-year post-implementation period. A critical challenge in malaria control is that certain interventions exhibit rapid efficacy decline following deployment, undermining their overall effectiveness. This observation underscores the rationale for our longitudinal efficacy assessment. Our results reveal distinct patterns across intervention strategies: Routine case management alone maintains consistent effectiveness due to its continuous availability throughout the study period. However, this sustained application comes at a cost, which is the progressive development of drug resistance. In contrast, standard SMC and MDA protocols

demonstrate durable efficacy one year post-implementation, with averted cases reaching approximately 10% when both cycle frequency and routine case management coverage are optimized. The combined triple-intervention strategy (routine case management, plus standard SMC and MDA) yields the most substantial long-term benefits, averting up to 35% of annual cases depending on the cycle frequency and routine case management coverage parameters. Notably, this effectiveness exhibits temporal variability, declining around Month 16 and coinciding with the peak malaria transmission season before recovering in subsequent months. This seasonal fluctuation likely reflects increased transmission pressure overwhelming intervention capacity during high-burden periods.

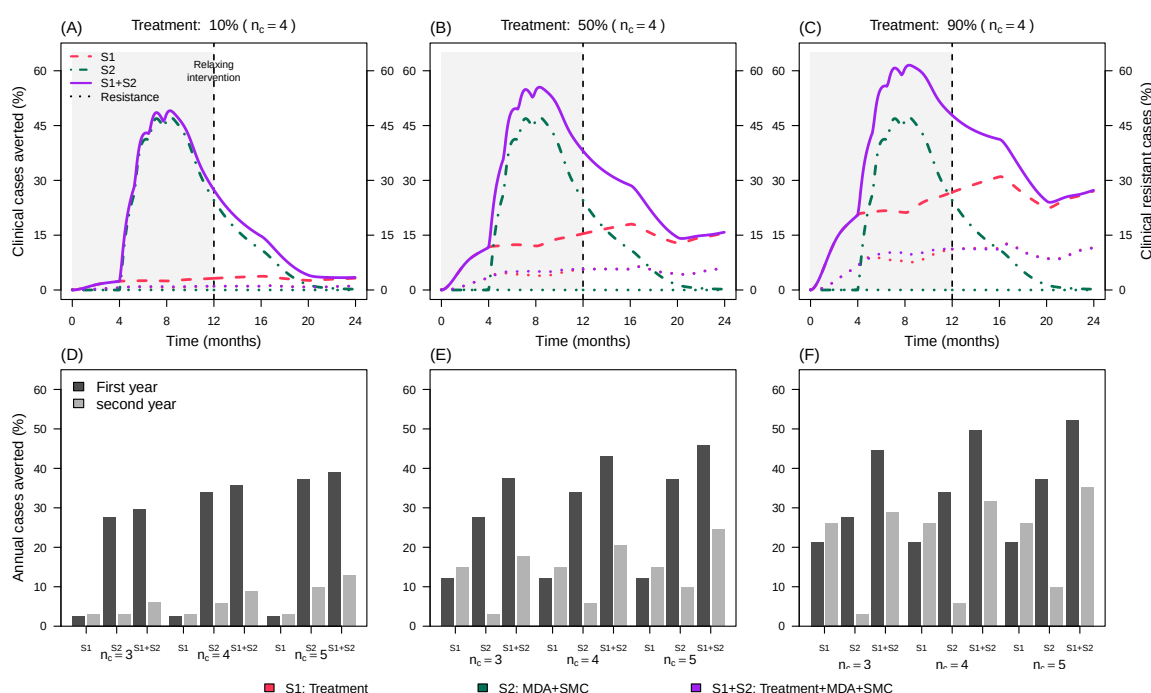


Figure 6. Dynamic of cases averted and resistant clinical cases during and after the intervention period. Row 1 is the cases averted and resistant clinical cases, for different scenarios of MDA, standard SMC, and various coverage of routine case management. Row 2 is the annual number of cases averted of the first and second year of intervention of different strategies with various number of cycles for standard SMC and MDA ($n_c = 3, 4, 5$).

5. Conclusions and discussion

Antimalarial drug resistance remains a major obstacle to malaria's control and elimination. By reducing the efficacy of first-line therapies, resistance leads to treatment failure, prolonged infectiousness, and increased transmission, particularly among young children and pregnant women. Resistant parasites propagate through the human-mosquito cycle via the forces of infection λ_h and λ_m , facilitating their spread. The emergence of resistance is strongly driven by repeated treatment of clinical cases with antimalarials [15, 17]. In this context, integrated strategies combining routine case management with preventive interventions such as SMC and MDA are increasingly viewed as promising approaches to reduce both the malaria burden and dissemination of resistance.

We developed an age-structured malaria transmission model incorporating drug resistance to evaluate these strategies. The age structure captures heterogeneities in susceptibility, exposure, and intervention coverage. Key demographic processes, including age-dependent and malaria-induced mortality, reflect higher risk in young children and pregnant women [27]. Age-dependent recovery represents the gradual acquisition of naturally acquired immunity [49]. Mosquito infection rates are higher when feeding on younger individuals (0–15 years), consistent with higher gametocyte carriage and lower immunity (Figure S1A). Age and sex structures also reflect intervention eligibility, particularly the exclusion of pregnant women from MDA and their increased susceptibility. To capture transient intervention effects, the model includes time since treatment and intervention administration, representing the waning protection induced by SMC and MDA. Drug action is modeled through (pharmacokinetics/pharmacodynamics) PK/PD relationships linking exposure to protection, with efficacy declining over time according to the dose-response parameters α_i and maximal efficacy D (Figure S1B).

Children and women of childbearing age exhibit distinct pharmacokinetic profiles, and drug evaluation for asymptomatic-targeting strategies depends on these parameters [50], including possible age- and sex-specific clearance differences. Although age-dependent rapid clearance is not explicitly modeled due to limited evidence, it may influence predictions if confirmed, and the framework remains compatible with such extensions. Achieving high MDA coverage is also operationally challenging: Mobility related to schooling and work, particularly among adolescents and adult males, limits sustained participation across rounds. Consequently, coverage near 90% is often unrealistic [31,51,52], motivating our focus on more plausible 50–70% scenarios.

The representation of MDA eligibility in women also involves a simplifying assumption. In the present simulations, women of reproductive age are excluded from MDA to account conservatively for potential pregnancy-related contraindications when pregnancy status is unknown. This assumption does not distinguish pregnant from non-pregnant women within this age group and may therefore underestimate the effective population coverage achievable by MDA. It may also overestimate the contribution of women of reproductive age to the residual parasite reservoir by systematically leaving this group untreated. Consequently, the magnitude of the predicted population-level impact of MDA should be interpreted conditional on this conservative eligibility assumption. A more detailed representation could explicitly distinguish pregnancy status and incorporate setting- and drug-specific eligibility criteria.

From a mathematical perspective, we established the well-posedness of the model using semigroup theory and derived the basic reproduction number, $\mathcal{R}_0$, through a next-generation operator framework [53,54]. It is important to emphasize that $\mathcal{R}_0$ is derived from the autonomous version of the model under the assumption that the SMC and MDA intervention rates are constant with respect to calendar time. The resulting threshold should therefore be interpreted as characterizing the constant-intervention approximation rather than the intermittent campaigns implemented in practice. In contrast, the full numerical model incorporates time-dependent intervention functions that explicitly represent campaign duration, timing, and repeated SMC and MDA rounds. Consequently, the $\mathcal{R}_0 < 1$ conditions identified in Figure 3 should not be directly interpreted as elimination thresholds for arbitrary time-varying intervention schedules; the epidemiological impact of such schedules is instead assessed through the time-dependent simulations. The sensitivity analysis (Figure 2) identifies ψ^s as the primary determinant of the reduction in total clinical cases, followed by θ , ϕ , and n_c . In contrast, the prevalence

of resistant infections is driven predominantly by θ , with ψ^s as the second most influential parameter, whereas the remaining parameters have comparatively minor effects.

