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Modeling Malaria Rebound After Mass Drug Administration: The Role of Importation and Waning Immunity in Lake Victoria, Kenya.

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Abstract

Background:

Mass Drug Administration (MDA) is a WHO-recommended strategy for accelerating malaria elimination. However, its effectiveness in highly mobile populations remains uncertain. Studies show rapid parasitological rebound after cessation of MDA, this suggests that drug-based clearance alone is insufficient in interconnected settings. Although the resurgence is attributed to a combination of waning chemoprophylaxis and parasite importation, the relative contribution of these mechanisms and the quantitative conditions required for sustained elimination remain poorly defined.

Methods:

We developed a stochastic model of Susceptible-Infected-Recovered-Susceptible (SIRS) compartmentalized to a longitudinal PCR prevalence trial Ngodhe Island (artemisinin-piperaquine + primaquine) in 2016. Based on Bayesian estimation of transmission potential and daily importation rates, we simulated scenarios for a period of 4 years (2016-2019). We compared the epidemiological effects of increasing the MDA schedules (annual versus bimodal, which is two rounds during the two low transmission seasons) and measured the combined effect of integrating enhanced vector control coverage (90% LLIN coverage), port-of-entry screening (80% reduction in importation) and reactive focal MDA.

Results:

Model simulations have indicated that an intensifying MDA schedule (annual versus bimodal) is not associated with a proportional decrease in mean prevalence, the mean prevalence plateaus at 4.1% as a result of an importation induced equilibrium. This finding implies that, without reducing external seeding, the system will have an equilibrium at the pace of importation faster than the drug pulses can suppress transmission rates. Single-intervention strategies did not meet elimination thresholds but a combination strategy with bimodal MDA combined with improved vector control and importation screening exhibited a non-linear type of intervention combination, as it was able to drive and maintain mean prevalence below the pre-elimination threshold (<1%).

Conclusions:

With high mobility like in Ngodhe Island, increasing the frequency of mass treatment is not a viable solution to suppress the reintroduction of parasites. Our results provide mechanistic evidence that

elimination requires a shift from the current mono-therapeutic scaling to interventions that are multi-modal. The rollout of importation control and vector control should be made a priority alongside MDA, as chemoprevention alone is not sufficient in interrupting transmission.

Keywords: Mass Drug Administration, Malaria elimination, Importation, Bayesian modelling, Force of infection, Posterior predictive checks.

Background

Malaria has been a leading health issue in the world. By 2023, it was estimated that there were 263 million malaria cases and 597,000 deaths worldwide (World Health Organization, 2023). The malaria cases and deaths were 95 percent in Africa. Over the decades, sub-Saharan Africa has carried the greatest malaria toll, despite the decades of intervention efforts. In the sub-Saharan area, East Africa, has high transmission that is perennial in most regions such as around the lakes and highland fringing. Kenya recorded 3.3M cases of malaria in the same year, which included 11,478 deaths (World Health Organization, 2023). Malaria is one of the major causes of morbidity and mortality in Sub-Saharan Africa, although decades of work have been made to address the disease. The disease occurrence remains with infection resurgence in areas where the rate of transmission is significantly high. Long-term progress is often hindered by ecological, epidemiological and social factors.

The World Health Organization (WHO) suggests MDA to interrupt malaria transmission in specific geographical regions, especially those that are approaching elimination and those facing multidrug resistance. MDA attempts to bring the basic reproductive number (R_0) below the threshold, eliminating asexual parasites and gametocytes in theoretically reducing the population of asymptomatic carriers which with time achieve sustainable elimination (Von Seidlein et al., 2021). Even though MDA has demonstrated effectiveness in producing rapid initial declines in prevalence, sub-Saharan Africa and Greater Mekong Subregion trials have reported rapid resurgence of transmission some months after the MDA rounds.

Post-intervention rebound is a significant policy challenge. It implies that the transient suppression by current artemisinin-based combination therapies (ACTs) is not enough to reset the epidemiological equilibrium in settings with high vector population or connectivity to endemic mainland regions. The durability of MDA is fundamentally constrained by two factors: the half-life with which the prophylaxis can prevent reinfection; since the pharmacokinetic half-life of most prophylaxis is several weeks, the population remains exposed to reinfection, whereas the importation rate through human movement reseeds infections. This assumption as to a closed system often fails in island environments in which geographic distance is often perceived as geographic isolation. There is the constant human mobility therefore the imported infections continually reseed the local transmission, making time-limited MDA campaigns ineffective as a standalone elimination strategy.

A paradigmatic case study of these dynamics is Ngodhe Island, which is in Lake Victoria in Kenya. Kagaya et al., (2016) did a trial with a two-round MDA campaign administering artemisinin-piperaquine (Artequick) and low dose primaquine. The intervention had a high coverage (>90%) and was able to lower the PCR-detectable prevalence to 2 percent compared to 10 percent. Yet despite this, prevalence had returned to approximately the baseline level (9%) in less than two months after the last round. While the parent study hypotheses that this resurgence was driven by a combination of residual local transmission as well as infected travelers on the mainland, it was observational in nature; hence could not quantitatively separate these two phenomena. Particularly, it is not clear whether it cannot be eliminated because of the specific drug regimen (the short period of prophylaxis) or the frequency of administration (two rounds are not sufficient) or because of structural limitations posed by the importation rates.

To address this knowledge gap, it is imperative to design future elimination strategies within the Lake Victoria endemic region and other archipelagic settings. If resurgence is primarily driven by short half life of drugs, switching to longer acting regimens or increasing frequency of rounds (e.g. bimodal administration) may be adequate. However, if the resurgence is structurally driven by importation, intensifying drug administration will only yield importation-driven equilibrium.

This paper uses a Bayesian SIRS (Susceptible-Infected-Recovered-Susceptible) modeling framework to evaluate the mechanistic drivers of the rebound in 2016 on Ngodhe Island. Calibration of the model to original longitudinal trial data recreated the transmission dynamics which led to the observed resurgence. Moreover, we simulated a four-year policy horizon (2016-2019) and ran counterfactual scenarios which were not feasible in the original trial. We determined whether intensifying MDA schedule to bimodal frequency could have sustainable suppression, and quantify the synergistic impact of port-of-entry screening and increased vector control coverage - 90% LLIN coverage as the coverage at 2016 was 53%. The purpose of this study is to provide a mechanistic reason which gives a quantitative roadmap towards attaining sustainable elimination in high-mobility island settings.

Methods

Setting and Data

This study used secondary data; epidemiological and ecological data from Ngodhe Island (0°42'S, 34°06'E), Homabay County, Lake Victoria region, Kenya, which were collected in 2016, to assess the impact of Mass Drug Administration (MDA) (Kagaya, et al., 2019). The monthly variation has been observed in rain patterns in the island. In 2016 (the period of study), rains varied between 6.6 mm (July 2016) and 204 mm (April 2016), the temperature did not exhibit substantial changes (between 19.0 o C to 23.2 o C). The population of the island is about 500 inhabitants, and the area that is covered has moderate to high malaria cases. In 2016, two rounds of MDA were conducted with artemisinin-piperaquine (Artequick) combined with single low dose primaquine with a 35 days interval between rounds. The reported compliance was about 90%.

Surveillance follow-ups were conducted at specific time points after MDA rounds, and blood samples were collected to check the prevalence of parasites and other factors such as haemoglobin levels. After the first round in January 2016 on Day 0, further blood sampling for microscopy and polymerase chain reaction (PCR) was done on Day 0, Day 2, and Day 7. 35 days after the first round, the second round was done, and further follow-ups were conducted on Day 35 and Day 42. Longer-term surveillance was conducted around Days 120 and 180 to measure the prevalence of PCR and microscopy. Prevalence decreased from 3% to 0% by microscopy and from 10% to 2% by PCR, but rebounded to 9% by PCR within three months after the second MDA round.

Importation pressure was quantified using the surveillance of 419 arrivals to Ngodhe Island between June 2016 and September 2017, with a prevalence of 4.6% by microscopy and 16% by PCR, highlighting human mobility as a significant source of reintroduction. Where direct importation records were unavailable, scaled indices were constructed from reported imported cases.

