Simulation of the dynamics of malaria resurgence following termination of insecticide-treated nets in Africa

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Abstract

Background: Insecticide-treated nets (ITNs) are the most common, and believed to be the most efficient, malaria intervention method. International funding is not sufficient to provide the desired coverage of ITNs, so resource allocation to maximize the benefit is an important topic. ITN programs also entail an unwelcome consequence. Reduced exposure to malaria due to ITNs weakens the population's immunity, increasing the risk of severe malaria outbreaks. This double-edged sword can be employed most efficiently if we understand the conditions where a rebound is likely.

Methods: Two sets of 30-year simulations were carried out using a field-tested malaria transmission simulator, HYDREMATS, to investigate the dynamics of malaria resurgence under several intervention scenarios with ITNs. Dynamic climate conditions were used as model forcing to generate a range of epidemiological conditions. The importance of resource allocation was investigated under two scenarios: 50% coverage of ITNs for the entire 30 years, and 100% coverage of ITNs for the first 15 years followed by another 15 years with 0% coverage. Another set of simulations examines the timing and the magnitude of resurgence, as well as its environmental and epidemiological determinants; scenarios tested were programs that provide 50% coverage of ITNs but with different termination points. The analyses were conducted for a Sahel village of Banizoumbou, Niger.

Results: The simulated total number of malaria infections was smaller in the scenario with the 30-year 50% coverage program than that with the 15-year 100% coverage program. This result indicates the risk of malaria outbreaks after the termination of ITN programs. Simulations with different termination points showed that the timing of malaria resurgence depends on the temporal variability of climate conditions, and that the magnitude of resurgence is determined by the interplay of the population-level immunity and the prevalence of malaria, as well as climate conditions.

Conclusions: Exposure-reducing malaria interventions, such as ITNs, may result in an overall negative impact on malaria reduction due to reduced immunity. In an environment with relatively high climate suitability for malaria, such as in Niger, limited resources can be used more effectively if interventions are placed throughout a target period, rather than concentrated

in a short period of time. Malaria resurgence does not necessarily occur soon after the termination of ITN programs. Exit strategies should be carefully planned to avoid malaria resurgence, monitoring closely the population's immunity level, malaria prevalence, and climate suitability for malaria transmission.

Keywords: Malaria control, malaria resurgence, ITN coverage, immunity

Background

Malaria is an ancient disease that has been noted for more than 4,000 years. The history of malaria control and elimination in Africa started in the late nineteenth century, when the human malaria parasites and the vectors of malaria were identified [1]. Due to the lack of continued efforts to sustain the control programs, most of the early interventions failed [1,2,15]. Efforts to control malaria have increased since the year 2000, when global financing for malaria control increased from US$100 million in 2000 to US$2.5 billion in 2014 [3]. The malaria interventions, particularly those contemporary interventions such as insecticide-treated bed nets (ITNs), indoor residual spraying (IRS), and artemisinin-based combination therapy (ACT), reduced malaria incidence by 37% between 2000 and 2015 [3]. Among all malaria control methods, ITNs are believed to be the most effective intervention method across Africa. It is estimated that 68% of the reduction in malaria prevalence in Africa is due to the distribution of ITNs [4].

On the other hand, these interventions entail concerns of diminishing immunity, which increases the vulnerability to malaria when the programs end. Although the primary drivers of malaria transmission dynamics are believed to be climate conditions, the role of acquired immunity has gained increasing recognition in understanding seasonal and multi-annual disease dynamics [18-20]. Humans build up immunity to malaria slowly along with receiving infectious bites [16], but lose immunity gradually in the absence of exposure [17]. Chemoprophylaxis prevents infection or lowers the severity of malaria, but it impairs the development of naturally acquired immunity; the overall benefit is believed to be positive but is still controversial [33-36]. Reducing exposure to infectious bites, ITNs lower the risk of contracting malaria, but also the opportunity to acquire immunity. As a result, termination of ITN programs is accompanied by the risk of severe malaria outbreaks. Resurgence of malaria has been observed on almost every continent—in Africa, Asia,

Europe, Central and South America—following the discontinuation or the weakening of control programs (

Figure 1) [1,2,8-10, 32].

The negative effect of ITNs has often been overlooked, yet the concern of malaria resurgence should not be dismissed, given the nature of ITNs. ITNs have a relatively short useful lifespan; even the effectiveness of long-lasting insecticidal nets (LLINs) typically lasts only for three years. According to the World Health Organization, at least 200 million ITNs will need to be distributed annually in order to protect the sub-Saharan population from malaria, which is unrealistic under the current malaria control budget [3]. In addition, some international funding has recently been redirected to other diseases like AIDs and tuberculosis, resulting in an 8% drop in funding for malaria control, from US$ 2.1 billion in 2013 to US$ 1.9 billion in 2014 [3]. Facing the resource limitations and the concern about the use of ITNs, it is essential to investigate the impact of discontinuation of ITN programs and to maximize the long-term benefits of malaria interventions by allocating resources effectively.

Although the impact of the population coverage of ITNs on malaria prevention has been an interest of many researchers and practitioners [11-13], the longitudinal impacts of those programs, including the risk of resurgence after the termination of the programs, have not been studied extensively. A few substantial simulation studies [10, 37] indicate that the potential for resurgence depends on the assumptions of immune response and pre-intervention transmission levels. In addition, Cohen et al. [9] identified in their systematic review of observational data that changing climate conditions are another cause of resurgence.

Understanding the complexity in the dynamics of malaria resurgence requires a comprehensive analysis and some assumptions. Assumptions are necessary due to limited data availability, undiscovered biological processes, or computational inefficiencies, all of which weaken conclusions. To analyze the dynamics of malaria resurgence, this study applies a comprehensive malaria transmission simulation model, HYDREMATS, which has been tested against observations from villages in Niger. This approach thus reduces assumptions used in the analyses. In addition, we use time series of weather conditions based on observations, so that the simulation conditions are both realistic and dynamic. In this way, we analyze intricate

interactions of entomological, immunological, and environmental factors that drive malaria resurgence.

Niger is one of the most malaria-afflicted countries, with 60% of the high-risk population having no access to ITNs. The world's malaria concentration map is highly heterogeneous, and sub-Saharan Africa is responsible for most of the mobility and mortality (89% of world malaria infections and 91% of malaria-related deaths) [31]. Of all geographical regions in sub-Saharan Africa, West Africa is the most affected, with 289 million people living at high risk of malaria [3]. Although enormous investments have been made to control malaria in West Africa, resources are still far from adequate. In 2014, more than half of the countries in West Africa had an ITN coverage of less than 60% [3,31]. Niger has the third lowest malaria control budget in West Africa, with less than US$1.50 per at-risk person per year [3]. For countries like Niger, it is particularly vital to ensure the effective use of limited resources and to obtain the best outcome from them to reduce malaria transmission.

The primary objective of this study is to analyze the longitudinal impact of ITN programs that may lead to malaria resurgence, considering the dynamic interactions of malaria prevalence, immunity levels, and climate conditions. In particular, the study investigates the impact of different resource allocation strategies and the conditions leading to malaria resurgence after the discontinuation of ITN programs for a village in Niger.