Numerical simulations highlight the importance of timing. As shown in Figure S2, interventions implemented one month before peak transmission achieve the highest reduction in cases, followed by peak and post-peak implementation. This reflects reduced parasite reservoirs before seasonal amplification. Combined SMC, MDA, and routine case management consistently outperform single interventions (Figure S2). Coverage analysis (Figure S3) reveals trade-offs between feasibility and impact. SMC alone does not achieve 10–30% reductions under low routine case management coverage and remains limited even at higher levels. In contrast, MDA performs better but depends strongly on cycle number and target threshold. Combined strategies (SMC + MDA) reduce required coverage but remain sensitive to routine case management and intervention frequency. Figure S4 shows that increasing cycles of SMC, MDA, and combined strategies increases both cases averted and resistant cases, especially under higher routine case management coverage. SMC produces fewer resistant and averted cases, reflecting its targeted deployment. The combined strategy yields the highest impact but also the strongest selection pressure for resistance. As shown in Figure S4, extending SMC eligibility from under 5 to under 10 produces only marginal differences when combined with MDA, consistent with the dominant role of overall coverage and similar protection durations across interventions (Figure S1).

Despite their effectiveness, SMC and MDA require repeated implementation and remain insufficient without sustained vector control. They do not eliminate the entomological reservoir, allowing continued transmission under suitable ecological conditions [55]. Moreover, repeated drug pressure may promote resistance selection in both humans and mosquitoes [56]. A comprehensive cost-effectiveness analysis jointly considering epidemiological impact and resistance risk would therefore be valuable. Finally, although highly effective, these interventions face operational constraints and evolutionary trade-offs, reinforcing the need for integrated and carefully timed strategies.

From an intervention design perspective, these results highlight that maximizing short-term cases averted and limiting the emergence of resistance represent distinct and potentially competing objectives. Figure 4 should therefore not be interpreted as identifying a single optimal coverage level, but rather as illustrating an epidemiological-evolutionary trade-off across intervention scenarios. Increasing routine case management coverage provides substantial immediate epidemiological benefits, while the associated increase in drug exposure may strengthen selection pressure for resistant parasites. These findings emphasize the importance of considering resistance dynamics alongside epidemiological impact when evaluating intervention strategies, and support the integration of resistance surveillance with sustained case management and preventive interventions. However, identifying a setting-specific balance between these objectives would require an explicit consideration of the operational constraints, economic costs, and acceptable levels of resistance, together with calibration to local epidemiological data. A multi objective optimization framework incorporating these dimensions therefore represents a natural extension of the present analysis.

The mosquito component of the model also involves a simplifying assumption. Mosquito infection is represented through an SI formulation, and the extrinsic incubation period (EIP) is therefore not explicitly modeled. Consequently, newly infected mosquitoes are assumed to become infectious without accounting for the delay required for parasite development or for mosquitoes mortality during this period. A natural extension would introduce an exposed mosquito class, potentially structured by

time since infection and by chronological age (eg., [27]), to explicitly represent the EIP and survival through parasite development. This would be particularly relevant for investigating the environmental drivers of transmission, such as temperature-dependent variation in the EIP.

Uncertainty in the parameters governing the time-dependent drug efficacy profiles should also be considered when interpreting the numerical results. Although the efficacy decay parameters used for SMC and MDA were informed by published studies, they were not varied in the present sensitivity analysis. Variation in the maximal efficacy, duration of protection, or rate of efficacy decay would modify both the magnitude and duration of post-intervention protection and could consequently affect the estimated benefit of increasing the number of intervention cycles or changing the interval between successive rounds. The quantitative results concerning intervention timing and coverage should therefore be interpreted conditional on the drug efficacy profiles considered here.

Another limitation of this work is that the model has not yet been calibrated against data from a specific malaria-endemic setting. Accordingly, the present simulations should be interpreted as mechanistic scenario analyses rather than setting-specific quantitative forecasts. A natural next step is therefore to develop a setting-specific calibration and validation framework. This will require combining age- and sex-stratified incidence and prevalence data for malaria with demographic information, interventions coverage and timing, pharmacokinetic and pharmacodynamic information for the drugs used in SMC and MDA, and longitudinal molecular or therapeutic efficacy surveillance of antimalarial resistance. These complementary data streams could be used to estimate uncertain transmission, progression, intervention, and resistance-related parameters, while independent temporal or spatial observations could be reserved for model validation. Such a calibrated framework would enable uncertainty-quantified, setting-specific projections and comparisons of intervention strategies under realistic operational constraints.

Overall, this study provides a unified age-structured framework to investigate the time-since-administration pharmacodynamic efficacy profile, demographic heterogeneity, and drug resistance in malaria transmission, and to identify strategies balancing short-term control with long-term sustainability.

Data sharing statement

The code (with the R Programming Language) used to simulate the model can be accessed through the Zenodo platform for reproducibility at <https://doi.org/10.5281/zenodo.21175620> [57].

Author contributions

Manuela M. Nimpa: Software, formal analysis, investigation, visualization, writing-original draft, validation; Franck J. Dongmo: Software, methodology, investigation, visualization, writing-original draft, validation; Charles S. Wondji: Writing-review and editing, validation; Ramsès Djidjou-Demasse: Conceptualization, methodology, investigation, visualization, supervision, writing-original draft, validation. All authors have read and approved the final version of the manuscript.

Use of Generative-AI tools declaration

The authors declare they have not used artificial intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors of this article declare that they have no financial conflicts of interest with the content of this article.

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Supplementary

A. Main ideas underlying the proof of Theorem 3.2

We introduce the following vectors notations

$$\begin{aligned}
 S_h &= (S_h^{\varnothing}, S_h^{\sigma})', \quad A_h = (A_h^{s,\varnothing}, A_h^{r,\varnothing}, A_h^{s,\sigma}, A_h^{r,\sigma})', \\
 I_h &= (I_{h,T}^{s,\varnothing}, I_{h,T}^{r,\varnothing}, I_{h,U}^{s,\varnothing}, I_{h,U}^{r,\varnothing}, I_{h,T}^{s,\sigma}, I_{h,T}^{r,\sigma}, I_{h,U}^{s,\sigma}, I_{h,U}^{r,\sigma})', \\
 R_h &= (R_h^{\varnothing}, R_h^{\sigma})', \quad y_h = (Y_{h,SMC}^{\varnothing}, Y_{h,SMC}^{\sigma}, Y_{h,MDA}^{\varnothing}, Y_{h,MDA}^{\sigma})', \\
 z_h &= (A_{h,SMC}^{s,\varnothing}, A_{h,SMC}^{r,\varnothing}, A_{h,SMC}^{s,\sigma}, A_{h,SMC}^{r,\sigma}, A_{h,MDA}^{s,\varnothing}, A_{h,MDA}^{r,\varnothing}, A_{h,MDA}^{s,\sigma}, A_{h,MDA}^{r,\sigma})', \\
 U_h(t, a) &= (S_h(t, a), A_h(t, a), I_h(t, a), R_h(t, a, \cdot))', \\
 W_h(t, a, \sigma) &= (y_h(t, a, \sigma), z_h(t, a, \sigma))', \\
 X_m(t) &= (S_m(t), I_m(t))',
 \end{aligned}$$

