Advances in Water Resources 000 (2016) 1–7

Contents lists available at ScienceDirect

Advances in Water Resources

journal homepage: www.elsevier.com/locate/advwatres

Hysteresis in simulations of malaria transmission

Teresa K. Yamana[a,*], Xin Qiu[b], Elfatih A.B. Eltahir[b]

[a] Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY 10032, USA
[b] Department of Civil and Environmental Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

ARTICLE INFO

Article history:
Received 30 April 2016
Revised 30 August 2016
Accepted 5 October 2016
Available online xxx

Keywords:
Malaria
Hysteresis
Initial conditions
Immunity
Environmental drivers

ABSTRACT

Malaria transmission is a complex system and in many parts of the world is closely related to climate conditions. However, studies on environmental determinants of malaria generally consider only concurrent climate conditions and ignore the historical or initial conditions of the system. Here, we demonstrate the concept of hysteresis in malaria transmission, defined as non-uniqueness of the relationship between malaria prevalence and concurrent climate conditions. We show the dependence of simulated malaria transmission on initial prevalence and the initial level of human immunity in the population. Using realistic time series of environmental variables, we quantify the effect of hysteresis in a modeled population. In a set of numerical experiments using HYDREMATS, a field-tested mechanistic model of malaria transmission, the simulated maximum malaria prevalence depends on both the initial prevalence and the initial level of human immunity in the population. We found the effects of initial conditions to be of comparable magnitude to the effects of interannual variability in environmental conditions in determining malaria prevalence. The memory associated with this hysteresis effect is longer in high transmission settings than in low transmission settings. Our results show that efforts to simulate and forecast malaria transmission must consider the exposure history of a location as well as the concurrent environmental drivers.

© 2016 Elsevier Ltd. All rights reserved.

1. Introduction

The relationship between malaria transmission and climate is the subject of numerous studies, for example, Thomson et al. (2005), Bomblies et al. (2008), Zhou et al. (2004), Yamana et al. (2013a) and Kilian et al. (1999). Rainfall is directly related to the abundance of mosquito breeding sites while temperature affects the lifecycle of the mosquito vector and the malaria parasite. Recognizing this dependence of malaria transmission on climate factors, there have been efforts to produce early warnings or long-term projections of malaria transmission given current or future climate conditions (Ebi et al., 2005; Yamana and Eltahir, 2010; Who, 2001; Van Lieshout et al., 2004; Tonnang et al., 2010; Thomson et al., 2006). The majority of these studies treat malaria transmission as a boundary value problem; that is, future malaria transmission depends only on the future climate forcing, ignoring the past climate and initial conditions of the system. However, hysteresis can arise in ecology and epidemiology, where the current state of the system depends not only on current conditions, but also on conditions at earlier times (Dobson, 2009; Gambhir and Michael, 2008; Koelle and Pascual, 2004; Rodó et al., 2013; Schwinning et al., 2004). Malaria is especially prone to hysteresis due to the long timescales over which humans acquire and retain immunity to the parasite (Childs and Boots, 2010; Laneri et al., 2015). This semi-protective immunity is gradually acquired after repeated exposure to the parasite over time scales of years or decades, and wanes in the absence of exposure (Langhorne et al., 2008). An individual's immune response to malaria is therefore influenced by the history of his or her past exposure to the parasite, which is in turn related to the climate and hydrologic conditions driving malaria transmission during that period. In some sense, the level of human immunity is an integral of past hydrologic variability and other variables.

In many areas, malaria transmission is highly seasonal, as the reproduction cycle of *Anopheles* mosquitoes is constrained to the rainy season. In these areas, the parasites retained within the human population over a dry season play an important role in seeding the following wet season's disease outbreak (Babiker et al., 1998; Nassir et al., 2005; Bousema et al., 2012). The parasite levels at the beginning of a malaria transmission season depend in part on the extent of the previous year's disease transmission dynamics, as well as human immunity factors influencing the rates at which infections are cleared. This initial prevalence rate may in turn influence the extent of the current year's outbreak, thus providing further possibilities of hysteresis in the system.

* Corresponding author.
E-mail address: tky2104@cumc.columbia.edu (T.K. Yamana).

http://dx.doi.org/10.1016/j.advwatres.2016.10.003
0309-1708/© 2016 Elsevier Ltd. All rights reserved.