Methods

A detailed mechanistic malaria transmission model, HYDREMATS (HYDRology, Entomology, Malaria Transmission Simulator), was used in this study [5, 12]. The malaria transmission module of HYDREMATS is comprehensive, with a stochastic agent-based mosquito population model, nonlinear thermodynamic parasite development model, inclusion of human agents and their responses to malaria infections, and spatially explicit representation of human houses and vector breeding pools. The comprehensive model structure aids in understanding of the dynamics of malaria transmission and potential resurgence, simulating complicated interactions between dynamic weather conditions, transmission intensity, and human immunity under minimum assumptions.

A recent improvement of HYDREMATS includes a human immunity model [7]. Each human acquires immunity with infectious bites, while gradually lose immunity in the absence of such bites. The probability and the duration of infection are simulated as a function of immunity levels. The severity of infection is not simulated. Acquired immunity is an important factor in malaria transmission dynamics [18-20]. The accurate estimation of immunity levels becomes particularly important for longitudinal simulations, where immunity levels may diverge significantly from initial levels assumed. Demographic dynamics were also simulated as the recruitment of a naïve birth cohort becomes a critical factor of population immunity in the long term. Although the HYDREMATS's immunity module may not include all details of the relevant processes, extensive model calibration using literature reported values of the model parameters has successfully reproduced age-specific prevalence for Garki, Niger (one of only a few villages in Niger where comprehensive observation data are available), and the observed relationship between the entomological inoculation rate (EIR) and malaria prevalence over West Africa [7, 22]. The HYDREMATS, therefore, requires limited assumptions for human immunity development and was calibrated for West Africa.

In this study, HYDREMATS was applied to the sub-Saharan village of Banizoumbou in Niger. Banizoumbou is one of the villages for which HYDREMATS has been extensively calibrated in previous studies [5,6]. The model parameters and the initial conditions for this simulation study were kept the same as those in Yamana et al. [22,6]. The initial prevalence in children aged 2 to 10 years old was set at 27%, according to the Malaria Atlas Project (MAP) estimate [26]. Each person's immunity level was initialized based on estimated EIR and the person's age. The estimated EIR was obtained from a long-term simulation, where the simulated prevalence at the equilibrium state was similar to the MAP prevalence value. The population's average initial immunity level was set at 0.17. The immunity level is defined as the relative human immunity used in HYDREMATS, which varies from 0 (immunologically naïve) to 1 (fully developed immunity) [7].

ITNs were modeled to provide a partial insecticidal effect due to limited efficacy and compliance [27-30]. The protection efficiency of ITNs was set at 70%, considering the observed compliance in Niger (20-25% [29]) and the imperfect efficacy. When mosquitoes attacked humans under ITNs, they were killed with 70% probability; otherwise, they successfully had a bloodmeal,

surviving to play a role in mosquito population and malaria transmission dynamics. No repelling effect was simulated. For simplicity, the ITNs were assumed not to deteriorate; 70% insecticidal efficiency was maintained throughout the period that the ITN programs were simulated to be in place, assuming ITNs are regularly maintained.

Two sets of 30-year simulations were conducted for the village of Banizoumbou, in order to examine the impact of resource allocation of ITN programs and to determine the key factors leading to malaria resurgence after the termination of those programs. The aim of this study is to analyze the dynamics of malaria resurgence for a study site, rather than to produce generalizable conclusions.

In the first part of the study, the importance of resource allocation was investigated. Simulations were carried out under the assumption that the funding for Banizoumbou is limited, such that it can provide either 50% coverage of ITNs for 30 years (scenario A1) or 100% coverage of ITNs for 15 years followed by another 15 years with 0% coverage of ITNs (scenario A2). In scenario A1, 50% of houses were selected as targets of ITN intervention, and all the members of selected houses were assumed to be protected by an ITN (coverage in terms of houses and people were both 50%). Through the period of the 30 years, the same population was assumed to be targeted. In scenario A2, every person was assumed to be protected by an ITN. In addition, for comparison, another simulation was run assuming no control programs for the entire 30 years (scenario A0).

The second part of the study investigates the dynamics of potential malaria resurgence after the discontinuation of ITN programs. Simulations were conducted under the following four scenarios: no ITN program is in place (scenario B0, same as A0), a program that provides 50% coverage of ITNs is discontinued after the 10^{th} year (scenario B1), a program that provides 50% coverage of ITNs is discontinued after the 15^{th} year (scenario B2), and a program that provides 50% coverage of ITNs is discontinued after the 30^{th} year (scenario B3).

The model forcing of 30-year climate data was prepared by repeating twice the observed 15-year data from 1998 to 2012, which is the period used in the previous study by Yamana et al. [22,6]

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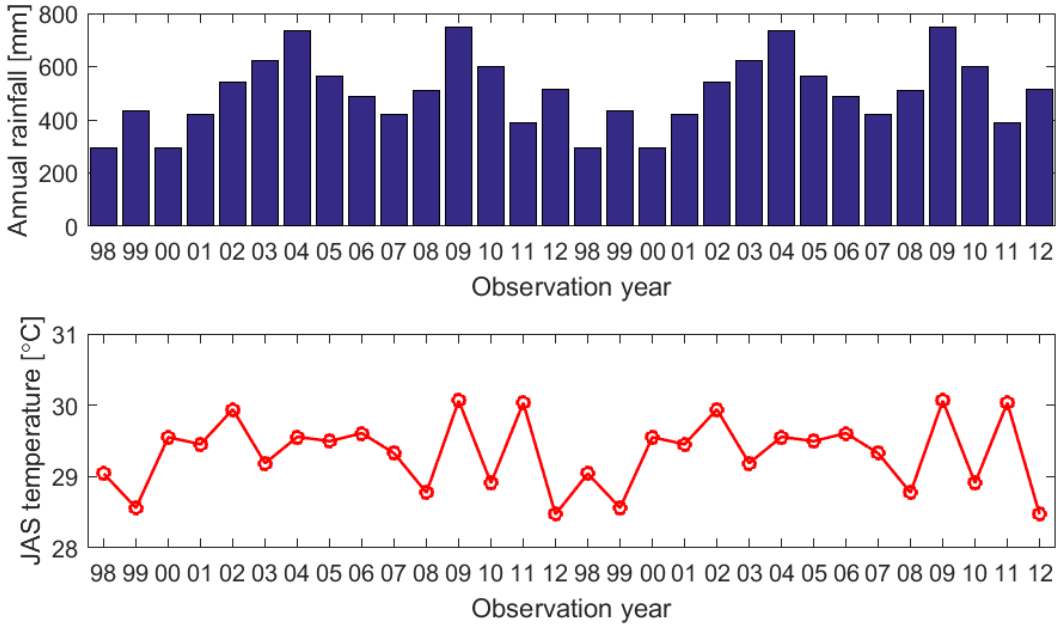

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213 Figure 2). This arrangement was to ensure that, in A1, the first half period with the 100%
214 coverage of ITNs and the second half period with no ITNs receive the same climate forcing. The
215 employed series of the climatological forcing was hypothetical, but it was based on actual
216 observations.