as well as the matrices

$$\begin{aligned}
 \Theta(t) &= \begin{pmatrix} \begin{pmatrix} \theta(t)I_2 \\ (1-\theta(t))I_2 \end{pmatrix} & \mathbf{0}_{4 \times 2} \\ \mathbf{0}_{4 \times 2} & \begin{pmatrix} \theta(t)I_2 \\ (1-\theta(t))I_2 \end{pmatrix} \end{pmatrix}, & \bar{\Lambda}_h &= (p\Lambda_h, (1-p)\Lambda_h)', \\
 I_1 &= (I_4 \quad \mathbf{0}_{4 \times 4}), & I_2 &= (\mathbf{0}_{4 \times 4} \quad I_4), \\
 \Delta_1 &= \begin{pmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 1 \end{pmatrix}, & \Delta_2 &= \begin{pmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{pmatrix}, \\
 \Delta_3 &= \begin{pmatrix} I_2 & \mathbf{0}_{2 \times 6} \\ \mathbf{0}_{2 \times 6} & I_2 \end{pmatrix}, & \Delta_4 &= \begin{pmatrix} 1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 \end{pmatrix}, \\
 e_1 &= (I_2 \quad \mathbf{0}_{2 \times 4} \quad I_2), & e_2 &= \begin{pmatrix} \Delta'_2 & \mathbf{0}_{4 \times 2} \\ \mathbf{0}_{4 \times 2} & \Delta'_2 \end{pmatrix}, \\
 e_3 &= \begin{pmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \end{pmatrix}, & \kappa_i(\sigma) &= \begin{pmatrix} \kappa_S(\sigma)I_4 & \mathbf{0}_{4 \times 4} \\ \mathbf{0}_{4 \times 4} & \kappa_M(\sigma)I_4 \end{pmatrix}, \\
 1_2 &= (1 \quad 1), & \beta_h(a) &= \text{diag}(\beta_h^k(a))_{k \in \{s,r\}}, \\
 \beta_m &= \text{diag}(\beta_m^k)_{k \in \{s,r\}}, & I_n &= \text{the identity matrix of order } n, \\
 \eta_i(\sigma) &= \begin{pmatrix} \eta_S(\sigma)I_4 & \mathbf{0}_{4 \times 4} \\ \mathbf{0}_{4 \times 4} & \eta_M(\sigma)I_4 \end{pmatrix}, & v_h(a) &= \begin{pmatrix} v_h^{\varnothing}(a)I_2 & \mathbf{0}_{2 \times 2} \\ \mathbf{0}_{2 \times 2} & v_h^{\sigma}(a)I_2 \end{pmatrix}, \\
 \psi_h(a) &= \begin{pmatrix} \psi_h^{\varnothing}(a)I_2 & \mathbf{0}_{2 \times 2} \\ \mathbf{0}_{2 \times 2} & \psi_h^{\sigma}(a)I_2 \end{pmatrix}, & \bar{\delta}_h(a) &= \begin{pmatrix} \text{diag}(\delta_h^{k,\ell}(a))_{k,\ell} & \mathbf{0}_{4 \times 4} \\ \mathbf{0}_{4 \times 4} & \text{diag}(\delta_h^{k,\ell}(a))_{k,\ell} \end{pmatrix}, \\
 \bar{\gamma}_h(a) &= \begin{pmatrix} \text{diag}(\gamma_h^{k,\ell}(a))_{k,\ell} & \mathbf{0}_{4 \times 4} \\ \mathbf{0}_{4 \times 4} & \text{diag}(\gamma_h^{k,\ell}(a))_{k,\ell} \end{pmatrix}, & P(a) &= \begin{pmatrix} \phi_h(a)I_2 \\ \Delta_2 \psi_h(a) \Delta_1 \end{pmatrix},
 \end{aligned}$$

$$\gamma_\kappa(a, \sigma) = \begin{pmatrix} \text{diag}(\text{diag}(\gamma_S^k(a, \sigma)), \text{diag}(\gamma_S^k(a, \sigma))) & \mathbf{0}_{4 \times 4} \\ \mathbf{0}_{4 \times 4} & \text{diag}(\text{diag}(\gamma_M^k(a, \sigma)), \text{diag}(\gamma_M^k(a, \sigma))) \end{pmatrix},$$

$$\varepsilon = \begin{pmatrix} 1 - \varepsilon_s & \varepsilon_r & 1 & 0 & 1 - \varepsilon_s & \varepsilon_r & 1 & 0 \\ \varepsilon_s & 1 - \varepsilon_r & 0 & 1 & \varepsilon_s & 1 - \varepsilon_r & 0 & 1 \end{pmatrix},$$

$$\bar{\lambda}_m = \begin{pmatrix} \text{diag}(\lambda_m) & \mathbf{0}_{2 \times 2} & \mathbf{0}_{2 \times 2} & \mathbf{0}_{2 \times 2} \\ \mathbf{0}_{2 \times 2} & \text{diag}(\lambda_m) & \mathbf{0}_{2 \times 2} & \mathbf{0}_{2 \times 2} \\ \mathbf{0}_{2 \times 2} & \mathbf{0}_{2 \times 2} & \text{diag}(\lambda_m) & \mathbf{0}_{2 \times 2} \\ \mathbf{0}_{2 \times 2} & \mathbf{0}_{2 \times 2} & \mathbf{0}_{2 \times 2} & \text{diag}(\lambda_m) \end{pmatrix},$$

$$\bar{\beta}_h(a) = \left(\text{diag}(\bar{\beta}_{h,S}^k(a))_k \quad \text{diag}(\bar{\beta}_{h,S}^k(a))_k \quad \text{diag}(\bar{\beta}_{h,M}^k(a))_k \quad \text{diag}(\bar{\beta}_{h,M}^k(a))_k \right).$$

The forces of infection λ_h and λ_m are rewritten as

$$\lambda_h(t) = \frac{1}{N_h(t)} \int_0^\infty \left(\beta_h(a)(e_3 A_h(t, a) + \varepsilon I_h(t, a)) + \int_0^\infty \bar{\beta}_h(a, \sigma) z_h(t, a, \sigma) d\sigma \right) da,$$

$$\lambda_m(t) = \frac{1}{N_h(t)} \beta_m I_m(t).$$

We then have the following compact system:

$$\begin{cases} (\partial_t + \partial_a) S_h(t, a) = \int_0^\infty \rho_h(\sigma) R_h(t, a, \sigma) d\sigma - ((\mu_h(a) + 1_2 \lambda_m(t) + \phi_h(a)) I_2 + \Delta_2 \psi_h(a) \Delta_1) S_h(t, a) \\ \quad + \int_0^\infty e_1 \kappa_i(\sigma) \Delta'_3 y_h(t, a, \sigma) d\sigma, \\ (\partial_t + \partial_a) A_h(t, a) = l_1 \bar{\lambda}_m(t) l'_1 \Delta'_2 S_h(t, a) - ((\mu_h(a) + \phi_h(a)) I_4 + \nu_h(a) + \psi_h(a)) A_h(t, a), \\ (\partial_t + \partial_a) I_h(t, a) = \Theta(t) \nu_h(a) A_h(t, a) - (\mu_h(a) I_8 + \bar{\delta}_h(a) + \bar{\gamma}_h(a)) I_h(t, a), \\ (\partial_t + \partial_a + \partial_\sigma) R_h(t, a, \sigma) = -((\mu_h(a) + \phi_h(a)) I_2 + \Delta_2 \psi_h(a) \Delta_1) R_h(t, a, \sigma) - \rho_h(\sigma) R_h(t, a, \sigma), \end{cases} \quad (\text{A.1})$$