To account for environmental drivers of malaria transmission, climate data were extracted from NASA Power. Temperature and rainfall were included as the primary covariates, since they influence mosquito feeding patterns, breeding conditions and seasonal transmission patterns (Beck-Johnson et al., 2017; Paaijmans et al., 2010; Siraj et al., 2014). These datasets were merged, with a 2-month lag on climate, and they collectively informed the calibration and validation of a mechanistic compartmental transmission model, which explicitly accounted for both local and imported transmission.

Transmission Model

To represent the transmission dynamics accurately and also isolate the effects of prophylaxis from importation, we developed a stochastic Susceptible-Infectious-Recovered-Susceptible (SIRS) compartmental model. This mechanistic framework was chosen in order to parsimoniously model the rapid acquisition of parasitemia and the subsequent loss of partial immunity, which are characteristic of high-transmission settings.

Model Structure: Population was segregated into four compartments, Susceptible (S) which is the baseline population at risk, infectious (I), are the individuals who are capable of transmitting parasites, and Recovered (R, protected/immune) are individuals that are protected either by temporary immunity or MDA prophylaxis. Transitions were simulated by the difference equations with daily time-step to include fine-scale intervention effects.

The system transitions were modeled using a stochastic discrete-time SIRS framework (Keeling & Rohani, 2008). Which was defined by the following state transitions:

$$S_{t+1} = S_t - \Delta I_{new} + \Delta S_{waning}$$
$$I_{t+1} = I_t + \Delta I_{new} - \Delta R_{recovery} + I_{imported}$$
$$R_{t+1} = R_t + \Delta R_{recovery} - \Delta S_{waning}$$

where the transition flows are defined as:

- New Infections ΔI_t are driven by the daily force of infection $\lambda(\boldsymbol{t})$

$$\Delta I_{new} = S_t \,.\, (1 - exp(-\lambda_t))$$

- Recovery (ΔR_t): The rate of natural clearance of parasites, γ (mean infectious period $1/\gamma$):

$$\Delta R_{recovery} = I_t . (I - exp(-\gamma)$$

- Waning Immunity (ΔS_t): Loss of protection (representing the combined duration of drug prophylaxis and temporal immunity) at rate ω (mean duration $1/\omega$):

$$\Delta S_{waning} = R_t . (1 - exp(-\omega \;\;)$$

Force of Infection and Climate Forcing

Force of Infection ($\lambda(t)$): The daily rate per capita risk of infection was modeled as the composite of local transmission and external importation:

$$\lambda_t = \beta_t \frac{I_t}{N} + \frac{l_t}{N}$$

The local effective contact rate β_t, was modulated by lagged standardized daily rainfall ($R_{t\text{-}lag}$) and the temperature ($T_{t\text{-}lag}$) anomalies using an exponential link function:

$$\beta_t = \beta_0 . exp(\beta_R R_{lag} + \beta_T T_{lag}). (1 - \kappa C_{net})$$

where β_0 is the baseline transmission rate, and β_R and β_T are coefficients to quantify the sensitivity of transmission to climatic variation and κC_{net} which represents the transmission-blocking efficacy of LLINs. For all baseline and MDA-only simulations, we utilized the historic LLIN coverage of 53% (C_{net} = 0.53), consistent with the coverage levels observed during the 2016 trial.

Imported infections were modelled as a time-varying latent process (l_t), which was estimated as a log-scale Gaussian Random Walk to capture unobserved fluctuations in external pressure, considering the actual data did not have arrivals data. Critically, importations were modelled to enter the Infectious (I) compartment, seeding new local transmission chains, which was defined as:

$$l_t = \beta_{imp} . exp(z_t)$$

where z_t follows a Gaussian Random Walk to allow the model to distinguish between intrinsic transmission and external seeding events:

$$z_t \sim N(z_{t-1}, \sigma_{imp})$$

Here, β_{imp} scales the importation magnitude, and σ_{imp} controls the volatility of the importation signal over time.

Intervention Modeling (MDA): MDA rounds were implemented as pulse events. On treatment days a proportion of individuals in the S and I compartments were sent directly to the Recovered (R) compartment (which was determined by the estimated efficacy parameter, ϵ). This transition mimics therapeutic clearance of parasites and the onset of temporary chemoprotection.

$$S_{post} = S_{pre}. (1 - \epsilon)$$
$$I_{post} = I_{pre}. (1 - \epsilon)$$
$$R_{post} = R_{pre} + \epsilon . (S_{pre} + I_{pre})$$

The duration of protection was determined by the waning rate, ω (transition R to S) which is the

combined duration of the drug's prophylactic window and temporary acquired immunity, thus making it possible to estimate the effective prophylactic half life ($t_{1/2} = \ln(2)/\omega$).

Observation Model and Bayesian Inference

The model was fitted to the daily surveillance information using a Bayesian framework implemented in with the cmdstanr package (Stan 2.33.0). A Binomial likelihood function was used to link the modelled daily prevalence (p_t) to the number of observed positive cases (y_t) among the tested individuals (n_t).

$$p_t = \frac{I_t}{N}$$

$$y_t \sim Binomial(n_t, p_t)$$

Priors

Priors were chosen to be weakly informative but biologically and epidemiologically plausible. The study incorporated knowledge from previous research in domains: epidemiology, pharmacology and statistics. Each prior used reflects empirical evidence from clinical trials, field studies or established mathematical and statistical practices.

Efficacy and protection:

Drug efficacy: $\varepsilon \sim Beta\ (8, 2)$

Protection decay: $decay \sim Lognormal\ (-2, 0.5)$

Prophylaxis half-life: $t_{1/2} = ln\ (2)/decay$

Transmission parameters:

Baseline FOI: $\beta_0 \sim Beta\ (4, 15)$

Climate effects: $\beta_R, \beta_T \sim N\ (0, 0.5)$

Incubation rate: $\sigma \sim N\ (0.1, 0.05)$

Recovery rate: $\gamma \sim N\ (0.1, 0.05)$

Waning/Prophylaxis rate: ω $\sim$ *Beta* (1, 100)

Importation process:

Importation scaling*:* $\beta_{imp} \sim N\ (0,\ 1)$

Innovation variance: $\sigma_{imp} \sim Exponential\ (50)$

Baseline importation: $imp_0 \sim N\ (-1.7,\ 0.5)$

Posterior distribution

The resulting posterior distribution is

$$p(\theta \mid y_{1:T}, n_{1:T}) \ \propto \ \prod_{t=1}^{T} \text{Binomial}\left(y_t \mid n_t, \frac{I_t(\theta)}{N}\right) \ \times \ \prod_{k} p(\theta_k)$$

Where,

$$p(\theta) = p(\varepsilon)p(\omega)p(\beta_0)p(\beta_R)p(\beta_T)p(\sigma)p(\gamma) \ \times \ p(\beta_{imp})p(\sigma_{imp})p(imp_0)$$

is the prior factorization assuming prior independence.

Intervention Efficacy and Prophylaxis: The Beta (8,2) prior on per-round drug efficacy reflects evidence from the clinical trials with artemisinin-based combination therapies (ACTs) with primaquine. A systematic review Stepniewska et al., (2019a) of the efficacy of single-dose primaquine in clearing gametocytes, discovered that when used in combination with ACT, primaquine clears gametocytes by approximately 74-87% in control trial scenarios, although in practice, the effectiveness in clearing gametocytes is less because of poor adherence and variable coverage. The Beta (8,2) distribution has a mean efficacy of 0.80 with a 95% interval of [0.44, 0.97]. The range captures the range of plausible efficacies, and is in addition allowing high-performing interventions (around 90% reduction) and more realistic performance to be observed.

Prophylactic Decay: Beta (1, 100) represents the rate of loss of protection (Recovered to Susceptible) which is a highly skewed distribution. The rate at which protection wanes is very slow (mean ≈ 0.01), which translates to a long period of protection. This prior captures the pharmacokinetics of the

artemisinin-piperaquine regimens which give a prophylactic window of about 5-6 months. The review of MDA programs by Schneider et al., (2023), demonstrated the MDA prophylaxis and interruption of transmission, lasting around 4-6 months in successful elimination settings.

Baseline transmission (β_0): A Beta (4, 15) prior was used to constrain the baseline transmission rate. This is equivalent to effective contact rate of about 0.21 on average, which is epidemiologically consistent with meso endemic (moderate transmission) elimination. While the observed prevalence at baseline was lower (≈ 10%), because this study occurred in dry seasons and climate-forcing modulates effective daily rate down to match the lower observed prevalence during dry seasons. With the modulation by the climate-forcing, it matches the pre-intervention prevalence in the parent study Kagaya et al., (2019) in the Lake Victoria area, while preventing the model from inferring implausibly large transmission rate during the rainy season.