217 Note that the imperfect protection efficiency of ITNs allowed transmission to occur even under
218 the 100% coverage scenario. In addition, it was assumed that a certain number of people bring
219 infection from outside the simulation domain. The case import rate was set at 0.001/month
220 (approximately 5 cases per month), following Yamana et al. [22, 6].

221

222 ## Results

223 ***Importance of resource allocation in the reduction of malaria transmission***

The simulated prevalence of malaria in children aged 2 to 10 is presented in

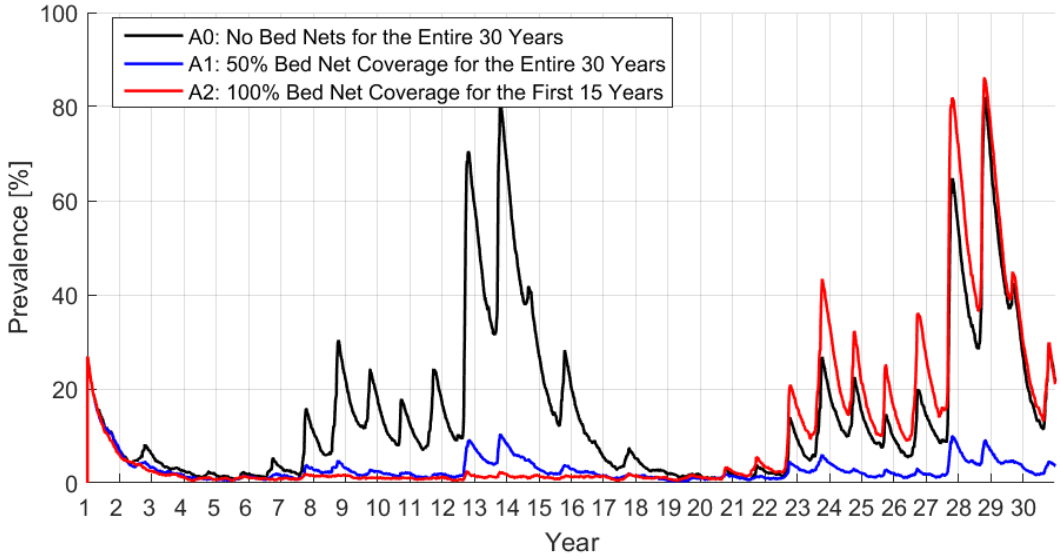


Figure 3, for the two resource allocation scenarios (A1 and A2) and for the no-intervention scenario (A0). In the first 15 years, as expected, malaria prevalence was reduced in the A1 experiment with 50% ITN coverage (blue), and even more with the A2 experiment with 100% ITN coverage (red), compared to the A0 experiment with 0% ITN coverage (black). In the 14th year, when the A0 experiment resulted in the highest prevalence in the first 15 years, the prevalence in A0, A1, and A2 experiments reached around 80, 10, and 2%, respectively.

In the latter 15 years, however, experiment A2 resulted in an intriguingly high prevalence of malaria. As expected from the repetitive climate forcing data, the dynamics of malaria prevalence in A0 (ITN coverage constantly 0%) and A1 (ITN coverage constantly 50%) during the latter 15 years were almost the same as those during the first 15 years, and the prevalence in A1 was lower than that in A0 throughout the simulation period. Experiment A2, which had 100% coverage and the lowest prevalence in the first 15 years, however, resulted in higher prevalence even than A0 in the latter 15 years, when the ITN coverage was dropped to zero, although the ITN coverage in the two experiments was zero for both.

The simulated malaria infections are summarized in Table 1. In the first 15 years, A2 resulted in lower malaria incidence (712 infections) compared to A1 (2,228 infections) and A0 (15,627 infections). However in the latter 15 years, A2 experienced higher malaria incidence (18,360 infections) versus A0 (14,599) and A1 (2,310). The malaria incidence between the first and the latter 15-year periods were comparable in A0 and A1; in A2, the incidence increased 17-fold

between the two periods. The total incidence over the 30 years of the simulation period was 29,866 in A0, 19,072 in A2, and 4,538 in A1, in descending order. The total incidence in A2 was significantly larger (about 4-fold) than in A1, although the two scenarios assume the same number of ITNs being provided in the 30-year span.

The reason why A2 resulted in a higher malaria incidence than A0 in the latter 15 years, although both scenarios assumed 0% ITN coverage during the period, can be explained by a human immunity factor.

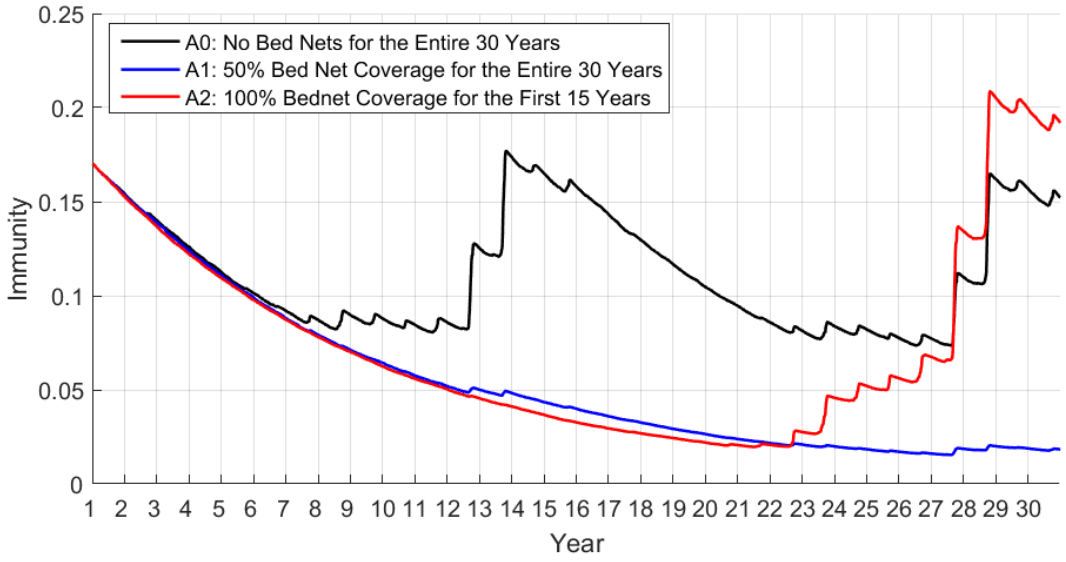


Figure 4 shows the simulated human immunity for the three resource allocation scenarios. In A1 and A2, human immunity was simulated to drop continuously through the first 15 years, during which ITNs were distributed, and for a few more years, during which climate was not suitable for malaria transmission. By the 22nd year, the immunity level in A1 and A2 dropped from the initial immunity of 0.17 to about 0.025, where humans became more susceptible to malaria transmission, while the population continuously exposed to malaria transmission in A0 maintained a relatively high level of immunity (0.09). A more severe outbreak of malaria transmission during the latter 15 years in A2 than in A0 can be explained by the difference in the history of exposures and the resulting immunity levels. In the next section, the determinants of malaria resurgence are investigated.