$$\begin{cases} (\partial_t + \partial_a + \partial_\sigma) y_h(t, a, \sigma) = -(\mu_h(a) I_4 + \Delta_3(\eta_i(\sigma) 1_2 \lambda_m(t) + \kappa_i(\sigma)) \Delta'_3) y_h(t, a, \sigma), \\ (\partial_t + \partial_a + \partial_\sigma) z_h(t, a, \sigma) = \eta_i(\sigma) \bar{\lambda}_m(t) e_2 y_h(t, a, \sigma) - (\mu_h(a) I_8 + \gamma_\kappa(a, \sigma)) z_h(t, a, \sigma), \end{cases}$$

$$\begin{cases} \dot{S}_m(t) = \Lambda_m - \mu_m S_m(t) - 1_2 \lambda_h(t) S_m(t), \\ \dot{I}_m(t) = \lambda_h(t) S_m(t) - \delta_m I_m(t), \end{cases}$$

$$\begin{cases} S_h(t, 0) = \bar{\Lambda}_h, \quad A_h(t, 0) = 0_{\mathbb{R}^4}, \quad I_h(t, 0) = 0_{\mathbb{R}^8}, \quad R_h(t, 0, \sigma) = 0_{L^1(\mathbb{R}_+, \mathbb{R}^2)}, \\ y_h(t, 0, \sigma) = 0_{L^1(\mathbb{R}_+, \mathbb{R}^4)}, \quad z_h(t, 0, \sigma) = 0_{L^1(\mathbb{R}_+, \mathbb{R}^8)}, \\ R_h(t, a, 0) = \Delta_4 \bar{\gamma}_h(a) I_h(t, a) + \int_0^\infty \Delta_2 I_2 \gamma_\kappa(a, \sigma) z_h(t, a, \sigma) d\sigma + \int_0^\infty \Delta_2 I_1 \gamma_\kappa(a, \sigma) z_h(t, a, \sigma) d\sigma, \\ y_h(t, a, 0) = P(a) \left(S_h(t, a) + \int_0^\infty R_h(t, a, \sigma) d\sigma \right), \quad z_h(t, a, 0) = \begin{pmatrix} \phi_h(a) I_4 \\ \psi_h(a) \end{pmatrix} A_h(t, a), \end{cases}$$

with the initial condition defined as follows:

$$\begin{cases} U_h(0, a) = U_{h0}(a), \\ W_h(0, a, \sigma) = W_{h0}(a, \sigma), \\ X_m(0) = X_{m0}. \end{cases} \quad (\text{A.2})$$

By setting

$$\begin{aligned} \mathcal{X}_{1h} &:= \mathbb{R}^2 \times L^1(\mathbb{R}_+, \mathbb{R}^2) \times \mathbb{R}^4 \times L^1(\mathbb{R}_+, \mathbb{R}^4) \times \mathbb{R}^8 \times L^1(\mathbb{R}_+, \mathbb{R}^8), \\ \mathcal{X}_{2h} &:= L^1(\mathbb{R}_+, \mathbb{R}^2) \times L^1(\mathbb{R}_+^2, \mathbb{R}^2), \\ \mathcal{X}_{3h} &:= L^1(\mathbb{R}_+, \mathbb{R}^4) \times L^1(\mathbb{R}_+^2, \mathbb{R}^4) \times L^1(\mathbb{R}_+, \mathbb{R}^8) \times L^1(\mathbb{R}_+^2, \mathbb{R}^8), \\ \mathcal{X}_m &:= \mathbb{R}^3, \end{aligned}$$

the linear operator $\hat{B}_{1,h} : D(\hat{B}_{1,h}) \subset \mathcal{X}_{1h} \longrightarrow \mathcal{X}_{1h}$ where $\hat{B}_{1,h}$ is defined as follows:

$$\hat{B}_{1,h} \begin{pmatrix} 0_{\mathbb{R}^2} \\ S_h(\cdot) \\ 0_{\mathbb{R}^4} \\ A_h(\cdot) \\ 0_{\mathbb{R}^8} \\ I_h(\cdot) \end{pmatrix} = \begin{pmatrix} -S_h(0) \\ -S'_h(\cdot) - ((\mu_h(\cdot) + \phi_h(\cdot))\mathbf{I}_2 + \Delta_2\psi_h(\cdot)\Delta_2)S_h(\cdot) \\ -A_h(0) \\ -A'_h(\cdot) - ((\mu_h(\cdot) + \psi_h(\cdot))\mathbf{I}_4 + \nu_h(\cdot) + \phi_h(\cdot))A_h(\cdot) \\ -I_h(0) \\ -I'_h(\cdot) - (\mu_h(\cdot)\mathbf{I}_8 + \bar{\delta}_h(\cdot) + \bar{\gamma}_h(\cdot))I_h(\cdot) \end{pmatrix}.$$

Let the Banach space $(\mathcal{Y}_\sigma, \|\cdot\|)$ be defined as follows:

$$\mathcal{Y}_\sigma = \left\{ u \in L^1(\mathbb{R}_+^2) : \frac{\partial u}{\partial a} \in L^1(\mathbb{R}_+), \quad \frac{\partial u}{\partial \sigma} \in L^1(\mathbb{R}_+) \right\},$$

associated with the norm

$$\|u\|_\sigma = \|u\|_{L^1(\mathbb{R}_+^2)} + \|\partial_a u\|_{L^1(\mathbb{R}_+^2)} + \|\partial_\sigma u\|_{L^1(\mathbb{R}_+^2)}, \quad \forall u \in \mathcal{Y}_\sigma.$$

Then $(\mathcal{Y}_\sigma, \|\cdot\|_\sigma)$ becomes a Banach space. Following [27], there is a unique linear operator $\Pi_{i,\sigma} \in \mathcal{L}(\mathcal{Y}_\sigma, L^1(\mathbb{R}_+))$ for each $i = 1, 2$ such that for all

$$u_\sigma \in C_c^1(\mathbb{R}_+^2) \cap \mathcal{Y}_\sigma : \quad \Pi_{1,\sigma} u_\sigma = u_\sigma(0, \cdot), \quad \Pi_{2,\sigma} u_\sigma = u_\sigma(\cdot, 0).$$