Environmental covariates (β_R, β_T): For the climate parameters, rainfall and temperature: (β_R, β_T) were assigned Normal (0,0.5) priors. These regularised priors incorporate findings by previous ecological studies that link climate variables to transmission while also letting it remain weakly informative. The study by Beck-Johnson et al., (2017) demonstrated the effect of climate on mosquito development and survival using temperature-dependent models, which translates to moderate regression coefficients, which supports the regularizing prior as used in this study.

Importation parameters (β_{imp}, σ_{imp}) Human mobility has a significant effect on malaria dynamics and the impact of MDA in a region without border controls. The study, Wesolowski et al., (2019)) quantified that mobility can contribute 16-60% of local transmission. The scaling factor was assigned (β_{imp}) was assigned a Normal (0,1) prior, while the innovation variance of the random walk (σ_{imp} **)** was constrained by Exponential(50) prior, which is a tight exponential prior to ensure that the latent importation process evolves smoothly over time rather than exhibiting unrealistic day-to-day volatility.

Computation and Bayesian Inference

The mechanistic SIRS transmission model was implemented in Stan 2.33.0 and fitted to the surveillance data using the cmdstanr 0.7.1 in R 4.5.1. Sampling used Hamiltonian Monte Carlo with four chains, 2000 warm-up iterations, and 2000 sampling iterations per chain. Computational stability was maintained using a target average acceptance probability (adapt_delta) of 0.99 and a maximum tree depth of 15.

Convergence of the model was assessed using Gelman-Rubin statistics ($\hat{R} < 1.01$) and Effective Sample Size (ESS) > 400. Model adequacy was evaluated using the Posterior Predictive Checks (PPC), comparing observed positivity rates against the 95% Bayesian credible intervals of the simulated data, and Probability Integral Transform (PIT), which was computed from repeated draws of the negative binomial likelihood. These diagnostics assessed how well the fitted SIRS model reproduced the observed data pattern and rebound following MDA, which occurred within three months for Ngodhe Island. Leave-one-out cross-validation was done to assess the predictive accuracy of the model.

Simulations of Counterfactual Policies

To characterize the long-term epidemiological impact of alternative intervention approaches beyond the historical rounds of interventions in 2016, we extended the fitted SIRS model to simulate counterfactual scenarios for a four-year period (Jan. 2016 - Dec. 2019). Simulations were initialized on January 27, 2016 (Day 0), when the prevalence and population status of MDA round 1 was observed. Daily force of infection was modulated by historical daily climate (rainfall and temperature) and importation events drawn from the posterior distribution of the fitted model.

Since the 2016 MDA intervention perfectly collinearized with the start of the "Long Rains" (March-May), it effectively obscured the climatic signal in the training data (posterior $\beta_R \approx$ -0.09). To ensure that the counterfactual simulations reflected known epidemiology of the Lake Victoria basin, we applied a fixed rainfall coefficient ($\beta_R \approx$ 0.50) and temperature coefficient ($\beta_T \approx$ 0.10) at the projection phase, which was in line with the regional transmission models (Smith et al., 2015). This sensitivity analysis makes sure that the simulated rebounds take into consideration the environmental forcing.

We compared seven scenarios to assess the likelihood of sustained suppression:

1. Historic (Actual): The baseline scenario mimicking the observed intervention: two MDA rounds in January and March 2016, with no further mass treatment.
2. Sustained Annual MDA: Hypothetical maintenance strategy in which the two round cluster (January and March) is repeated annually for four years of repeated MDA rounds (sustained silencers).
3. Bimodal MDA: This was a high-frequency regimen, where MDA rounds were done during the two low transmission seasons. This scenario was a test of whether or not the MDA pulse method of suppression could help close the temporal window of susceptibility to the parasite to its host, where the parasite reservoir cannot recover between rounds despite pressure of

importation.

4. Annual MDA + Border Screening: This approach comprised the sustained annual schedule, with an 80 percent reduction in the rate of daily importation (l_t). This, operationally, simulates extremely effective screening and treatment at ferry terminals. It is mathematically calculated by testing the sensitivity of the system to external seeding, actually turning the island into an open system, rather than a semi-closed one.
5. Annual MDA + Vector Control (LLIN 90%): In this case, scale-up with a scale-up of vector control from the historic 53% to 90% coverage. This lowers the basic reproductive number (R_0) via the ($1 - \kappa C_{net}$) term in the transmission equation, which prevents imported cases from establishing a sustained transmission chain within the months when the drug protection has waned.
6. Annual MDA + Longer-Acting Prophylaxis: We modeled a hypothetical pharmacological advancement of a comparison by reducing the waning rate parameter (ω) by 50%. This creates a scenario where we can test whether the failure of the 2016 campaign was largely due to the short period of time of the respective drug regimen (Artequick + Primaquine) used, as opposed to the intervention strategy.
7. Combine Elimination Strategy: This scenario was a combination of the most effective strategies according to the model simulations, it combines bimodal MDA, 90% LLIN coverage and Border Screening, testing whether a combination of interventions would overcome the importation floors and achieve sustainable elimination.

For each strategy, we projected daily trajectories of the prevalence and calculated the cumulative probability of elimination, which we strictly regard as the maintenance of zero local infectious cases (I_t =0) through December 2019.

Results

The Bayesian SIRS transmission model yielded three key findings. First, MDA provided substantial protection with efficacy of 0.65 but this protection was transient. Secondly, the estimated prophylactic half-life was short (≈ 53 days), leading to a rapid rebound, which was within ≈ 3 months of the intervention. Third, counterfactual simulations showed that without combining MDA with increased clinical and surveillance coverage, sustained elimination is not possible with yearly MDA alone, while progression to a reactive model of surveillance response or combining MDA with vector control substantially improved the chances of elimination to encompass >90%.

Model Calibration and Parameter Estimation

The SIRS model had a great convergence and sampling performance. The Gelman-Rubin statistic ($\hat{R}$) value was 1.00 in all parameters, with the bulk and tail effective sample size exceeding 3,500, indicating reliable exploration of the posterior distribution (Table 1). These divergent transition proportions were very low at 0.01 percent and the values of E-BFMI were between 0.89 and 1.19 which is significantly higher than the generally accepted efficiency thresholds of the Hamilton Monte Carlo sampling. The forest plot (fig 1) shows the mean and credible intervals of the posterior estimates.

Remarkably, model posterior estimates revealed that the model was not sensitive to anomalies in rainfall and temperature, as the values of the coefficient were negligible: -0.03. Although malaria in the Lake Victoria basin is typically seasonal, the absence of a climate signal in this analysis is probably due to the confounding impact of the MDA intervention. The rapid decline in prevalence was precisely at the beginning of the long rains (March-May), effectively masking the natural seasonal signal.