These highly intertwined and nonlinear factors make it difficult to determine the contributions of each to overall malaria transmission dynamics (Dobson, 2009). Many studies focus on either environmental drivers (Bomblies et al., 2008; Kilian et al., 1999) or intrinsic disease dynamics (Griffin et al., 2016; Chitnis et al., 2008), but few consider the effects of both sets of drivers together. A recent study by Laneri et al. (2015) made progress in teasing apart the two sets of factors using a time-series approach to fit a model to observational data from two communities with similar environmental conditions but different levels of immunity. However, this approach is complicated by the fact that many of the relevant variables, such as the immunological history of a population and the basic reproduction number, are unobserved, making it impossible to fully separate the roles of the environment from those of immunity and previous exposure.

Here, we use a mechanistic modeling tool to investigate the effects of hysteresis in malaria transmission in Banizoumbou, a small village in Niger. By using a process-based model to simulate the dynamics of malaria transmission, we benefit from having full knowledge of all relevant variables, including those that would be impossible to observe in a field setting. We are thus able to separate the external environmental drivers (as expressed through mosquito biting rates, parasite development rate, etc.) from the intrinsic factors (immunity, prior infections, replenishing susceptible population), which we describe as initial conditions of the system. This allows us to explore the role of each set factors separately. Specifically, we advance understanding of hysteresis in malaria transmission by:

1. Quantifying the influence of initial conditions on the simulated system.
2. Quantifying the persistence of hysteresis in simulated malaria transmission.

2. Methods

2.1. Model description

The simulations were conducted using the Hydrology, Entomology and Malaria Transmission Simulator (HYDREMATS), a mechanistic model of malaria transmission with high spatial and temporal resolution. HYDREMATS was developed by Bomblies et al. (2008) and has been used in numerous malaria transmission studies (e.g., Yamana and Eltahir, 2010; Yamana and Eltahir, 2013; Gianotti et al., 2009; Bomblies et al., 2009; Bomblies, 2014). The model contains three main components: Hydrology, Entomology, and Immunity, shown in Fig. 1. The development and validation for the model components are described extensively in Bomblies et al. (2008), Bomblies et al. (2009) and Yamana et al. (2013b). The key model features are summarized here, and described in greater detail in the Supplemental Information.

The hydrology component of the model simulates the formation of water pools, which can act as breeding sites for mosquitoes. Model inputs include topography, vegetation and soil type, temperature, rainfall, relative humidity, wind speed and direction, and solar radiation. Water pool formation is simulated using a distributed flow routing model. The amounts of routed and pooled water at each time step are determined by numerically solving the diffusion wave approximation to the St. Venant equations. Flow velocities are obtained by solving the formulation of Lal (1998) using the Alternate-Direction Implicit (ADI) method. Depth and temperature of the pools are recorded in a raster format. From the raster files, users can interpret the location, depth, temperature, and persistence of the simulated water pools, which become the input for the entomology model.

The entomology component of HYDREMATS is an agent-based model simulating the life cycle of *Anopheles gambiae* mosquitoes. We simulate the aquatic stage of immature mosquitoes in the water pools simulated in the hydrology component of the model. Surviving mosquitoes emerge as adults. Every female mosquito is tracked at an hourly time step, with decision rules applied to set the probability of different events occurring such as resting, biting, and egg-laying. When the mosquito enters a structure housing or containing human beings, it can take its blood meal from the residents according to a preset decision rule. The mosquito will become infected if the person it bites happens to be carrying malaria. If the mosquito survives the disease's extrinsic incubation period (EIP), then all the mosquito's subsequent bites will become infectious.

The immunity component of the model simulates acquired immunity within individual human agents. At the start of the simulation, each human subject is assigned an age and initial immunity level. The age depends on local demographics, and the initial immunity is proportional to the person's age. Immunity varies from 0 (immunologically naïve) to 1 (fully developed immunity) and is updated at a daily time step depending on whether the subject receives infectious bites or not. Immunity increases each time the subject gets bitten by an infected mosquito, and decreases in the absence of exposure. Immunity confers partial protection from infection, decreasing the probability that a bite from an infectious mosquito results in infection. The immunity level also affects the duration of infection, with a higher immunity level resulting in a faster disease clearance rate. This model of human immunity has been shown to accurately simulate observed relationships between the entomological inoculation rate and malaria prevalence, as well as appropriate age structures of malaria prevalence (Yamana et al., 2016).