We can then define the linear operators

$$\hat{B}_{2,h} : D(\hat{B}_{2,h}) \subset \mathcal{X}_{2h} \longrightarrow \mathcal{X}_{2h}, \quad \hat{B}_{3,h} : D(\hat{B}_{3,h}) \subset \mathcal{X}_{3h} \longrightarrow \mathcal{X}_{3h}$$

as

$$\begin{aligned} \hat{B}_{2,h} \begin{pmatrix} 0_{L^1(\mathbb{R}_+, \mathbb{R}_+^2)} \\ R_h(\cdot, -) \end{pmatrix} &= \begin{pmatrix} -\Pi_{2,\sigma} R_h \\ -(\partial_a + \partial_\sigma)R_h(\cdot, -) - ((\mu_h(\cdot) + \rho_h(\cdot) + \phi_h(\cdot))\mathbf{I}_2 + \Delta_2\psi_h(\cdot)\Delta_1)R_h(\cdot, -) \end{pmatrix}, \\ \hat{B}_{3,h} \begin{pmatrix} 0_{L^1(\mathbb{R}_+, \mathbb{R}_+^4)} \\ y_h(\cdot, -) \\ 0_{L^1(\mathbb{R}_+, \mathbb{R}_+^8)} \\ z_h(\cdot, -) \end{pmatrix} &= \begin{pmatrix} -\Pi_{2,\sigma} y_h \\ -(\partial_a + \partial_\sigma)y_h(\cdot, -) - (\mu_h(\cdot)\mathbf{I}_4 + \Delta_3\kappa_i(\cdot)\Delta'_3)y_h(\cdot, -) \\ -\Pi_{2,\sigma} z_h \\ -(\partial_a + \partial_\sigma)z_h(\cdot, -) - (\mu_h(\cdot)\mathbf{I}_8 + \gamma_\kappa(\cdot, -))z_h(\cdot, -) \end{pmatrix}. \end{aligned}$$

The domain of $\hat{B}_{1,h}$, $\hat{B}_{2,h}$, and $\hat{B}_{3,h}$ are

$$\begin{aligned} D(\hat{B}_{1,h}) &= \{0_{\mathbb{R}^2}\} \times W^{1,1}(\mathbb{R}_+, \mathbb{R}^2) \times \{0_{\mathbb{R}^4}\} \times W^{1,1}(\mathbb{R}_+, \mathbb{R}^4) \times \{0_{\mathbb{R}^8}\} \times W^{1,1}(\mathbb{R}_+, \mathbb{R}^8), \\ D(\hat{B}_{2,h}) &= \{0_{L^1(\mathbb{R}_+, \mathbb{R}_+^2)}\} \times (\mathcal{Y}_\sigma \cap \ker(\Pi_{1,\sigma})), \\ D(\hat{B}_{3,h}) &= \{0_{L^1(\mathbb{R}_+, \mathbb{R}_+^4)}\} \times (\mathcal{Y}_\sigma \cap \ker(\Pi_{1,\sigma})) \times \{0_{L^1(\mathbb{R}_+, \mathbb{R}_+^8)}\} \times (\mathcal{Y}_\sigma \cap \ker(\Pi_{1,\sigma})). \end{aligned}$$

Moreover, the linear operator $B_m : D(B_m) \subset \mathcal{X}_m \longrightarrow \mathcal{X}_m$, is defined as

$$B_m = -\text{diag}(\mu_m, \delta_m), \quad \text{with} \quad D(B_m) = \mathbb{R}^3.$$

Now, consider the Banach space $\mathcal{X} = \mathcal{X}_{1h} \times \mathcal{X}_{2h} \times \mathcal{X}_{3h} \times \mathcal{X}_m$ associated with the product norm $\|\cdot\|$.

Let $B : D(B) \subset \mathcal{X} \longrightarrow \mathcal{X}$ be the linear operator defined by

$$B = \text{diag}(\hat{B}_{1,h}, \hat{B}_{2,h}, \hat{B}_{3,h}, B_m),$$

with

$$D(B) = D(\hat{B}_{1,h}) \times D(\hat{B}_{2,h}) \times D(\hat{B}_{3,h}) \times D(B_m).$$

The closure of $D(B)$ is given by

$$\begin{aligned} \overline{D(B)} &= \{0_{\mathbb{R}^2}\} \times L^1(\mathbb{R}_+, \mathbb{R}^2) \times \{0_{\mathbb{R}^4}\} \times L^1(\mathbb{R}_+, \mathbb{R}^4) \\ &\quad \times \{0_{\mathbb{R}^8}\} \times L^1(\mathbb{R}_+, \mathbb{R}^8) \times \{0_{L^1(\mathbb{R}_+, \mathbb{R}^2)}\} \times L^1(\mathbb{R}_+^2, \mathbb{R}^2) \\ &\quad \times \{0_{L^1(\mathbb{R}_+, \mathbb{R}^4)}\} \times L^1(\mathbb{R}_+^2, \mathbb{R}^4) \times \{0_{L^1(\mathbb{R}_+, \mathbb{R}^8)}\} \times L^1(\mathbb{R}_+^2, \mathbb{R}^8) \\ &\quad \times \mathbb{R}^3 \\ &:= \mathcal{X}_0, \end{aligned}$$

and we can clearly see that $D(B)$ is not dense in $\mathcal{X}$. Let $\mathcal{X}_{0,+} = \mathcal{X}_+ \cap \mathcal{X}_0$, with $\mathcal{X}_+$ being the positive cone of $\mathcal{X}$.

The nonlinear component of Eqs (A.1) and (A.2) is defined as follows:

$$\mathcal{F}(w) = \begin{pmatrix} \bar{\Lambda}_h \\ \int_0^\infty \rho_h(\sigma) R_h(\cdot, \sigma) d\sigma - 1_2 \lambda_m I_2 S_h(\cdot) + \int_0^\infty e_1 \kappa_i(\sigma) \Delta'_3 y_h(\cdot, \sigma) d\sigma \\ 0_{\mathbb{R}^4} \\ I_1 \bar{\lambda}_m I'_1 \Delta'_2 S_h(\cdot) z_h(\cdot, \sigma) d\sigma \\ 0_{\mathbb{R}^8} \\ \Theta v_h(\cdot) A_h(\cdot) \\ \Delta_4 \gamma_h(\cdot) I_h(\cdot) + \int_0^\infty \Delta_2 I_2 \gamma_\kappa(\cdot, \sigma) z_h(\cdot, \sigma) d\sigma + \int_0^\infty \Delta_2 I_1 \gamma_\kappa(\cdot, \sigma) z_h(\cdot, \sigma) d\sigma \\ 0_{L^1(\mathbb{R}_+^2, \mathbb{R}^2)} \\ P(\cdot) \left(S_h(\cdot) + \int_0^\infty R_h(\cdot, \sigma) d\sigma \right) - \Delta_3 \eta_i(-) \Delta'_3 1_2 \lambda_m y_h(\cdot, -) \\ \begin{pmatrix} \phi_h(\cdot) I_4 \\ \psi_h(\cdot) \end{pmatrix} A_h(\cdot) \\ \eta_i(-) e_2 \bar{\lambda}_m y_h(\cdot, -) \\ \Lambda_m - 1_2 \lambda_h S_m \\ \lambda_h S_m \end{pmatrix}, \quad (\text{A.3})$$

with

$$w = \left(0_{\mathbb{R}^2}, S_h(\cdot), 0_{\mathbb{R}^4}, A_h(\cdot), 0_{\mathbb{R}^8}, I_h(\cdot), 0_{L^1(\mathbb{R}_+, \mathbb{R}^2)}, R_h(\cdot, -), 0_{L^1(\mathbb{R}_+, \mathbb{R}^4)}, y_h(\cdot, -), 0_{L^1(\mathbb{R}_+, \mathbb{R}^8)}, z_h(\cdot, -), S_m, I_m \right)'.$$