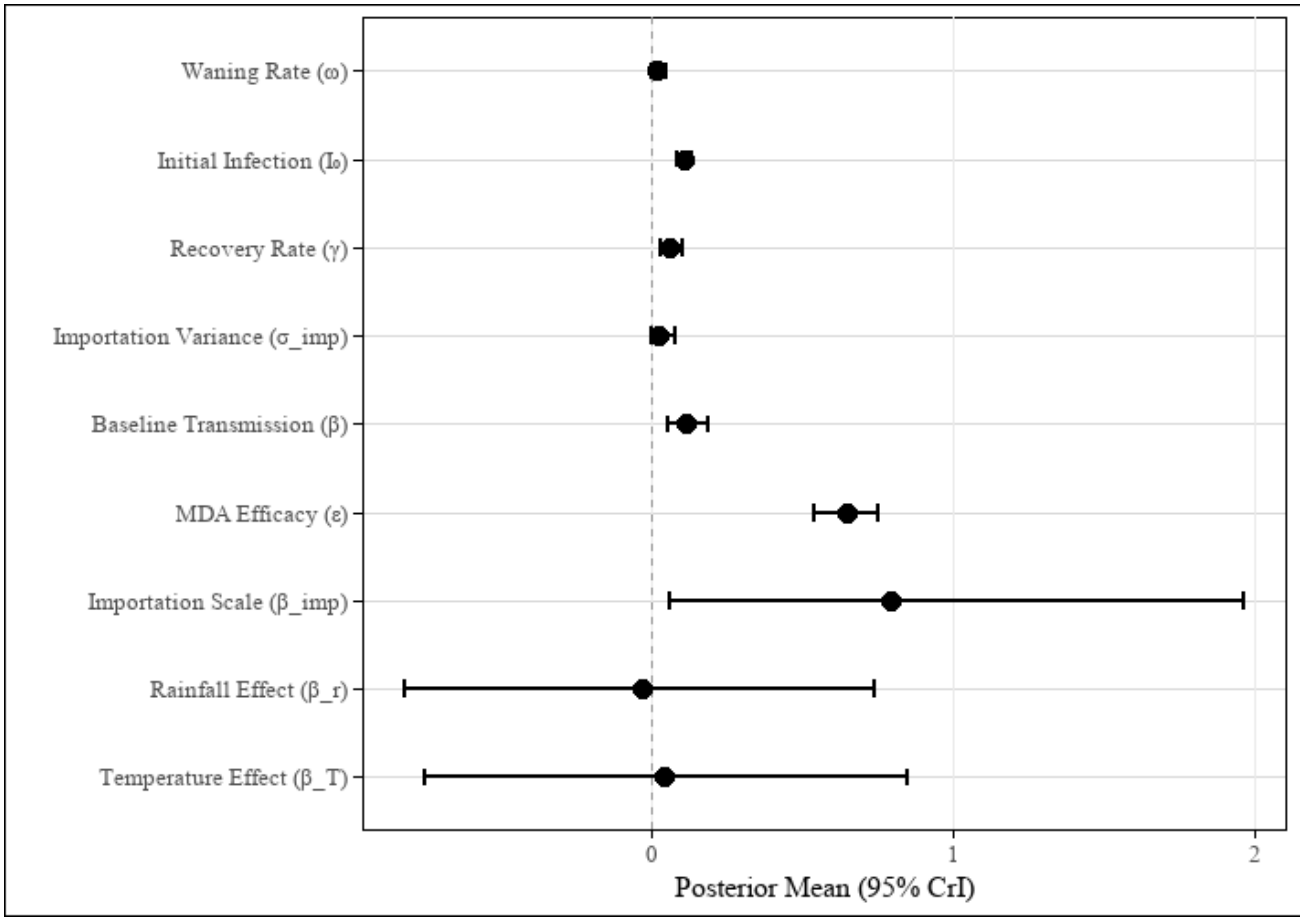


Figure 1: *Forest plot of posterior parameter estimates (posterior mean and 95% credible interval). Parameters are ordered vertically, with uncertainty intervals reflecting the range of plausible values.*

Table 1: Posterior estimates and diagnostics for key model parameters. Reported values include posterior mean and standard deviation (SD), 95% credible intervals (q5–q95).

Parameter	**Symbol**	**Mean**	**95% CrI**	**Interpretation**
MDA Efficacy	ε	0.65	0.54 – 0.75	~65% of infections cleared per round.

Waning Rate	ω	0.020	0.002 – 0.046	Prophylactic half-life approximately 35 days. Mean Duration: approximately 50 days (1.7 months). Effective Window: approximately 115 days (3.8 months).
Baseline Trans.	β_0	0.12	0.06 – 0.19	Moderate baseline transmission potential.
Importation Scale	β_{imp}	0.80	0.06 – 1.97	Significant contribution of external seeding.
Recovery Rate	γ	0.063	0.03 – 0.10	Mean infectious period approximate 16 days.
Climate (Rain)	β_R	-0.03	-0.82 – 0.75	Weak climatic forcing detected.

Observed Dynamics

Mass drug administration (MDA) produced immediate reductions in malaria case counts, but these effects were short-lived, figure 2. Each campaign was followed by a sharp decline in observed cases, indicating a substantial short-term impact of treatment. However, cases subsequently rebounded within months, returning near-baseline levels by July, showing the temporary nature of MDA-driven suppression (Schneider et al., 2023). The SIRS model successfully captured this dynamic and the posterior median trajectory (blue line) tracked the observed sharp decline and a subsequent resurgence within the 95% credible intervals.

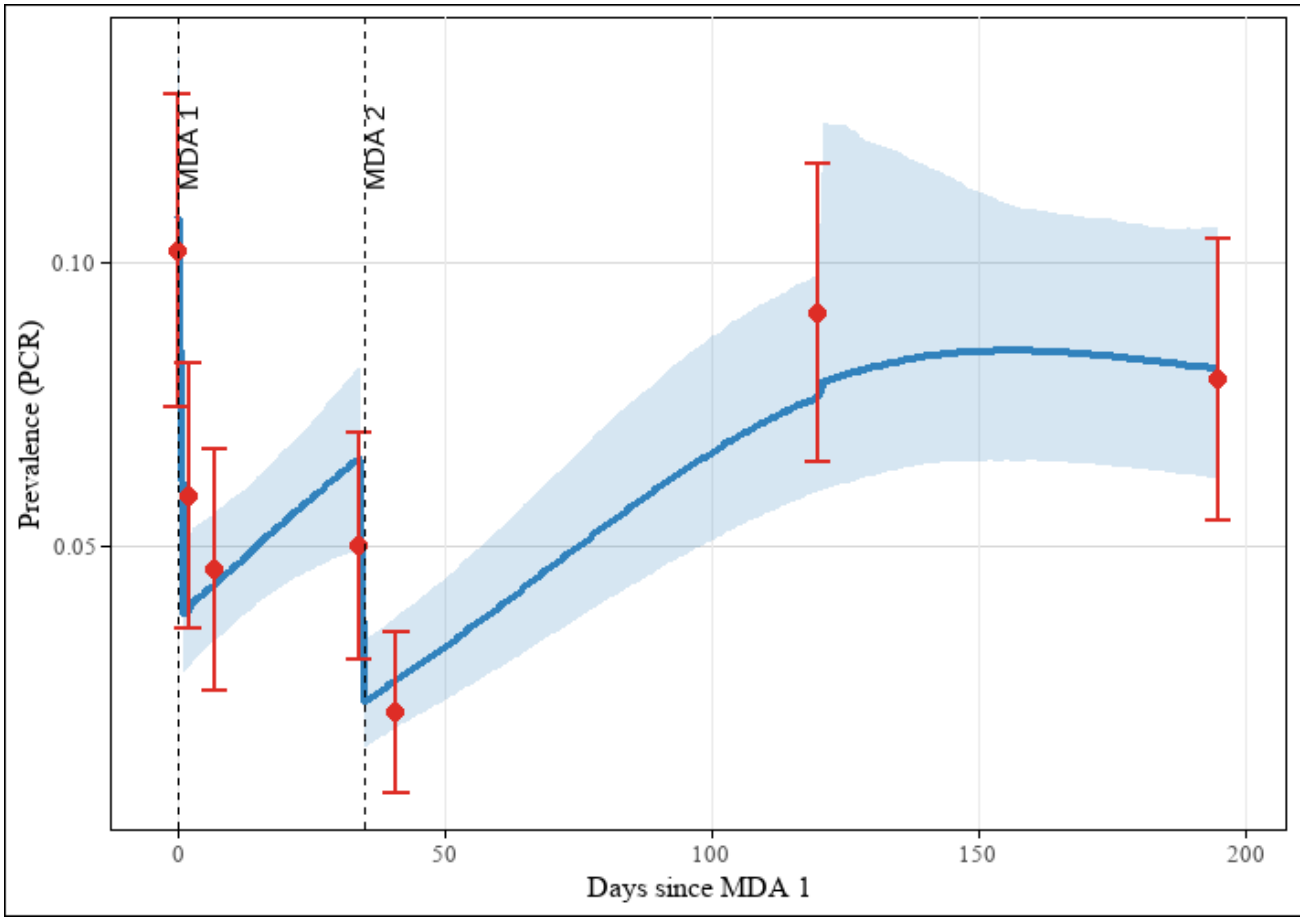


Figure 2 Fit of SIRS model on observed prevalence after mass drug administration. Red points indicate 95 percent binomial confidence intervals, whereas the blue line and shaded band are indicating the posterior median and 95 percent credible interval of the SIRS model, respectively, and the dashed vertical lines indicate MDA rounds.