2.2. Description of modeling experiments

Our study location is the village of Banizoumbou in Niger, which is where the HYDREMATS model was originally developed and validated, and has been the primary setting of previous studies using this model (Bomblies et al., 2008; Gianotti et al., 2009; Bomblies et al., 2009; Bomblies, 2014; Yamana et al., 2013b). Environmental inputs used for the model simulation are summarized in Supplemental Table 1.

In this study, simulation experiments were conducted to investigate the hysteresis effect in malaria transmission, i.e., the dependence of malaria transmission on initial conditions of the system, which characterize the system by the end of the dry season. We use this modeling tool to investigate two questions, using high-resolution (30 min) rainfall data, available for the period 1998–2012. The first question is the whether there exists any hysteresis effect in malaria transmission in this setting, and if so what is the extent of this effect. The second question addressed concerns the length of the system memory reflected in the persistence of the hysteresis effect in malaria transmission.

2.2.1. Experiment 1

To explore hysteresis in malaria transmission, we simulated the impact of prior climate conditions on malaria prevalence in the period 2009–2012. Malaria transmission was simulated between 2009 and 2012, preceded by different sequences of climate data. Specifically, the 11-year climate sequence from 1998 to 2008 was reordered based on the total rainfall in each year.

Four different scenarios were designed using different sequences of climate inputs (Fig. 2):

➢ Scenario 1: Original sequence (1998–2008), followed by observed sequence in 2009–2012

Please cite this article as: T.K. Yamana et al., Hysteresis in simulations of malaria transmission, Advances in Water Resources (2016), http://dx.doi.org/10.1016/j.advwatres.2016.10.003