The nonlinear component of Eqs (A.1) and (A.2) is not well defined on $\mathcal{X}_0$ due to the presence of the term $N_h(t)$, which results in a lack of local Lipschitz continuity. To handle the issue of (A.3), set

$$\Omega_\epsilon = \{w \in \mathcal{X}_0, \mathcal{T}(w) \geq \epsilon\} \subset \mathcal{X}_0,$$

where ϵ is defined in Eq (3.1), and $\mathcal{T} : \mathcal{X} \rightarrow \mathcal{X}$ is the operator defined by

$$\mathcal{T}(w(t)) = \sum_{\mathcal{V} \in \{S, A, I, R\}} \|\mathcal{V}_h(t, \cdot)\|_{L^1(\mathbb{R}_+)} + \|y_h(t, \cdot, -)\|_{L^1(\mathbb{R}_+^2)} + \|z_h(t, \cdot, -)\|_{L^1(\mathbb{R}_+^2)}.$$

It is clear that for $\epsilon = 0$, Ω_ϵ becomes $\Omega_0 = \overline{D(B)}$. Hence, define $\mathcal{F}_\epsilon : \Omega_\epsilon \rightarrow \mathcal{X}$ by $\mathcal{F}_\epsilon \equiv \mathcal{F}$. Therefore, the abstract Cauchy problem associated with Systems (A.1) and (A.2) can be expressed as follows:

$$\begin{cases} \frac{dw(t)}{dt} = Bw(t) + \mathcal{F}_\epsilon(w(t)), & \text{for all } t > 0 \text{ and } \epsilon > 0, \\ w(0) = w_0 \in \mathcal{X}_{0,+}. \end{cases} \quad (\text{A.4})$$

From here, we follow the framework proposed in [27] for the well-posedness of epidemiological models with multiple continuous structures to complete the proof of Theorem 3.2.

B. Detailed computations of the disease-free equilibrium and basic reproduction number

The disease-free equilibrium results from solving the following system when

$$g \in \{\varnothing, \sigma\}, \quad k \in \{s, r\}, \quad \ell \in \{T, U\},$$

$$\begin{aligned} A_h^{k,g}(a) &= 0_{L^1(\mathbb{R}_+, \mathbb{R}_+)}, \quad I_{h,\ell}^{k,g}(a) = 0_{L^1(\mathbb{R}_+, \mathbb{R}_+)}, \quad R^g(a, \sigma) = 0_{L^1(\mathbb{R}_+^2, \mathbb{R}_+)}, \\ A_{h,\text{SMC}}^{k,g}(a, \sigma) &= 0_{L^1(\mathbb{R}_+^2, \mathbb{R}_+)}, \quad A_{h,\text{MDA}}^{k,g}(a, \sigma) = 0_{L^1(\mathbb{R}_+^2, \mathbb{R}_+)}, \quad \text{and } I_m^k = 0_{\mathbb{R}}. \end{aligned}$$

$$\begin{cases} \bar{S}_h^{g'}(a) = -(\mu_h(a)\phi_h(a) + \psi_h^g(a))\bar{S}_h^g(a) + \int_0^\infty \kappa_S(\sigma)Y_{h,\text{SMC}}^g(a, \sigma) d\sigma + \int_0^\infty \kappa_M(\sigma)Y_{h,\text{MDA}}^g(a, \sigma) d\sigma, \\ (\partial_a + \partial_\sigma)\bar{Y}_{h,\text{SMC}}^g(a, \sigma) = -(\mu_h(a) + \kappa_S(\sigma))\bar{Y}_{h,\text{SMC}}^g(a, \sigma), \\ (\partial_a + \partial_\sigma)\bar{Y}_{h,\text{MDA}}^g(a, \sigma) = -(\mu_h(a) + \kappa_M(\sigma))\bar{Y}_{h,\text{MDA}}^g(a, \sigma), \\ \Lambda_m - \mu_m\bar{S}_m = 0, \\ \bar{S}_h^\varnothing(0) = p\Lambda_h, \quad \bar{S}_h^\sigma(0) = (1-p)\Lambda_h, \quad \bar{Y}_{h,\text{SMC}}^g(a, 0) = \phi_h(a)\bar{S}_h^g(a), \quad \bar{Y}_{h,\text{MDA}}^g(a, 0) = \psi_h^g(a)\bar{S}_h^g(a). \end{cases}$$

The $\bar{Y}_{h,\text{SMC}}^g$ and $\bar{Y}_{h,\text{MDA}}^g$ equations give

$$\begin{aligned} \bar{Y}_{h,\text{SMC}}^g(a, \sigma) &= \mathbf{1}_{a>\sigma}(a, \sigma)\phi_h(a - \sigma)e^{-\left(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_S(\eta) d\eta\right)}\bar{S}_h^g(a - \sigma), \\ \bar{Y}_{h,\text{MDA}}^g(a, \sigma) &= \mathbf{1}_{a>\sigma}(a, \sigma)\psi_h^g(a - \sigma)e^{-\left(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_M(\eta) d\eta\right)}\bar{S}_h^g(a - \sigma). \end{aligned}$$

From this, the $\bar{S}_h^g$ -equation becomes

$$\begin{aligned}\bar{S}_h^{g'}(a) &= -(\mu_h(a)\phi_h(a) + \psi_h^g(a))\bar{S}_h^g(a) \\ &\quad + \int_0^\infty \kappa_S(\sigma)\mathbf{1}_{a>\sigma}(a, \sigma)\phi_h(a - \sigma)e^{-(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_S(\eta) d\eta)}\bar{S}_h^g(a - \sigma) d\sigma \\ &\quad + \int_0^\infty \kappa_M(\sigma)\mathbf{1}_{a>\sigma}(a, \sigma)\psi_h^g(a - \sigma)e^{-(\int_{a-\sigma}^a \mu_h d\eta + \int_0^\sigma \kappa_M d\eta)}\bar{S}_h^g(a - \sigma) d\sigma.\end{aligned}$$

Setting

$$\chi_h^g(a, \sigma) = \kappa_S(\sigma)\phi_h(a - \sigma)e^{-(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_S(\eta) d\eta)} + \kappa_M(\sigma)\psi_h^g(a - \sigma)e^{-(\int_{a-\sigma}^a \mu_h(\eta) d\eta + \int_0^\sigma \kappa_M(\eta) d\eta)},$$

we obtain

$$\bar{S}_h^g(a) = \bar{S}_h^g(0)e^{-\int_0^a (\mu_h(u) + \phi_h(u) + \psi_h^g(u)) du} + \int_0^a \int_s^a e^{-\int_\eta^a (\mu_h(u) + \phi_h(u) + \psi_h^g(u)) du} \chi_h^g(\eta, s) \bar{S}_h^g(\eta - s) d\eta ds.$$

Furthermore, the $\bar{S}_m$ equation gives $\bar{S}_m = \Lambda_m/\mu_m$.