Model Fit and Diagnostics

The stochastic model of SIRS was able to show a strong convergence and show a strong fit to the surveillance data. MCMC trace plots (Figure 3a) showed well-mixed chains with no divergent transitions for all parameters, confirming that the sampler adequately explored the posterior distribution. The Posterior Predictive Density overlay confirms this model is able to replicate the distribution of the observed data. The density overlay plot (Figure 3b) indicated that the simulated counts of cases were close to the empirical density of observed cases in estimating the central tendency and the dispersion. In particular, the kernel density estimate of the observed response (y) is fully within the envelope of the simulated posterior predictive draws (y_{rep}), resulting in a good description of the central tendency and

dispersion of the results. Furthermore, the Posterior Predictive Intervals plot (Figure 3c) shows excellent Pointwise coverage, having predicted mean quite similar to the observed values, indicating that the model is quite reliable in its explanation of the variability of the data.

Fig 3a.

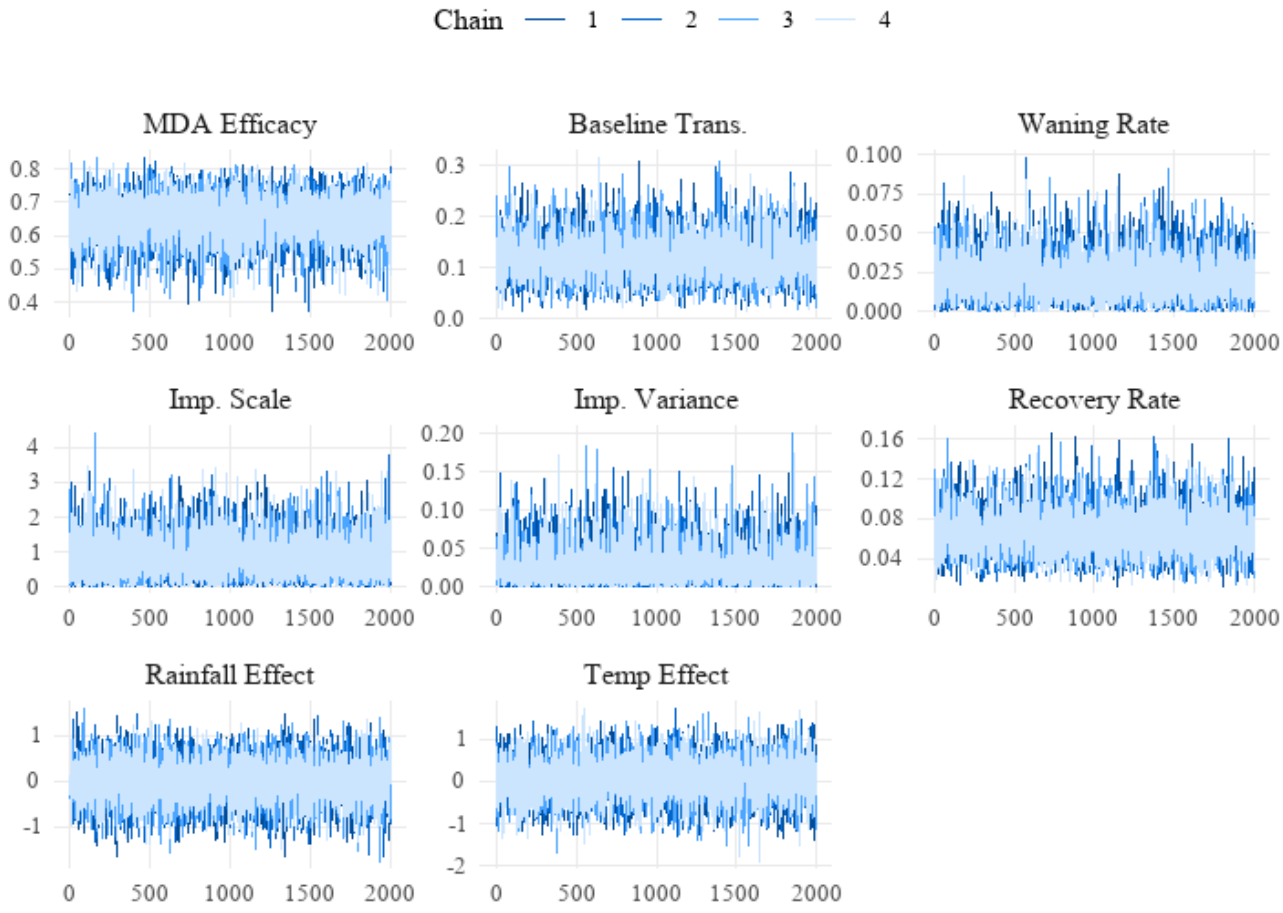


Fig 3b.

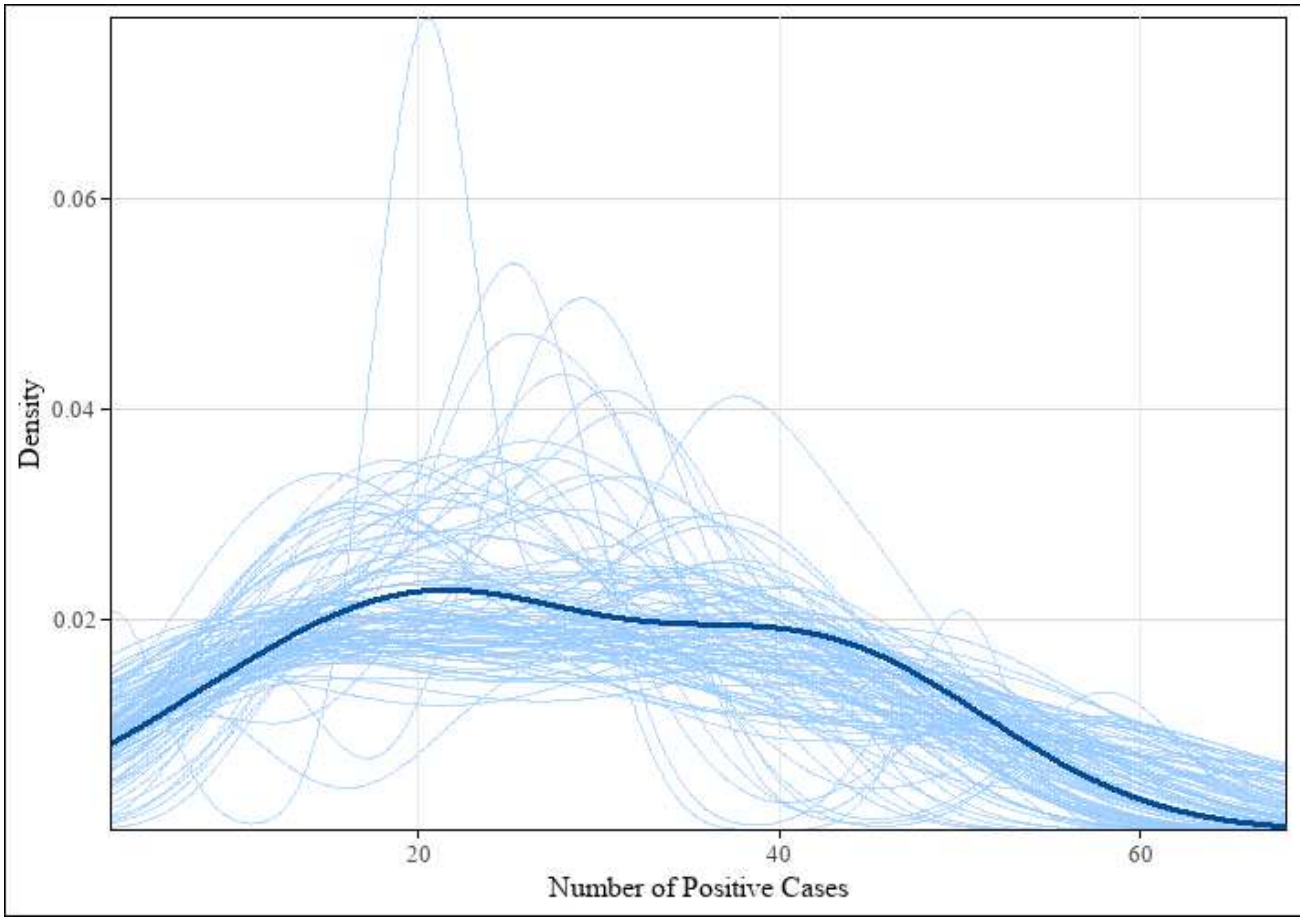


Fig 3c.