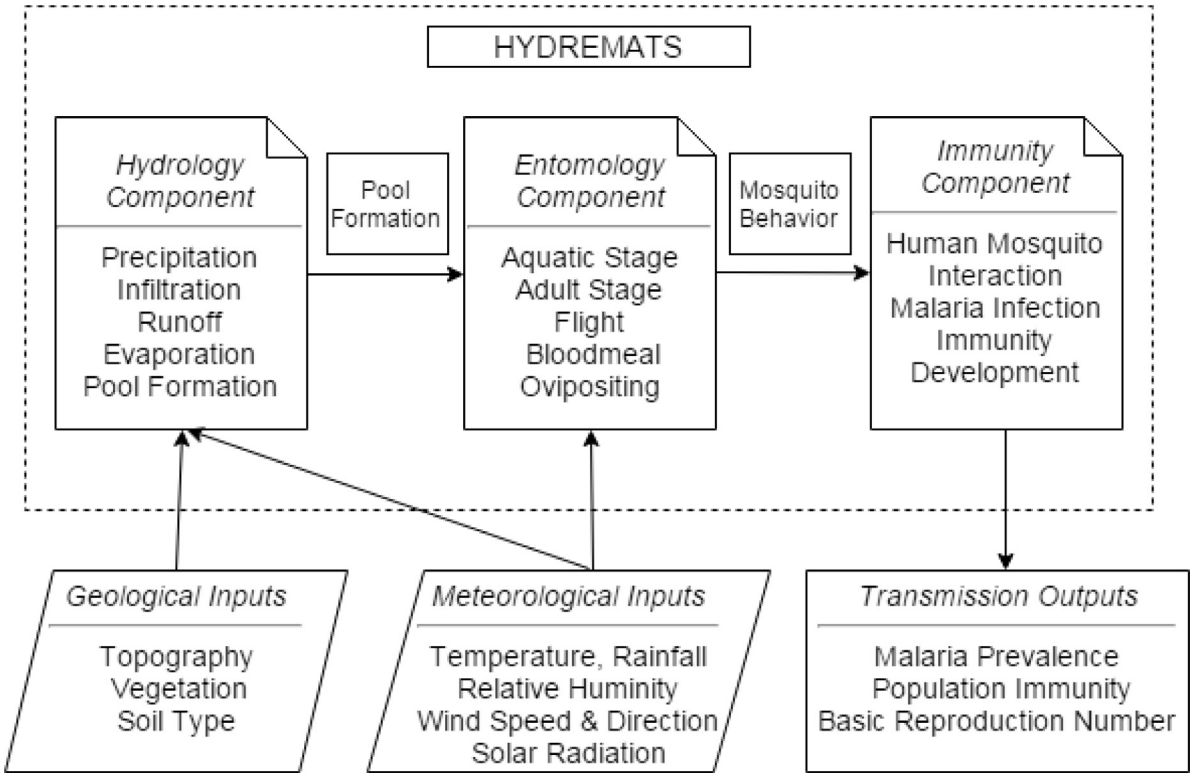

Fig. 1. Schematic of HYDREMATS model.

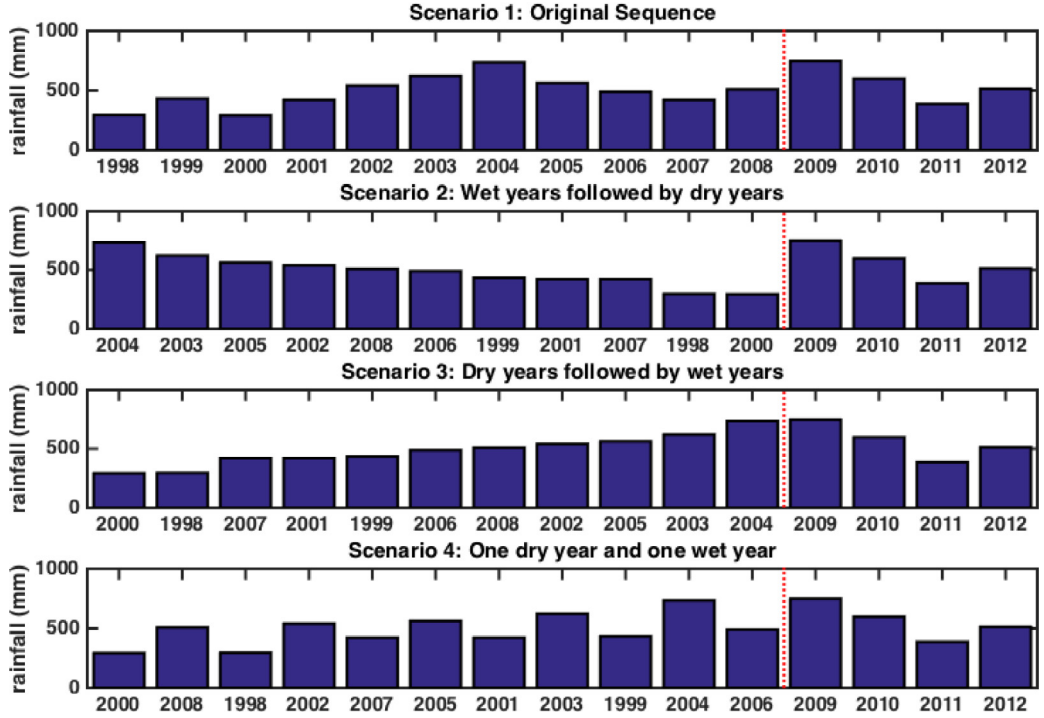

Fig. 2. Annual rainfall for each of the four climate sequences used in Experiment 1. The x-axis indicates the year of observed rainfall data used to maufacture the synthetic rainfall sequences.

- ➢ Scenario 2: Wet years followed by dry years in a descending order followed by observed sequence in 2009–2012
- ➢ Scenario 3: Dry years followed by wet years in an ascending order followed by observed sequence in 2009–2012
- ➢ Scenario 4: Alternating wet and dry years followed by observed sequence in 2009–2012

Differences in simulated 2009–2012 malaria transmission between the four scenarios would indicate the presence of hysteresis in the system. The initial malaria prevalence was set to be 27% of the population, based on the Malaria Atlas Project estimate for the study location. Each individual person's initial immunity level was assumed to be proportional to his/her initial age

Please cite this article as: T.K. Yamana et al., Hysteresis in simulations of malaria transmission, Advances in Water Resources (2016), http://dx.doi.org/10.1016/j.advwatres.2016.10.003

(Yamana et al., 2013b). The average initial immunity level in the population was 0.17, the same for all scenarios.