Dynamics of malaria resurgence after the discontinuation of ITN programs

A set of 30-year simulations was conducted in order to understand the mechanisms of malaria resurgence. The following four scenarios with different timing of ITN-project discontinuance were tested: no ITN coverage for the entire 30 years (scenario B0), 50% ITN coverage for the first 10 years only (scenario B1), 50% ITN coverage for the first 15 years only (scenario B2), and 50% ITN coverage for the entire 30 years (scenario B3).

The simulated prevalence and immunity levels are shown in

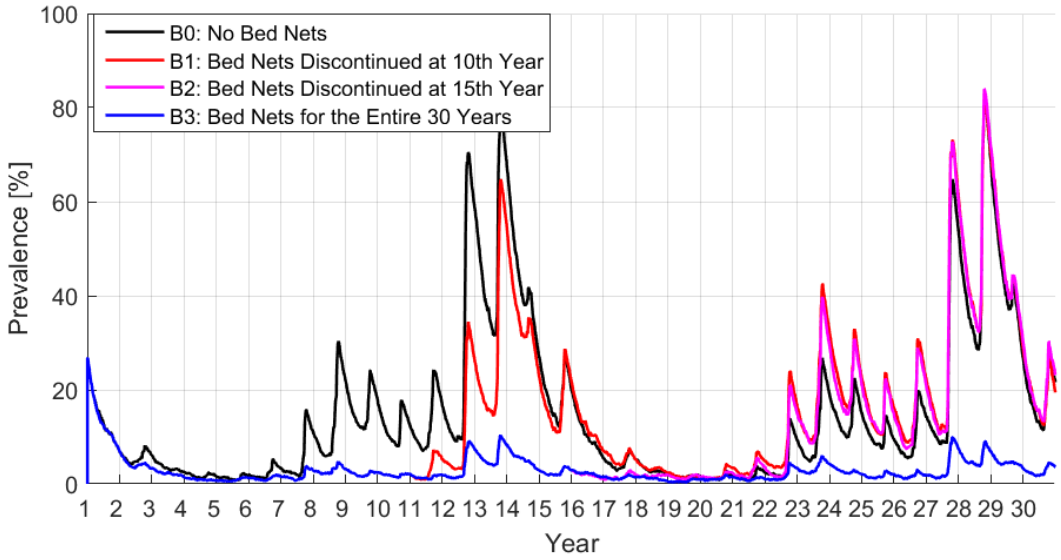


Figure 5 and

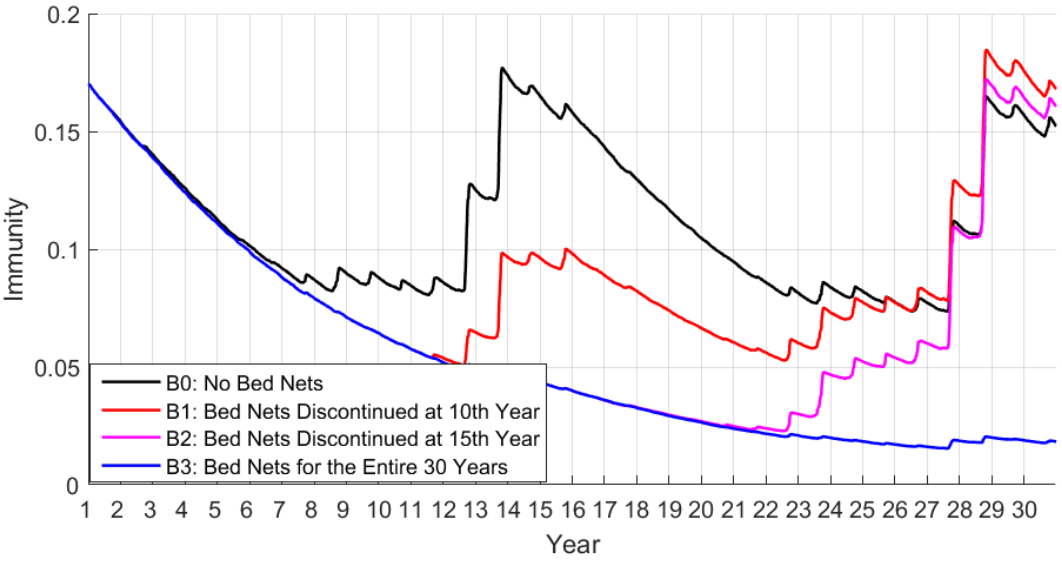


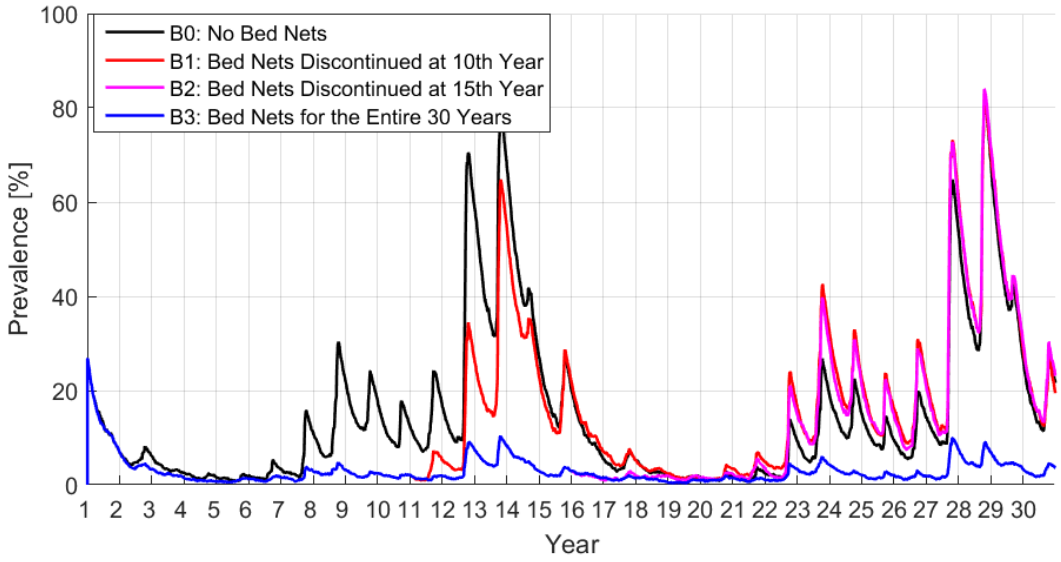
Figure 6, respectively, for B0 (black), B1 (red), B2 (pink), and B3 (blue). The B3 experiment resulted in constantly lower prevalence than B0 due to the protection by ITNs, while the population immunity level kept declining.

The scenarios with the discontinuation of ITN programs led to malaria resurgence, but at different timings. In B1, when ITNs were removed at the end of the 10th year, malaria resurgence occurred during the 12th year, raising the peak prevalence from 2% in the 10th year to 35%. The discontinuation of the ITN program resulted in a resurgence of malaria in two years. The B2 experiment assumes a different timing of the ITN-program discontinuation: ITNs are removed at the end of the 15th year. In contrast with the B1 experiment, it took seven years to observe malaria resurgence. Since the termination of the ITN-program in the end of the 15th year, malaria prevalence hovered around 2% until the 21st year, when the prevalence increased slightly to about 5%. In the 22nd year, malaria resurged and the peak prevalence reached approximately 21%.