For computation of the basic reproduction number, we linearize Systems (2.2)–(2.4) at the equilibrium $\bar{E}$ and get

$$\begin{aligned}\lambda_m^k(t) &= \frac{1}{\bar{N}_h} \beta_m^k \bar{S}_m \int_0^t \lambda_h^k(t - \eta) e^{-(t-\eta)\delta_m^k} d\eta, \quad k \in \{s, r\}, \\ \lambda_h^s(t) &= \frac{1}{\bar{N}_h} \int_0^\infty \sum_{g \in \{\bar{\varphi}, \bar{\sigma}^g\}} \beta_h^s(a) \left(A_h^{s,g}(t, a) + I_{h,U}^{s,g}(t, a) + \varepsilon_r I_{h,T}^{r,g}(t, a) + (1 - \varepsilon_s) I_{h,T}^{s,g}(t, a) \right) da \\ &\quad + \frac{1}{\bar{N}_h} \int_0^\infty \sum_{g \in \{\bar{\varphi}, \bar{\sigma}^g\}} \int_0^\infty \left(\bar{\beta}_{h,S}^s(a, \sigma) A_{h,SMC}^{s,g}(t, a, \sigma) + \bar{\beta}_{h,M}^s(a, \sigma) A_{h,MDA}^{s,g}(t, a, \sigma) \right) d\sigma da, \quad (\text{B.1}) \\ \lambda_h^r(t) &= \frac{1}{\bar{N}_h} \int_0^\infty \sum_{g \in \{\bar{\varphi}, \bar{\sigma}^g\}} \beta_h^r(a) \left(A_h^{r,g}(t, a) + I_{h,U}^{r,g}(t, a) + \varepsilon_s I_{h,T}^{s,g}(t, a) + (1 - \varepsilon_r) I_{h,T}^{r,g}(t, a) \right) da \\ &\quad + \frac{1}{\bar{N}_h} \int_0^\infty \sum_{g \in \{\bar{\varphi}, \bar{\sigma}^g\}} \int_0^\infty \left(\bar{\beta}_{h,S}^r(a, \sigma) A_{h,SMC}^{r,g}(t, a, \sigma) + \bar{\beta}_{h,M}^r(a, \sigma) A_{h,MDA}^{r,g}(t, a, \sigma) \right) d\sigma da,\end{aligned}$$

wherein

$$\begin{aligned}I_m^k(t) &= \bar{S}_m \int_0^t \lambda_h^k(t - \eta) e^{-(t-\eta)\delta_m^k} d\eta, \\ A_h^{k,g}(t, a) &= \int_0^a \lambda_m^k(t - a + \eta) \bar{S}_h^g(\eta) \vartheta_h^g(\eta, a) d\eta, \\ I_{h,T}^{k,g}(t, a) &= \int_0^a \theta v_h^g(\eta) A_h^{k,g}(t - a + \eta, \eta) \xi_{h,T}^k(\eta, a) d\eta, \\ I_{h,U}^{k,g}(t, a) &= \int_0^a (1 - \theta) v_h^g(\eta) A_h^{k,g}(t - a + \eta, \eta) \xi_{h,U}^k(\eta, a) d\eta, \\ A_{h,SMC}^{k,g}(t, a, \sigma) &= \phi_h(a - \sigma) A_h^{k,g}(t - \sigma, a - \sigma) \pi_{h,S}(a, \sigma)\end{aligned}$$

$$\begin{aligned}
& + \int_0^\sigma \eta_S(u) \lambda_m^k(t-u) \bar{Y}_{h,\text{SMC}}^g(a-u, \sigma-u) \pi_{h,S}(a, u) \, du, \\
A_{h,\text{MDA}}^{k,g}(t, a, \sigma) &= \psi_h^g(a-\sigma) A_h^{k,g}(t-\sigma, a-\sigma) \pi_{h,M}(a, \sigma) \\
& + \int_0^\sigma \eta_M(u) \lambda_m^k(t-u) \bar{Y}_{h,\text{MDA}}^g(a-u, \sigma-u) \pi_{h,M}(a, u) \, du,
\end{aligned}$$

with

$$\begin{aligned}
\vartheta_h^g(\eta, a) &= e^{-\int_\eta^a (\mu_h(u) + \nu_h^g(u) + \phi_h(u) + \psi_h^g(u)) \, du}, \\
\xi_{h,\ell}^k(\eta, a) &= e^{-\int_\eta^a (\mu_h(u) + \delta_h^{k,\ell}(u) + \gamma_h^{k,\ell}(u)) \, du}, \\
\pi_{h,S}(a, \sigma) &= e^{-\int_0^\sigma (\mu_h(a-r) + \kappa_S(r)) \, dr}, \\
\pi_{h,M}(a, \sigma) &= e^{-\int_0^\sigma (\mu_h(a-r) + \kappa_M(r)) \, dr}.
\end{aligned}$$

Thus

$$\begin{aligned}
I_{h,T}^{k,g}(t, a) &= \int_0^a \lambda_m^k(t-a+\eta) \bar{S}_h^g(\eta) \left[\theta \int_\eta^a \nu_h^g(s) \vartheta_h^g(\eta, s) \xi_{h,T}^k(s, a) \, ds \right] \, d\eta, \\
I_{h,U}^{k,g}(t, a) &= \int_0^a \lambda_m^k(t-a+\eta) \bar{S}_h^g(\eta) \left[(1-\theta) \int_\eta^a \nu_h^g(s) \vartheta_h^g(\eta, s) \xi_{h,T}^k(s, a) \, ds \right] \, d\eta, \\
A_{h,\text{SMC}}^{k,g}(t, a, \sigma) &= \phi_h(a-\sigma) \pi_{h,S}(a, \sigma) \int_0^{a-\sigma} \lambda_m^k(t-a+\eta) \bar{S}_h^g(\eta) \vartheta_h^g(\eta, a-\sigma) \, d\eta \\
& + \int_0^\sigma \eta_S(u) \lambda_m^k(t-u) \bar{Y}_{h,\text{SMC}}^g(a-u, \sigma-u) \pi_{h,S}(a, u) \, du, \\
A_{h,\text{MDA}}^{k,g}(t, a, \sigma) &= \psi_h^g(a-\sigma) \pi_{h,M}(a, \sigma) \int_0^{a-\sigma} \lambda_m^k(t-a+\eta) \bar{S}_h^g(\eta) \vartheta_h^g(\eta, a-\sigma) \, d\eta \\
& + \int_0^\sigma \eta_M(u) \lambda_m^k(t-u) \bar{Y}_{h,\text{MDA}}^g(a-u, \sigma-u) \pi_{h,M}(a, u) \, du.
\end{aligned} \tag{B.2}$$

Substituting (B.2) into (B.1), we then have the following renewal system:

$$\begin{aligned}
I_m^k(t) &= \int_0^t \lambda_h^k(t-\eta) K_m^k(t-\eta) \, d\eta, \\
\lambda_h^s(t) &= \sum_{g \in \{\mathcal{Q}, \mathcal{Q}^g\}} \int_0^\infty \lambda_m^s(t-\tau) K_g^{s \rightarrow s}(\tau) \, d\tau + \sum_{g \in \{\mathcal{Q}, \mathcal{Q}^g\}} \int_0^\infty \lambda_m^r(t-\tau) K_g^{r \rightarrow s}(\tau) \, d\tau, \\
\lambda_h^r(t) &= \sum_{g \in \{\mathcal{Q}, \mathcal{Q}^g\}} \int_0^\infty \lambda_m^r(t-\tau) K_g^{r \rightarrow r}(\tau) \, d\tau + \sum_{g \in \{\mathcal{Q}, \mathcal{Q}^g\}} \int_0^\infty \lambda_m^s(t-\tau) K_g^{s \rightarrow r}(\tau) \, d\tau.
\end{aligned}$$

with the $K_{j,s}$ defined earlier as in (3.2).