2.2.2. Experiments 2 and 3

The next experiments concerned the length of the system memory reflected in the persistence of hysteresis effect in malaria transmission. If malaria transmission in the present depends on initial conditions and climate of the past, then how long do we have to consider past climate conditions in order to determine present-day malaria transmission? To explore this question, the experiment in the previous section was modified. Again, the 11-year sequence of 1998–2008 was reordered based on the annual rainfall amount. However, this time, the reordered 11-year sequences were followed by a repetition of a single year twenty times. In other words, the four scenarios differ only in the order of the first 11-year sequence, and have identical climate forcing in the final twenty years of simulations. We can then observe the time required for the four scenarios to converge as an indication of the persistence of hysteresis.

This experiment was repeated twice: once with a relatively wet year (Experiment 2; year 2009; Supplemental Fig. 3), and once with a relatively dry year (Experiment 3; year 2011; Supplemental Fig. 4). The wet year represents a relatively high malaria transmission setting, while the dry year represents a lower malaria transmission setting.

The revised four scenarios are as follows:

- Scenario 1: Original sequence (1998–2008) followed by a single year repeated twenty times
- Scenario 2: Wet years followed by dry years in a descending order followed by a single year repeated twenty times
- Scenario 3: Dry years followed by wet years in an ascending order followed by a single year repeated twenty times
- Scenario 4: Alternating wet and dry years followed by a single year repeated twenty times

We call the first 11 years of each scenario years Y1–Y11, and the twenty years driven by repeating climate data years R1–R20.

2.2.3. Experiment 4

Finally, we explore the relationship between initial conditions, as defined as the conditions at the beginning the rainy season (June 1st) and maximum prevalence level at the peak of the seasonal malaria outbreak. A set of 212 yearly simulations were performed under identical climate forcing (year 2009), but with different initial conditions of prevalence and population immunity levels. These initial conditions were drawn from a prior suite of simulations giving feasible and representative combinations prevalence and immunity levels at the beginning of a wet season.

3. Results and discussion

3.1. Evidence of hysteresis effect in simulated malaria transmission

Fig. 3 shows the simulated malaria prevalence in children aged 2 through 10 for each of the four scenarios. The peaks and valleys of the plot reflect the seasonal variability of malaria transmission and climate. The purple curve represents the simulated prevalence for the original time sequence (1998–2012). The simulated prevalence for the year 2009 was very different between Scenario 2 (wet years followed by dry years) and Scenario 3 (dry years followed by wet years), with peak prevalence levels of 80% and 17%, respectively. Since all four scenarios use identical model inputs for years 2009–2012, these differences in simulated malaria prevalence are the result of climate conditions and malaria transmission during the 11 preceding years. This demonstrates that malaria prevalence is in fact dependent on the transmission history of the population.

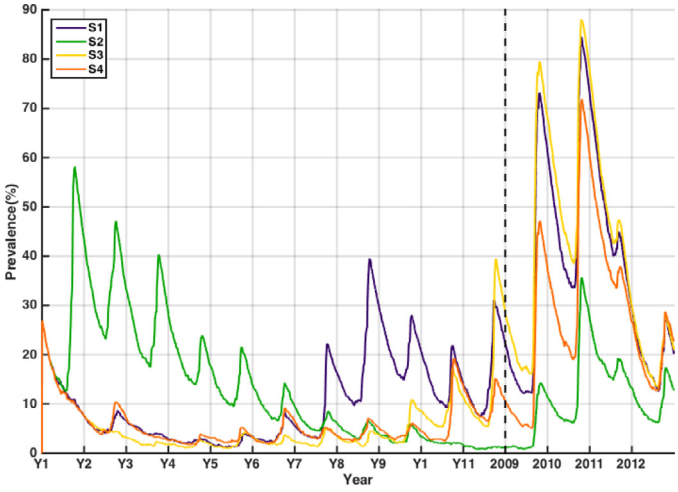

Fig. 3. Experiment 1, simulated prevalence (in children aged 2–10) for different climate scenarios. The simulations were driven by different sequences of environmental data during years Y1 through Y11, and by identical climate data during years 2009–2012.