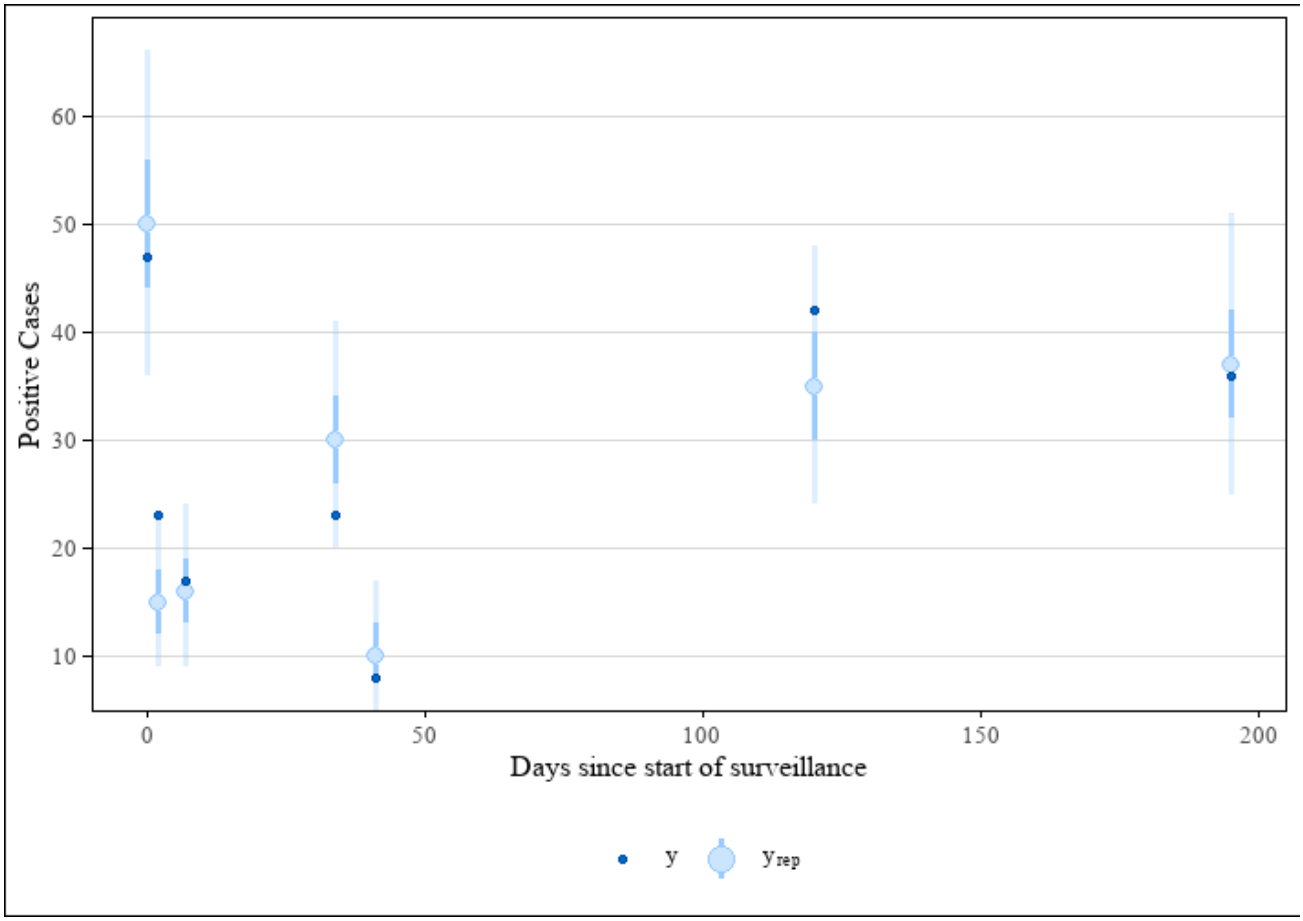


Figure 3. Posterior predictive checks for the SIRS model. (a) MCMC trace plots showing convergence of four independent chains. (b) The posterior predictive density overlay comparing the distribution of the observed cases (dark dot) against the simulated cases. (c) The posterior predictive intervals showing temporal coverage of the observed data.

Projected Impact of Sustained Interventions

In order to determine the optimal strategy for sustained suppression of infections we extended the fitted model and simulated seven counterfactual scenarios over a 4-year period (2016-2019). These simulations were a comparison of the "Historic" baseline (with the actual data, 2 MDA rounds in 2016, no further intervention) implemented against "Sustained" strategies with annual or increased amounts of intervention. All scenarios were initiated from the state of the population on Day 0 (January 27, 2016) as figure 4 shows.

The Structural Limits of MDA Scheduling:

Figure 4 a, proved that without follow-up interventions prevalence returned to the equilibrium levels (approximately 10-12%) after 12 months of the 2016 campaign. By introducing a Sustained Annual MDA strategy, in which the typical two-round cluster was repeated every January and March, the average longitudinal average was lower but failed to interrupt the transmission dynamics. This scenario had a typical sawtooth prevalence pattern: the infections were successfully contained within the treatment window, but the population soon returned to its susceptibility because the drug regimen had a very short prophylaxis half-life, 35 days. The parasite reservoir was re-established fully through importation during the period between the rounds of treatment (the treatment interval is 12 months and the protective window is only approximately 1.7-3.8 months).

The Bimodal scenario (4 rounds/year) revealed a fundamental limitation of the system, since despite doubling administration frequency, the mean prevalence was plateaued at approximately 6.6% (Figure 4, Green Line). This phenomenon is the Importation Floor--a balance at which the achievable clearance by mass treatment exactly offsets the rate of seeding of new infections by the mainland. This finding demonstrates that increased frequency of mono-therapeutic intervention, used in the open system, like Ngodhe, only yields diminishing returns: the importation pressure overwhelms the clearance rate regardless of schedule intensity.