The cause of the stark difference in the timing of the malaria resurgence requires investigation. One hypothesis is that the high immunity level of the population prevented the outbreak of malaria for a longer time in B2 than in B1. In B1, the population's immunity level was around 0.06 at the end of the 10th year, when the ITN-program was discontinued. In B2, the value was slightly lower (around 0.04) at the point of discontinuation in the 15th year. This observation conflicts with the hypothesis.

Another hypothesis is that the climate was more favorable for malaria transmission after the 10th year than the 15th year. The years of malaria resurgence (12th year in B1 and 22nd year in B2) correspond to the two wettest years (climate data for 2009 and 2004, respectively) in terms of annual rainfall. For six years from the termination of the ITN program in B2, the precipitation was not sufficient (annual rainfall around <600 mm) to cause malaria resurgence, despite the low immunity level of the population. In our case, whether malaria resurgence occurred immediately after the discontinuation of the programs depended primarily on the climate conditions, rather than the population's immunity levels.

300 Another intriguing observation is the intensity of resurgence. The comparison between the B0 (black) and
301 B1 (red) in



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303 Figure 5, for example, demonstrates factors that contribute to malaria transmission dynamics
304 other than climatological factors. The figure shows that malaria prevalence from the 11th to 15th
305 year in B1 was smaller than that in B0, but that the prevalence from the 26th to 30th year in B1
306 exceeded that in B0, though the model forcing of climate conditions was identical between the
307 two periods. Both B0 and B1 had no coverage of ITNs during the periods.

308 The explanation for this difference is the combination of immunity levels and malaria prevalence that has
309 been built over the previous decades. At the beginning of the 11th year, the immunity level in B1 (red in

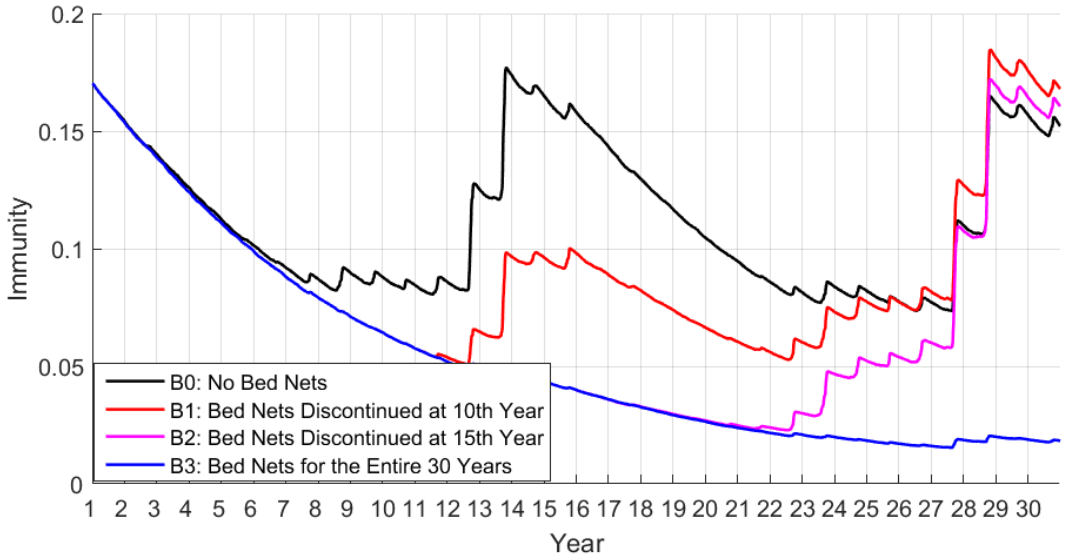

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Figure 6) was lower than that in B0 (black in

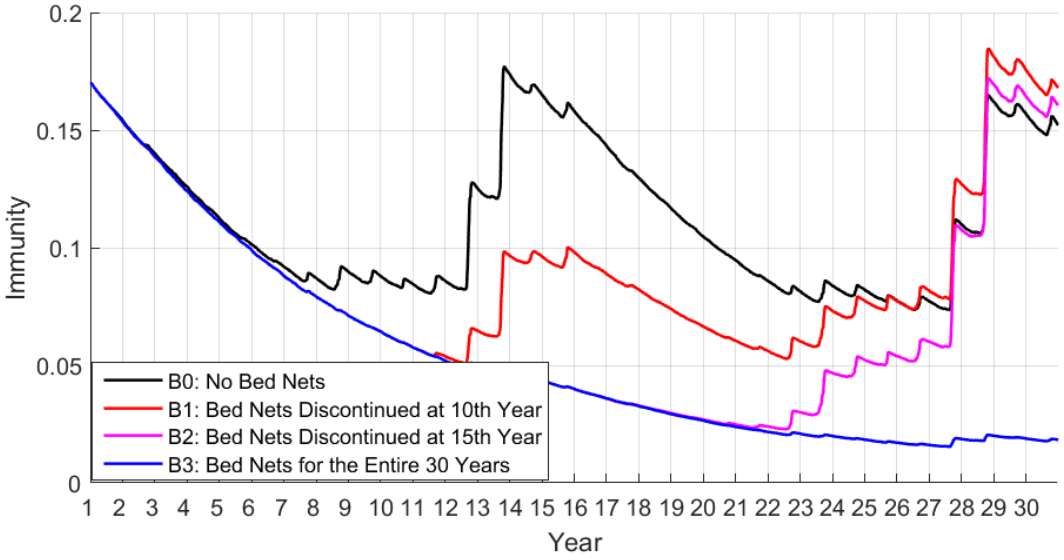

Figure 6); this factor alone would have led B1 to have a larger malaria outbreak than B0. However, at the same time, prevalence of malaria in B1 (red in