For comparison, we simulated mosquito density and malaria prevalence for each year's climate forcing individually, holding the initial conditions constant for each simulation, in order to isolate differences in prevalence that can arise from differences in environmental conditions alone (Supplemental Fig. 2). The resulting peak prevalence levels ranged from 13% in 1998 to 68% in 2009. This shows that the roles of initial conditions and environmental drivers in determining malaria infection rates are of comparable magnitudes. Hence, this first experiment demonstrates that in order to accurately predict future malaria transmission, past transmission conditions should be considered as well as concurrent environmental conditions.

3.2. Relationships between persistence of hysteresis, memory, and level of transmission

The simulated prevalence and mean population immunity level for the Experiments 2 and 3 are displayed in Figs. 4 and 5, respectively. To better visualize the convergence time, the largest scenario difference in simulated peak prevalence is calculated (Fig. 6). The largest scenario difference is defined as the maximum difference among the results for the four scenarios. For example, if the four scenarios generate peak prevalence of 10%, 20%, 50%, and 70%, respectively, then the largest scenario difference will be equal to 70%−10%=60%.

In Experiment 2, the simulated prevalence for the four scenarios first converged during the fourth repeated year, R4 (Fig. 6). However, they soon start to diverge with the maximum scenario difference reaching almost 30% during the year R6. The second convergence happens at year R8. From that time moving forward, the maximum scenario difference is relatively stable, with differences less than 10% most of the time. Because the model simulates spatial and temporal variability in malaria transmission using random functions to describe processes such as survival of mosquito and chances of infection, we do not expect to see complete convergence.

Although malaria prevalence in year R4 is very similar for the four scenarios (Fig. 6), the population under the Scenario 2 climate sequence (green curve) has a much lower mean immunity (around 0.2) than those under the Scenario 3 climate sequence (yellow curve, mean immunity around 0.4). As a result, during the year R5, despite similar initial prevalence, the population simulated under Scenario 2 was more likely to be infected, as individuals had

Please cite this article as: T.K. Yamana et al., Hysteresis in simulations of malaria transmission, Advances in Water Resources (2016), http://dx.doi.org/10.1016/j.advwatres.2016.10.003