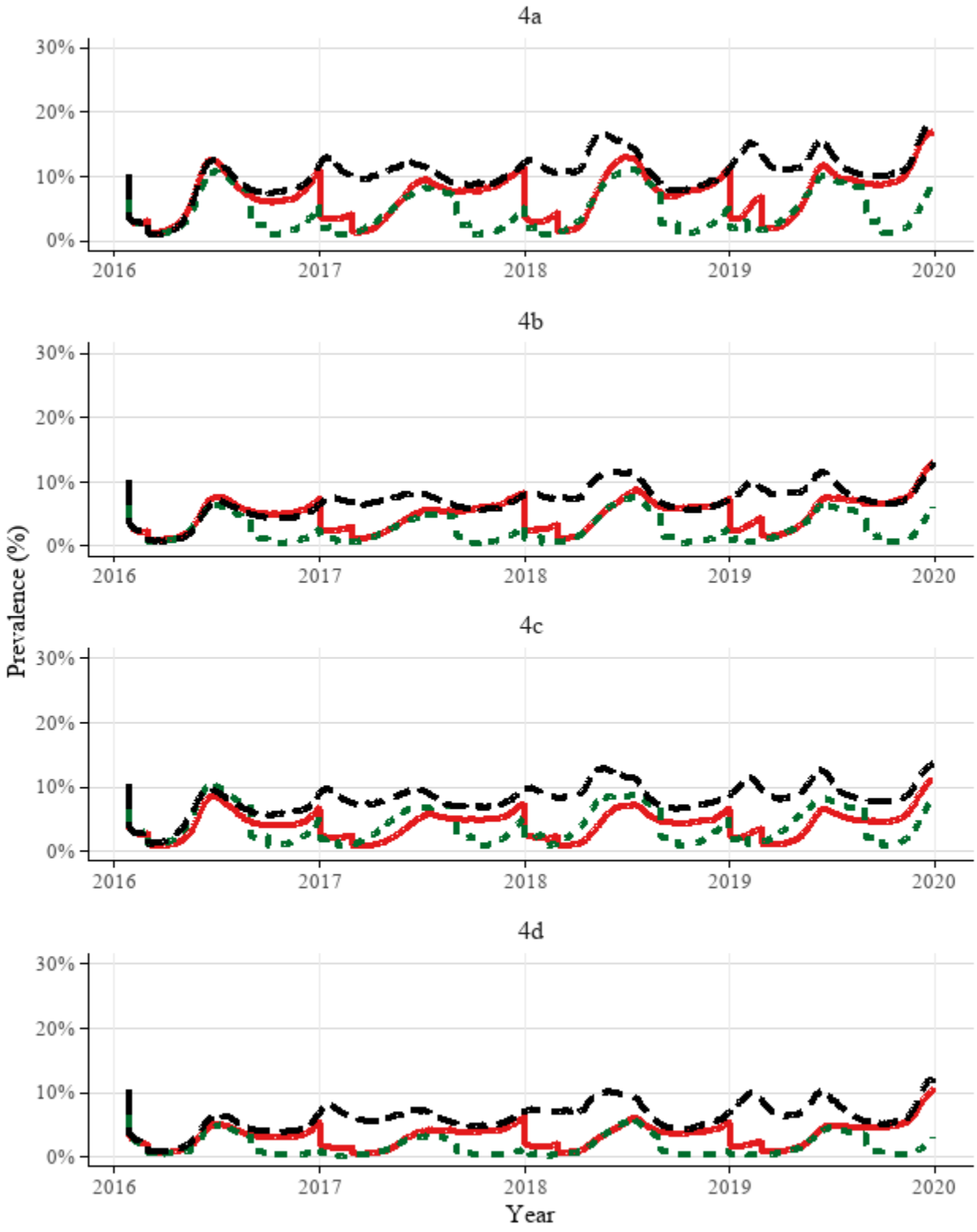

4a
4b
4c
4d
30%
20%
10%
0%
2016
2017
2018
2019
2020
Prevalence (%)
Year
Schedule
Annual (2-Rounds)
Bimodal (4-Rounds)
Historic (Control)

Figure 4: Projected prevalence trajectories (2016-2019) of five intervention strategies. The rows are different intervention strategies (Baseline, Vector Control, Screening, Prophylaxis, Reactive). The colors indicate the intensity of MDA schedule: Historic (Black), Annual (Red) and the Bimodal (Green).

The “annual scenario of MDA + Border Screening” (Figure 4, Row 3) which assumed a 80% decrease in daily importation events slackened the rate of reseeding though not suppress local transmission driven by the residual reservoir. Similarly, the "Annual MDA + Vector Control" scenario (Figure 4, Row 2), where we simulate a scale-up to 90% LLIN coverage from the historic 53%, reduced the basic reproductive number (R_0) and reduced the equilibrium prevalence to ~8%, but failed to drive the system to extinction.

We also tested a hypothetical pharmacological advancement in the "Longer-Acting Prophylaxis" scenario (Figure 4, Row 4). We simulated a drug with double the half-life of the standard regimen. Although this delayed the post-MDA rebound, it failed to bridge the temporal gap between annual rounds. This confirms that while short prophylaxis contributed to the resurgence in 2016, the primary barrier to elimination is structural (Importation) and not pharmacological

Only the combined intervention strategy had a high probability of elimination, where it sustained zero autochthonous cases through 2019:

1. The combination of Bimodal MDA with Border Screening (90% Vector Control) (Figure 5). Although all these interventions individually failed to sustain low prevalence, a combination of them could have successfully driven the mean prevalence below the pre-elimination target (<1%) by the mid - 2017. This strategy mechanistically attacks the transmission cycle in all three most crucial nodes, MDA drains reservoir, Vector Control suppresses local propagation (R_0), Screening acts a gatekeeper to reduce reseeding. This multi-modal approach effectively breaks the importation floor that constrains mono-therapeutic strategies.

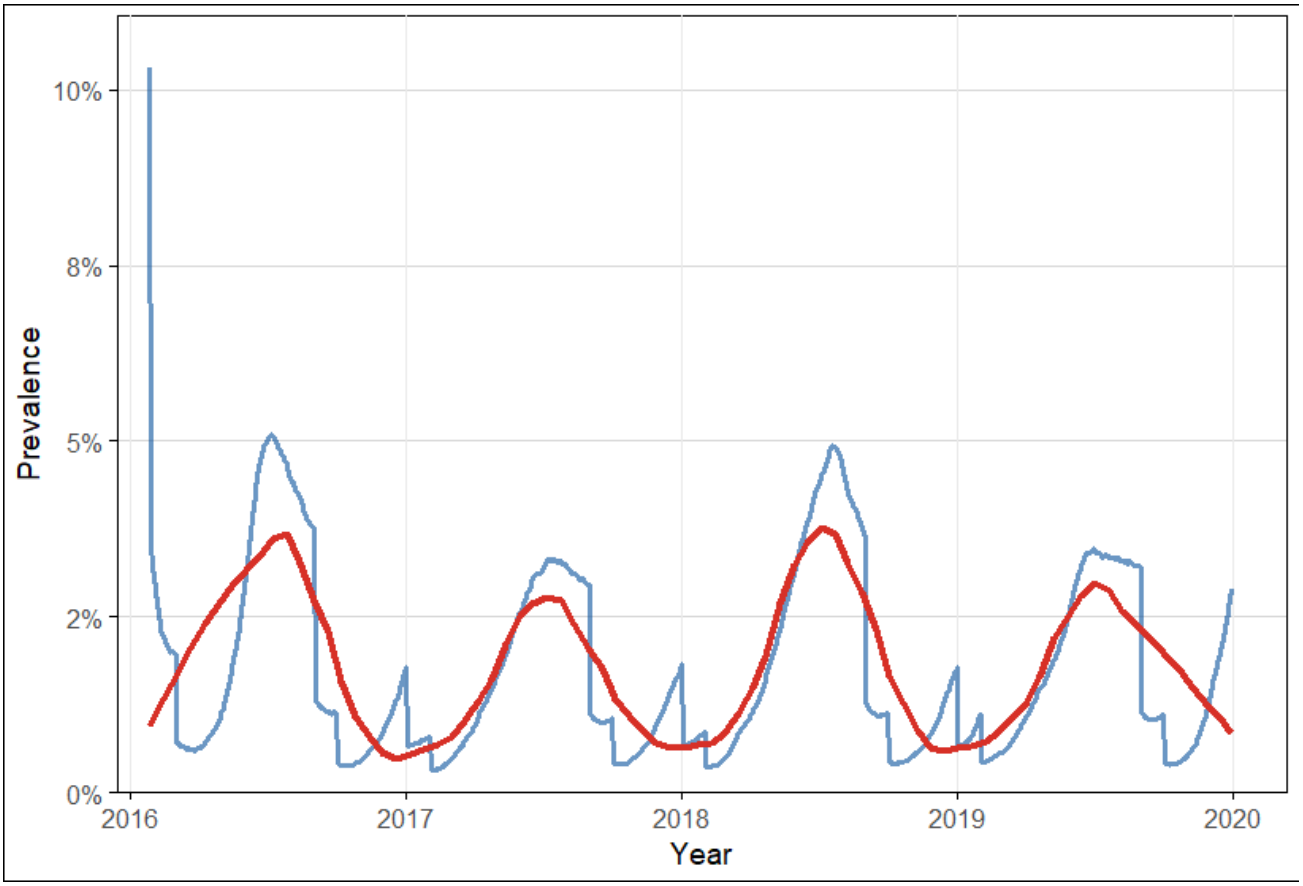


Figure 5: The "Combined Elimination Strategy" (Blue) successfully drives prevalence below the 1% threshold (dashed line) to break the "Importation Floor" on which single interventions (Red/Grey) level.

Discussion

This study shows that although MDA can significantly lower the prevalence of malaria in the short term, its effects are short-lived in places like Ngodhe Island, where importation and waning prophylactic effects rapidly re-establish transmission (Kagaya, et al., 2019). Specifically, MDA campaigns produced immediate reductions in malaria cases, their impact is transient, with rebounds occurring within 2-3 months (Schneider et al., 2023). This rapid resurgence reflects both the limited durability of drug-based suppression, with an estimated effective half-life of approximately 35 days (1.2 months) and the steady background of imported infections, which consistently reseed local transmission (Le Menach et al., 2011b; Wesolowski et al., 2012b). The combination of short-lived prophylaxis ($\omega \cong 0.020$) and persistent importation pressure presents a fundamental challenge to sustained malaria elimination on Ngodhe Island. Quarterly MDA alone is unlikely to suppress transmission without mobility-targeted surveillance or longer-acting chemoprotection. The results are consistent with previous studies in (Bhatt et al., 2015; Smith & Hay, 2015) that demonstrated that, in high-transmission or high-mobility settings, drug-based campaigns alone are inadequate for sustained elimination.