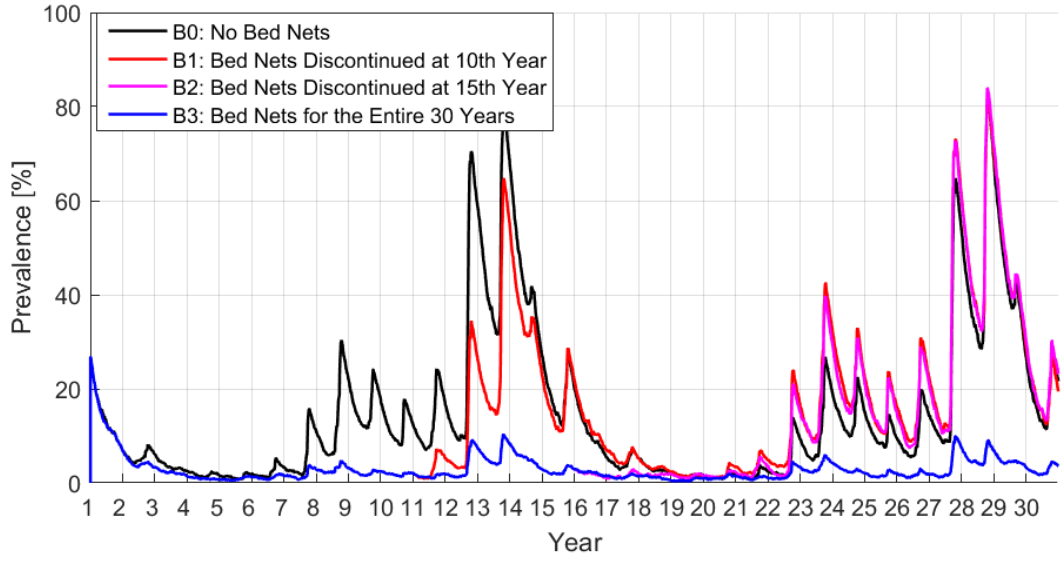

Figure 5) was lower than that in B0 (black in

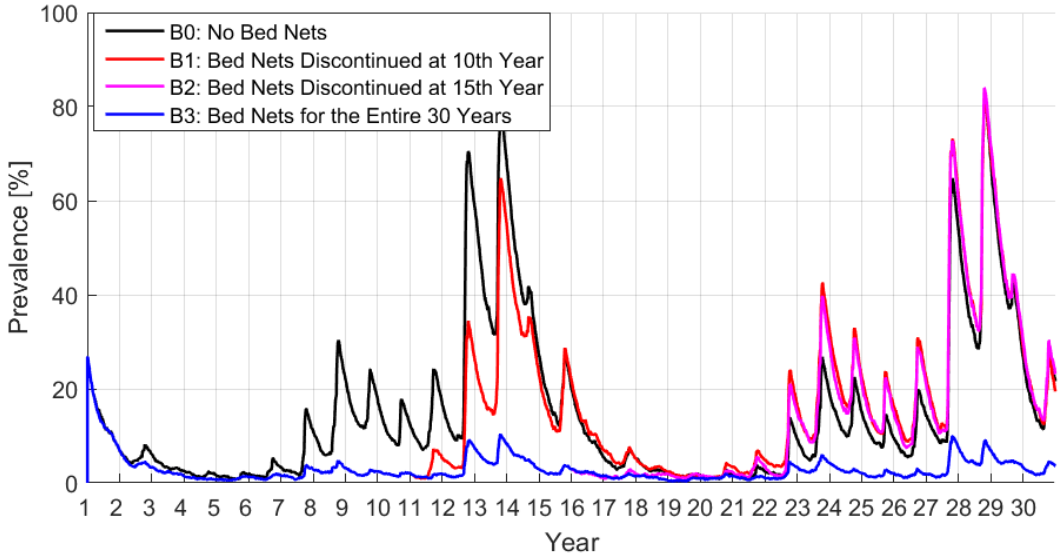

Figure 5). Lower malaria prevalence reduces the probability of mosquitoes' taking infectious bites, and makes transmission more difficult, which makes B0 more likely to have more transmissions than B1. The simulation result indicates that the latter factor was dominant in causing malaria outbreaks from the 11th year through 15th year in B0 and B1.

At the beginning of the 26th year, the prevalence was higher in B1 than B0, while the immunity level in B0 and B1 was comparable. As a result, B1 experienced larger malaria outbreaks in the following years. The shift in the prevalence levels occurs around the 16th year. The gap in prevalence between B0 and B1 shrank gradually after the 10th year; a larger increase of prevalence in B1 was realized due to lower immunity. The shift in the prevalence levels was thus brought by the long-term effect of immunity. Note again that the different behaviors between the 11-15th year and the 26-30th year were observed despite the identical climatological forcing, and that the only differences were the immunity levels and the prevalence at the beginning of these periods.

Discussion

A large need for malaria control and insufficient funding require resources to be allocated wisely. This study showed, for our study site in Niger, that continuous control strategies are more effective than intense but short-term interventions. ITN campaigns can protect people from

malaria infections during the period when they are deployed; however, they result in a loss of acquired immunity due to the reduced exposure. Once the campaigns are over, there may be increased chances of malaria outbreak. For Banizoumbou, the total incidence over 30 years was simulated to be over four times smaller when ITNs were distributed with 50% coverage throughout the period than the case where all the resources were concentrated in the first 15 years. Moreover, not only was the number of malaria infection small, but the severity of infections was expected to be lower in the case of continuous deployment. Higher immunity not only prevents people from contracting malaria but also lessens the severity of the disease. One should be aware of the potential resurgence of malaria after a long control program because the population is more vulnerable to malaria due to reduced immunity. For Banizoumbou, an effective malaria control program in the long run favors continuous interventions over short intensive interventions. The result is not necessarily generalizable to other regions, and the potential of malaria resurgence depends on vector abundance and climate suitability of malaria [37]. Nonetheless, in designing malaria control programs and resource allocation, it is crucial to consider the long-term immunity impact of exposure-reducing interventions.

A counterargument is that a partial coverage of bednets is less favorable than a full coverage. With a partial coverage of ITNs, it is argued that *Anopheles* are repelled from protected users to non-protected users, making the overall transmission prevention less effective [11,12,14]. In HYDREMATS, the repelling effect was not simulated. Thus, the efficiency of the 50% simulation might have been slightly overestimated; however, the previously-mentioned conclusion for Banizoumbou stays the same, given the significant difference in the simulated total number of malaria infections (Table 1).

Although the resurgence of malaria is always possible after the discontinuation of malaria control programs, unless malaria is completely eliminated, the timing of resurgence may or may not be immediate. A quick resurgence is expected under the climates favorable for malaria transmission, but it may take a decade to see a resurgence under unfavorable climates. Even though malaria prevalence is low for many years, malaria outbreaks may occur when climate become suitable for malaria transmission.

The exogenous causes of malaria resurgence studied in this paper were the termination of ITN programs and climate factors. Other exogenous causes include weakening of control activities,

human movement, drug resistance, industrial or agricultural development, and strife [9]. Continuous monitoring and reporting of these factors will provide advance warning for potential malaria resurgence.

The magnitude of malaria resurgence depends on the population's immunity level and the prevalence of malaria, as well as the future climate. Yamana et al. [23] describe the dependence of malaria transmission on initial immunity levels and prevalence as "hysteresis." Low immunity makes the population more vulnerable to malaria, increasing the intensity of potential outbreaks; low prevalence makes malaria transmission less likely, decreasing the intensity of potential outbreaks. Exposure-reducing interventions, such as ITN programs, reduce both human immunity and malaria prevalence; the consequence is thus not straightforwardly predictable.

As is documented for many infectious diseases, malaria transmission depends not solely on current conditions, but also on conditions at earlier times [18,24,25]. The population's immunity levels and malaria prevalence reflect the history of malaria endemicity and intervention programs. The investigation of the efficacy of malaria intervention programs, thus, requires a longitudinal analysis on how and when resources should be allocated.

The problem of malaria resurgence after the termination of ITN programs indicates the importance of exit strategies, as history has witnessed that the discontinuation or weakening of control programs led to resurgence of malaria in many countries [8,9]. For sustainable suppression and elimination, malaria prevalence should be brought sufficiently low before the termination of control programs, so that malaria will not reemerge even under low levels of population's immunity. *Sufficient* prevalence levels may depend on climatological, ecological, and social conditions. *Sufficient* conditions where malaria resurgence is unlikely should be investigated further taking into account the variability of environments. Achieving and maintaining malaria elimination require long-term and sustainable commitment to health systems, human capacity, and community involvement. Even at the pre-elimination phase, continuous monitoring and enabling infrastructure are desired.