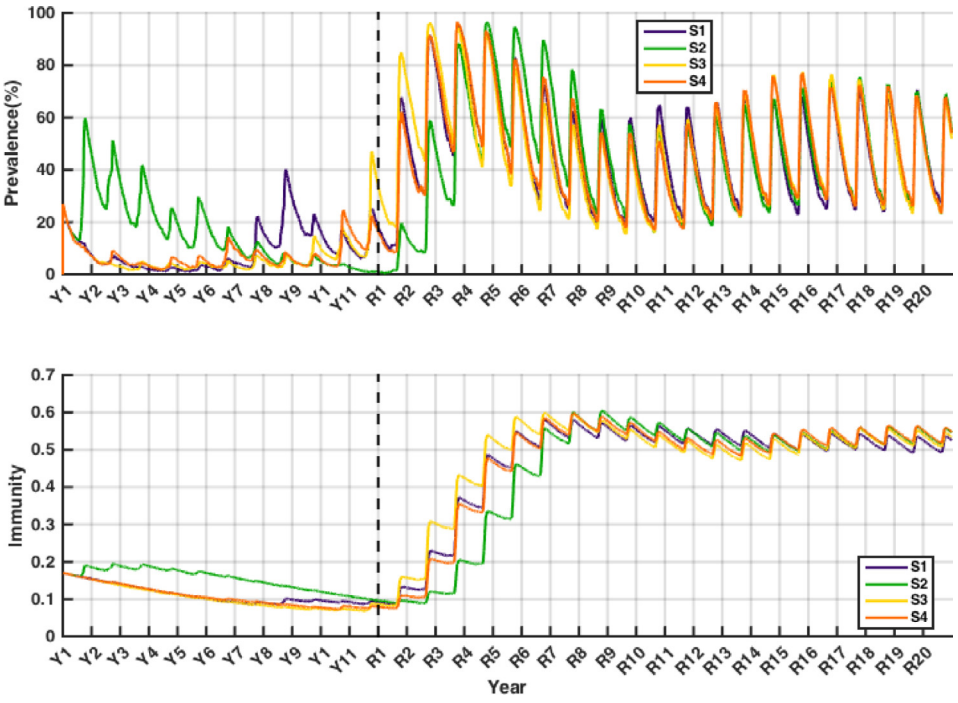

Fig. 4. Simulation results from Experiment 2 in high malaria transmission setting. The simulations were driven by different sequences of environmental data during years 1 through 11 (labeled Y1–Y11), and by identical climate data (observed data from 2009) during years 12 through 31 (labeled R1–R20). The upper panel shows simulated malaria prevalence and the lower panel shows simulated mean immunity index.

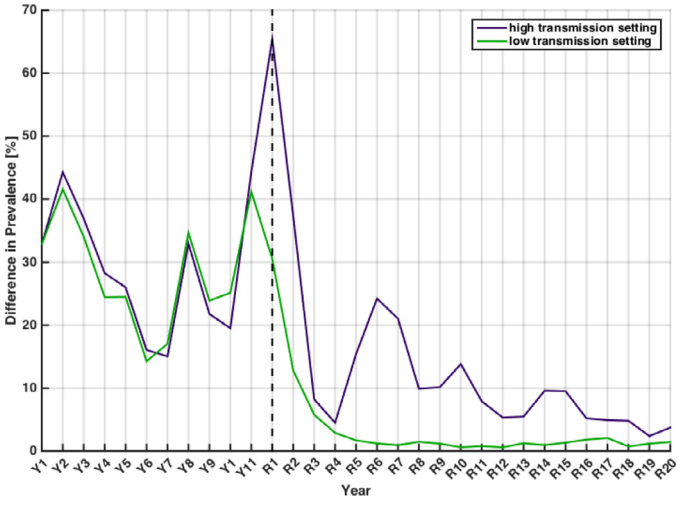

Fig. 5. Maximum difference in simulated peak malaria prevalence between the four scenarios in Experiment 2 (blue) and Experiment 3 (green). The simulations were driven by different sequences of environmental data during years Y1–Y11, and by identical climate data (observed data from 2009 for Experiment 2, 2011 for Experiment 3) during years R1–R20. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

lower levels of immunity. The memory of the conditions experienced during the first 11 years lasted 8 years under year 2009's relatively wet climate forcing.

In Experiment 3 (repeating conditions for the year 2011 twenty times), immunity levels converge in year R3, and the prevalence curves converge in year R4, implying that memory of the conditions experienced during the first 11 years lasts only 4 years under the relatively dry 2011's climate forcing.

To compare the case of repeating climate conditions for 2011 twenty times with the case repeating the climate conditions for 2009 twenty times, the annual maximum prevalence for the two cases are presented in Fig. 5. The annual maximum prevalence converges in year R4 under 2011's climate forcing, and converges in year R8 under 2009's climate forcing. Therefore our results suggest, consistent with the findings of Laneri et al. (2015), that the persistence of the hysteresis effect is stronger, and the system's memory is longer, in high malaria transmission settings than in low malaria transmission settings.

3.3. Relationship between initial conditions and maximum prevalence level

Fig. 7 displays the annual maximum prevalence level for 212 simulated years under the year 2009's climate forcing. Each point is a single simulated year with color representing the maximum prevalence during that year. The horizontal axis represents the initial prevalence of the simulated year, and the vertical axis relates the initial immunity index of the simulated year, both defined at the beginning of the wet season. A contour plot was created for these points using polynomial fitting up to the third degree. It can be seen that the maximum prevalence depends on both the initial prevalence and the initial immunity. A high initial prevalence results in a higher maximum prevalence, while a high immunity index results in a lower maximum prevalence. Therefore, the maximum prevalence is highest when the immunity level is low and the initial prevalence is high.

The fact that the contour lines are neither straight nor parallel indicates that the maximum prevalence is not a simple function of initial prevalence and immunity index, but a complex non-linear function of initial prevalence and immunity index.

3.4. Summary of results

Overall, our findings emphasize the importance of considering initial conditions in environmentally driven models of malaria transmission. These results demonstrate the importance of including the effects of immunity in models of malaria transmission.