C. Supplementary figures

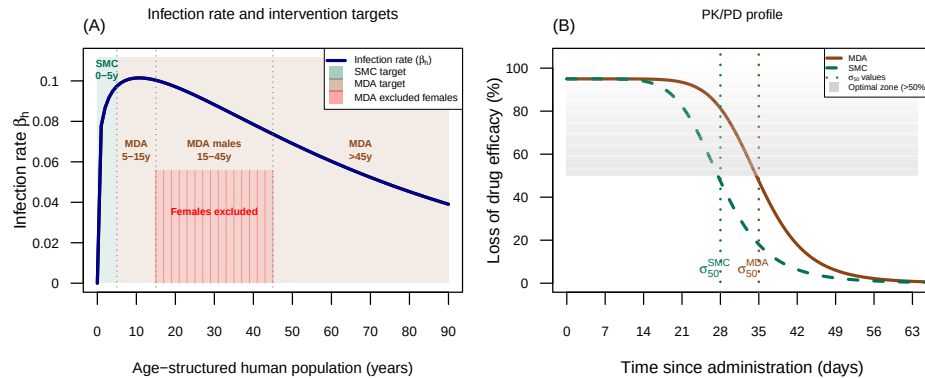


Figure S1. (A) The typical representation of the infection rate from human to mosquito, with the different target groups for MDA and standard SMC. (B) Pharmacokinetic and pharmacodynamic profile of SMC and MDA. The vertical dotted lines represent the median effective dose represented by σ_{50}^{SMC} for SMC and σ_{50}^{MDA} for MDA.

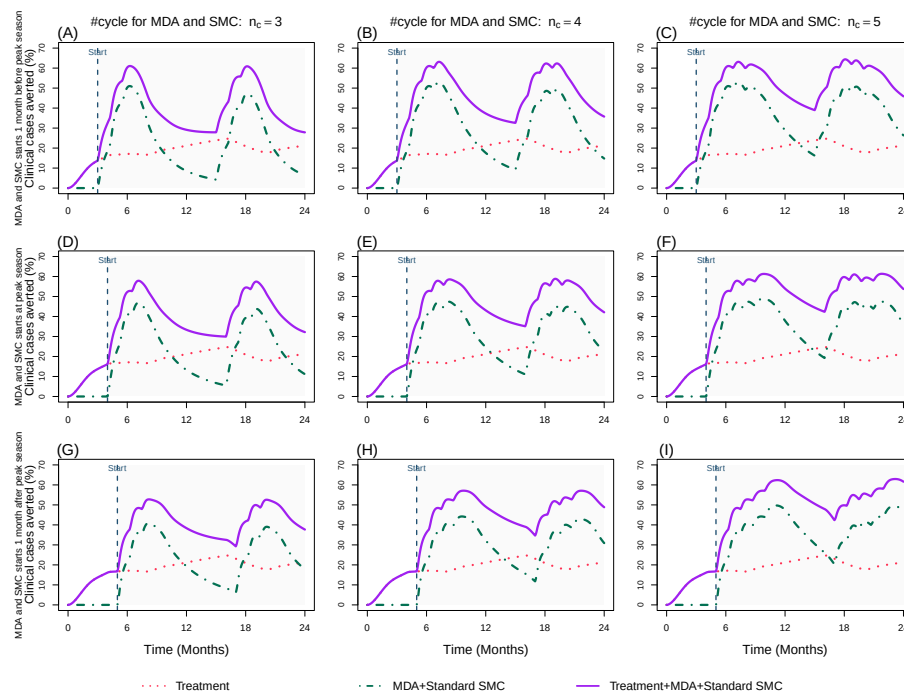


Figure S2. Dynamic of the clinical cases averted for various combinations of 70% of routine case management, standard SMC and MDA coverage, with various number of cycles for standard SMC and MDA by column (e.g., A–C) and various starting campaign by row (e.g., A–G).

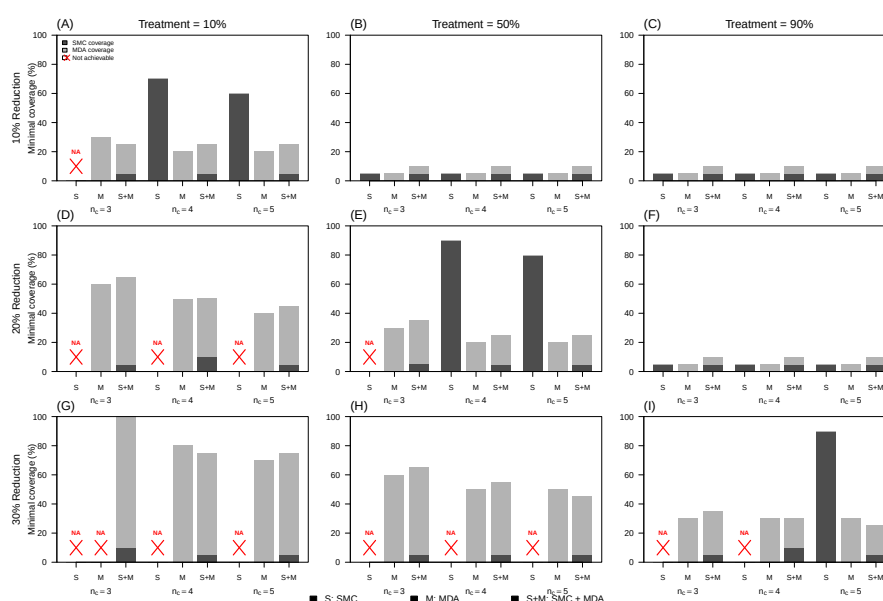


Figure S3. Minimal coverage of strategies using standard SMC and MDA combined with various coverage levels of routine case management needed to reduce 10%, 20% and 30% of clinical cases for different numbers of cycles ($n_c = 3, 4, 5$).

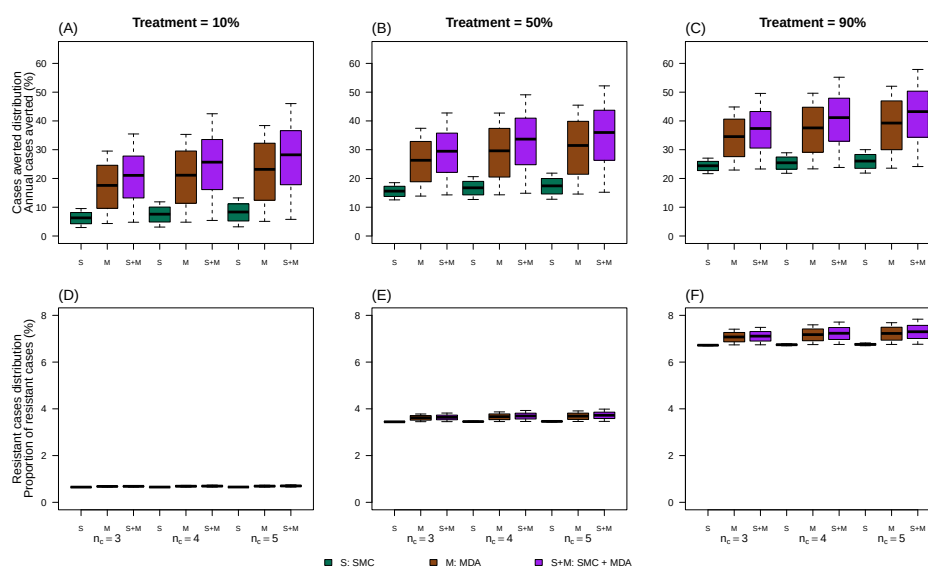


Figure S4. Annual cases averted and resistant clinical cases obtained for different scenarios using 70% of standard SMC and MDA, with various values of routine case management coverage. Row 1 and 2 are, respectively, the annual cases averted and resistant clinical cases obtained for different scenarios S, M, and S + M for different numbers of cycles ($n_c = 3, 4, 5$).