The use of the comprehensive simulation model rigorously calibrated for Banizoumbou and the surrounding region lends support to the simulation results presented in this study. The HYDREMATS was shown to reproduce mosquito and malaria transmission dynamics [5, 21], age-dependent prevalence [22], and the relationship between the EIR and malaria prevalence

over West Africa [22]. Although the intervention scenarios and the 30-year climate forcing were hypothetical, the climate forcing was prepared based on real observation, and the simulation model was proven to reproduce the malaria transmission dynamics under the non-intervention condition.

Conclusion

The importance of resource allocation and the dynamics of malaria resurgence were studied based on the field-tested malaria transmission simulator, assuming a certain sequence of climate conditions and intervention scenarios with ITNs. We used the sub-Saharan village of Banizoumbou in Niger as our study site.

The study demonstrates for Banizoumbou that allocating ITNs throughout a longer period is more efficient in suppressing malaria than concentrating the same resources for a shorter period, since people may encounter an outbreak of malaria once resources run out. The potential outbreak is due to the lowered acquired immunity, as a result of reduced exposure by ITNs. With the limited resources for malaria control, their allocation should be planned wisely to maximize the outcome.

When exposure-reducing programs, such as ITN programs, are discontinued after a period of time, a malaria outbreak may occur with a large number of infections and severe cases. Whether a resurgence occurs immediately after the discontinuation of control programs depends mainly on climate conditions. The magnitude of resurgence is determined by the population's immunity level and the prevalence of malaria, which reflect the history of malaria endemicity and interventions, as well as climate conditions. Exit strategies should be carefully planned, monitoring malaria prevalence and climate conditions among other socioeconomic conditions, to prevent potential resurgence of malaria.

Declarations

List of abbreviations (no need to be printed)

ACT: Artemisinin-based combination therapy

DALYs: Disability adjusted life years

HYDREMATS: Hydrology, Entomology and Malaria Transmission Simulator

IRS: Indoor residual spraying

ITNs: Insecticide-treated nets

LLINs: Long-lasting insecticidal nets

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All the data used in this study are available upon request.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

XQ and EABE conceived and designed the study. EABE supervised the research. XQ performed the computational experiments, with an assistance of NE. XQ and NE wrote the manuscript. All the authors read and approved the final manuscript.

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Figures

Figure 1: Malaria resurgence in Africa observed following malaria intervention programs. Figure adapted from Cohen et al. (2012) [9].

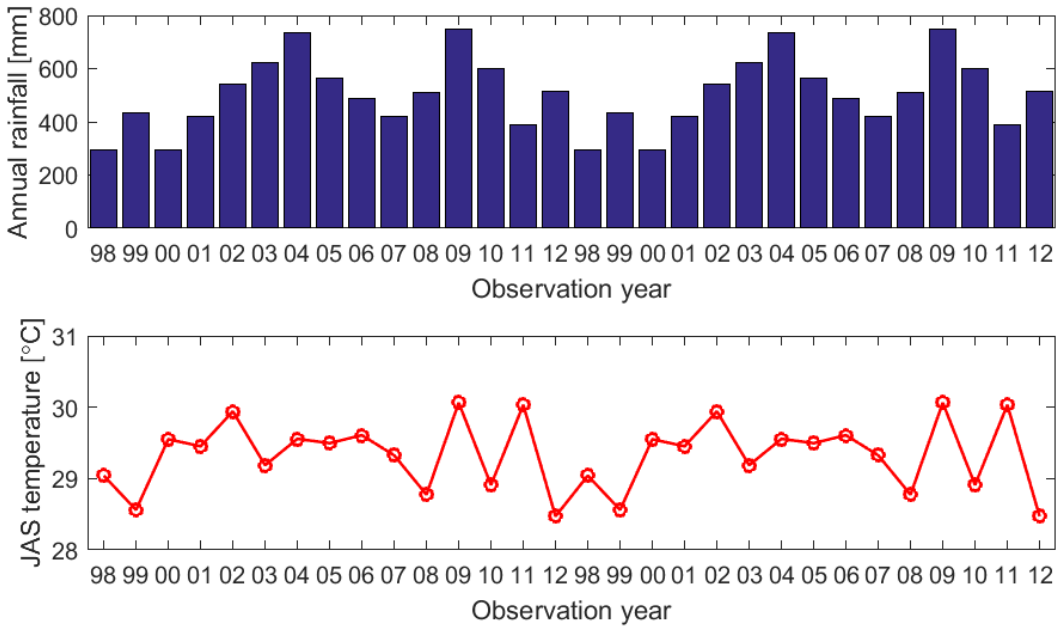


Figure 2: Annual rainfall and July-to-September temperature of the model forcing.
Annual rainfall (top) and July-to-September temperature (bottom) of the climate sequence used in this study are shown. July-to-September receives most of the annual rainfall (around 80%) and is the most important season for the dynamics of mosquito population and maalria transmission at Banizoumbou. Fifteen years (1998-2012) of observed climate data at Banizoumbou were repeated twice to construct a 30-year climate forcing.

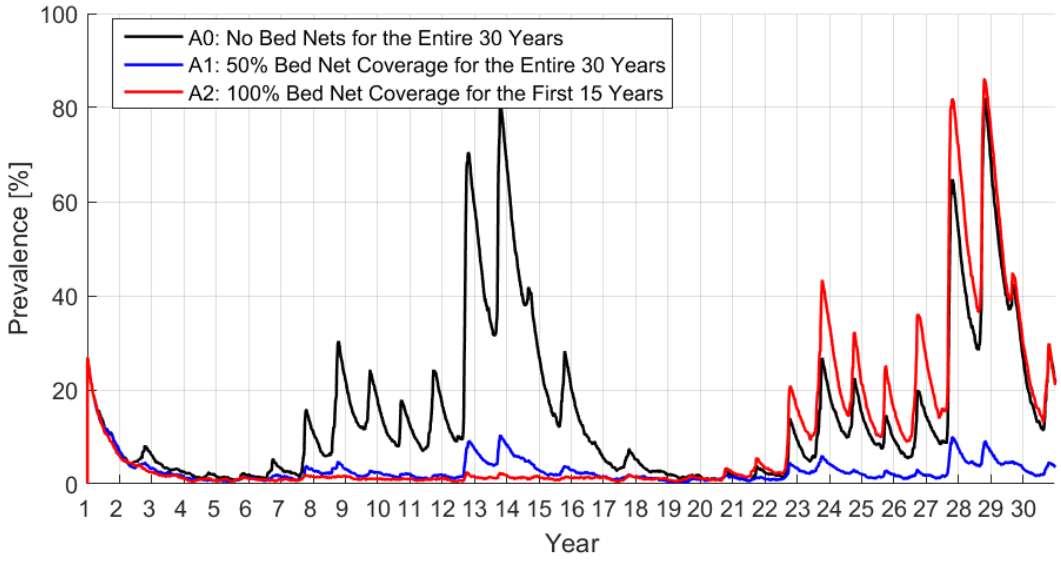


Figure 3: Simulated malaria prevalence (in children aged 2 to 10) for the three resource allocation scenarios.
The simulated malaria prevalence is shown for A0 (black), A1 (blue), and A2 (red).