The estimated prophylactic half-life ($\sim$ 35 days) and per-round efficacy (57-65%) are in line with field observations from similar lake regions and pharmacological data on artemisinin–piperaquine (Schneider et al., 2023). Therefore, the rapid rebound seen, 3 months, is biologically plausible and emphasises how challenging it is to sustain suppression using only drug-based methods. A key variable that emerged as the key driver of malaria transmission was importation, the estimated importation scale ($\beta_{imp} \cong 0.80$) was substantially higher than baseline local transmission ($\beta \cong 0.17$). Despite high MDA coverage, a persistent background of external introductions was identified by both the proxy-based and latent random-walk approaches, at levels sufficient to compromise elimination. In line with research conducted in the Greater Mekong Subregion and other island settings (Schneider et al., 2023), our results emphasize how vital human mobility is in determining the dynamics of malaria. Connectivity to neighbouring mainland regions serves as a structural barrier for Ngodhe, making elimination unattainable without addressing importation (Griffin et al., 2010). This modelling approach provides a flexible framework for distinguishing local and external transmission drivers by combining climate covariates, importation processes, and joint inference from cases and PCR surveys.

Our counterfactual simulations provide critical findings on how to overcome such structural barriers,

and move beyond retrospective analysis to evaluating prospective maintenance strategies. One of critical findings is the insufficiency of the "Sustained Annual MDA" strategy. It was not feasible to obtain an elimination despite repeating the 2016 two-round cluster annually because the interval between yearly rounds (12 months) was much longer than the duration of chemoprotection (months). This mismatch made it possible for the parasite population to rebound every year so the prevalence pattern became "sawtooth" in nature, but never dropped to zero. This finding has important policy implications for annual MDA programs in the region, as they may represent a "suppressive" and not "eliminating" way, if not complemented by some other interventions.

In contrast, the Reactive Focal MDA (rfMDA) scenario was found to be the most efficient elimination pathway, keeping a close to 0% prevalence throughout the 4-year simulation period. By changing the approach from mass clearance to surveillance-fueled maintenance, rfMDA effectively neutralized importation sparks before they had a chance to re-establish local transmission. This is in line with the theoretical argument that once the prevalence is brought low through an initial MDA 'debulking', that resources should be directed to high-fidelity surveillance and rapid response. However, reactive strategies require robust surveillance systems that may not always be feasible, in operational contexts where imported cases are missed, the strategy would have a lower impact in suppressing transmissions.

Acknowledging the feasibility of the reactive MDA, our simulations identified “Combined Elimination Strategy” (Bimodal MDA + 90% LLIN + Screening) as a highly effective alternate approach. Reducing transmission efficiency (simulating scale up of LLIN) prevented the inter-round rebound. While MDA cleared the human reservoir, vector control reduced the reproductive number (R_0) of the remaining parasites, and border screening prevented re-seeding by external infections, ensuring there was no the seasonal resurgence that occurred in the Annual MDA-only scenario, as drug level waned. This confirms that other interventions must be integrated: relying solely on drugs leaves the system vulnerable to rebound. Furthermore, scenarios such as Annual MDA + Border Screening, assuming a reduction in importation of 80% , delayed the rebound but failed to prevent it. This suggests that although importation is a drive, the residual local reservoir is to restart the transmission chain. Similarly, increasing the half-life of the drug ("Longer-Acting Prophylaxis") could not achieve elimination as rebound occurred as the drug's prophylaxis waned.

There are several limitations in this study. It was a limited population size with seven cross-sectional

surveys only that reduces the statistical power and makes it difficult to identify longer-term patterns of transmission. Mapping between force of infection and a PCR prevalence was based on a simplified relationship which fails to describe the variation in immunity, parasite density, or subpatent infections (Okell et al., 2012), and the model did not include species-specific differences affecting detectability (Chua et al., 2021). Even though the population was repeatedly sampled, the infections were only monitored at specific occasions instead of continuous surveillance and thus it is not clear when the transmission actually occurred. The model also made a homogeneous population assumption and considered the susceptible pool as the total population, which does not consider age-related and behavioral variations in exposure and immunity (Griffin et al., 2015). Lastly, poor mobility and entomology data necessitated our imprecise estimation of importation and vector dynamics, which decreases our capacity to discriminate between local and brought sources of transmission (Tatem, 2022; Wesolowski et al., 2012b).

Notwithstanding these limitations: the results are clear MDA alone cannot achieve sustained eradication in settings where re-introductions are frequent even in low-transmission settings such as Ngodhe. Comparative scenario analyses show that increasing the period of suppression requires a "phase-shift" approach; using MDA to aggressively reduce prevalence followed immediately by reactive surveillance or enhanced vector control (Newby et al., 2016). These observations highlight the delicate balance between prophylactic decay and importation pressure which determines the sustainability of the impact on transmission. In areas on the mainland with higher transmission potential, sustained elimination is likely to need a holistic combination of enhanced chemoprophylaxis, effective vector control both together with regional surveillance.

Conclusion

In conclusion, results show that while Mass Drug Administration (MDA) using artemisinin-piperaquine can suppress the malaria infection on Ngodhe Island quickly, they are thermodynamically unstable in the presence of persistent infection importation. This immediate resurgence observed following the campaign in 2016 was not a compliance failure, but a biological inevitability driven by mismatch between a temporary prophylaxis period (approximately 35 days) and the unremitting pressures of external re-introductions. Drug only interventions, when applied as isolated pulses, are only short-lived suppressants and not sufficient for long term elimination in such spatially connected environments.

Critically, our counterfactual simulations reveal that achieving long run eradication, requires a permanent strategic pivot from periodic clearance to sustained suppression of transmission. We demonstrate a "Sustained Annual MDA" strategy, simply repeating annually what our historical regimen did, is not enough to interrupt transmission as the 12-month interval between rounds allows complete recovery of the parasite reservoir, leading to a futile "sawtooth" pattern of prevalence. Moreover, our sensitivity analysis indicates that single-intervention strategies are structurally incapable of addressing the high rate of importation that is observed in Ngodhe Island. Our modeling therefore finds that the only tested strategy to have the theoretical ability to reduce the reproductive number (R_0) to values below one in the face of the two pressures: seasonal climatic forcing and constant re-seeding is the Combined Elimination Strategy (Bimodal MDA + Border Screening + Vector Control).

By using the first MDA to "debulk" the reservoir and to immediately switch to a high-fidelity surveillance-response mode, is an approach that will effectively neutralize importation events before they have a chance to establish their own local chains of transmission. Furthermore, where an operationally-based high precision surveillance is not possible, our results emphasise that the synergistic integration of improved Vector Control from the historic coverage 53% to 90 % with annual MDA could potentially prevent the inter-round rebound that is undermining drug-only approaches.

Ultimately, the design of a post-intervention consolidation phase for MDA may be just as important as the intervention itself. Reducing malaria transmission in areas of high mobility such as Ngodhe requires a biphasic strategy, with the use of mass treatment that rapidly reduces prevalence by clearing the human reservoir, combined with robust intervention and surveillance measures, either reactive detection of cases or effective vector control such as bed nets, which has been done in Homabay, to sustain low prevalence.

List of Abbreviations

MDA - Mass Drug Administration

FOI - Force of Infection

CrI - Credible Interval

PCR - Polymerase Chain Reaction

ACT - Artemisinin-based Combination Therapy

LOO - Leave-One-Out cross-validation

PPC - Posterior Predictive Check

PIT - Probability Integral Transform

ESS - Effective Sample Size

MCMC - Markov Chain Monte Carlo

Declarations

Ethics approval and consent to participate

The study was approved by the Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee in Kenya (registration number: P609/10/2014), and performed in accordance with relevant guidelines and regulations. Community consent to study participation was sought through workshops and sensitization meetings with the island communities. Informed consent was obtained from all study participants at enrollment.

Consent for publication

Not Applicable

Availability of data and code

Data are available from the corresponding author upon reasonable request. Model code is available in a private GitHub repo, and access can be provided upon a reasonable request.

Competing interests

The authors declare that they have no competing interests.

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