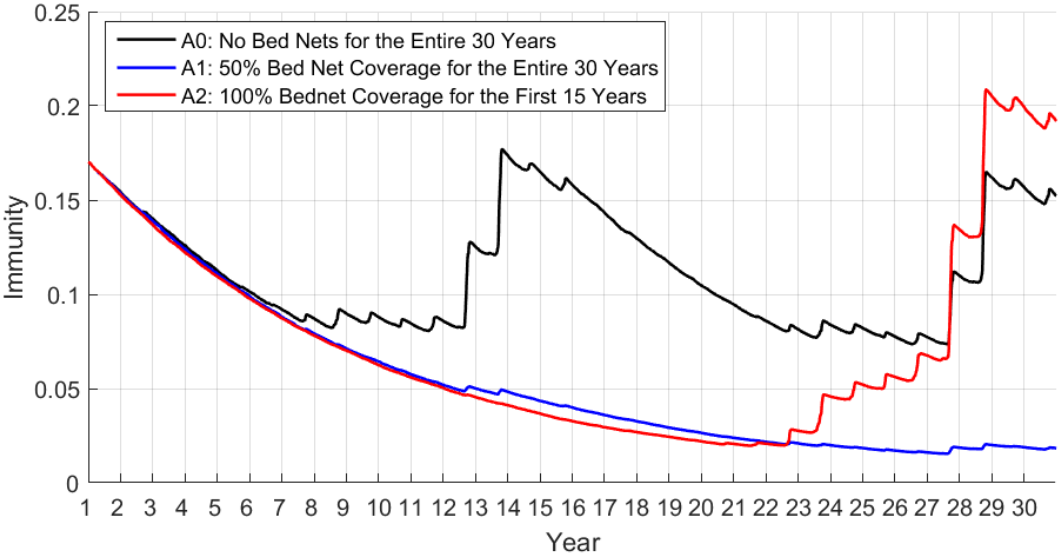
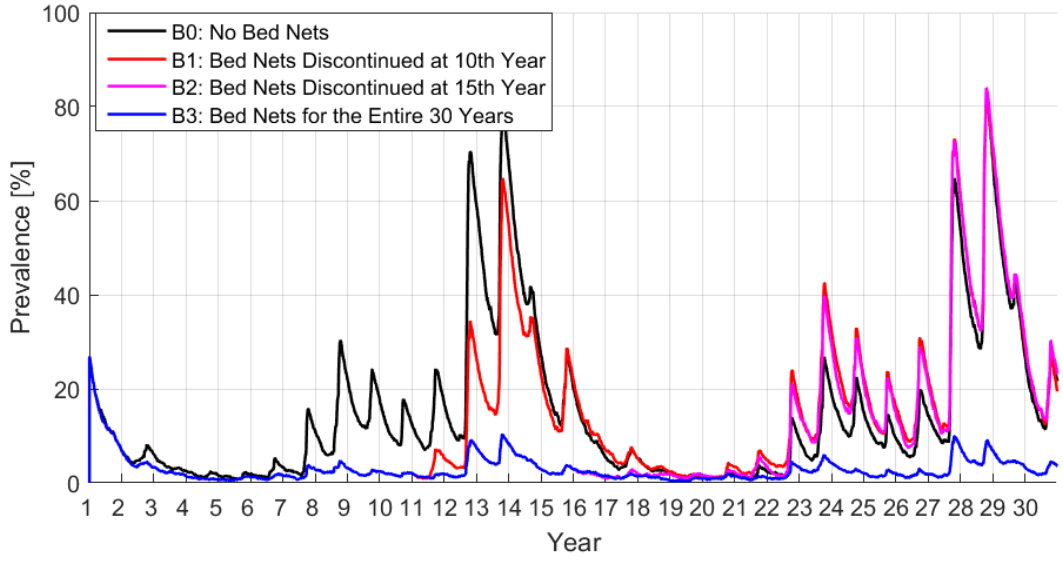


Figure 4: Simulated human immunity for the three resource allocation scenarios.
The simulated immunity levels are shown for A0 (black), A1 (blue), and A2 (red).



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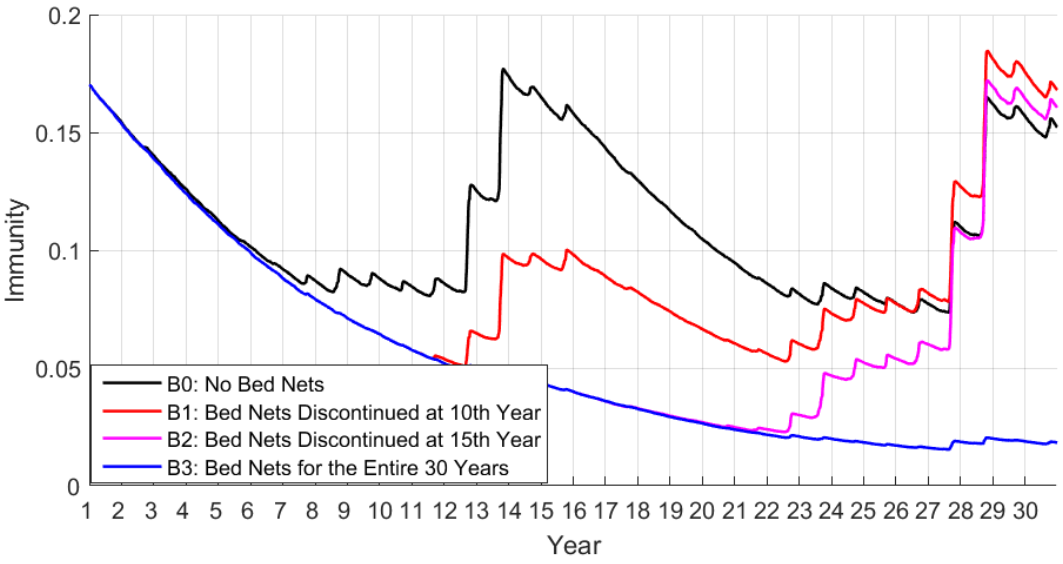
580 Figure 5: Simulated prevalence (children aged 2 to 10) for different termination years of 50%-coverage
581 ITN projects.
582 The simulated malaria prevalence is shown for B0 (black), B1 (red), B2 (pink), and B3 (blue).



583

584 Figure 6: Simulated immunity for different termination years of 50%-coverage ITN projects.
585 The simulated immunity levels are shown for B0 (black), B1 (red), B2 (pink), and B3 (blue).

586

587

588 Table 1: Number of simulated malaria infections for the three resource allocation scenarios

	First 15 years	Latter 15 years	30 years total

A0: 0% coverage for 30 years	15,627	14,599	29,866
A1: 50% Coverage for 30 years	2,228	2,310	4,538
A2: 100% Coverage for 15 years	712	1,8360	19,072

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