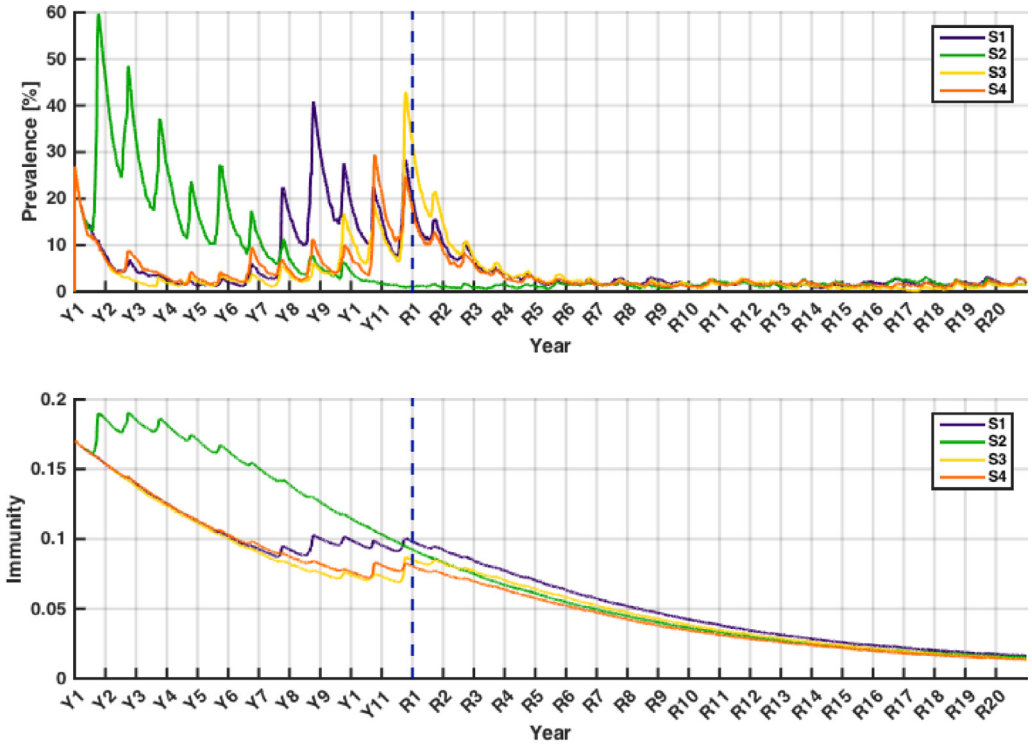

Fig. 6. Simulation results from Experiment 3 in low malaria transmission setting . The simulations were driven by different sequences of environmental data during years 1 through 11 (labeled Y1–Y11), and by identical climate data (observed data from 2009) during years 12 through 31 (labeled R1–R20). The upper panel shows simulated malaria prevalence and the lower panel shows simulated mean immunity index. (For interpretation of the references to color in the text, the reader is referred to the web version of this article.)

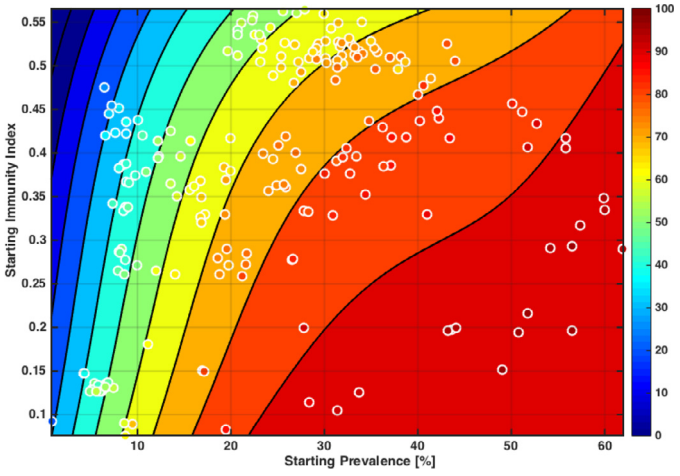

Fig. 7. Contour plot of yearly maximum prevalence in children aged 2–10 using identical climate forcing (observations from the year 2009). The horizontal axis represents the initial prevalence of the simulated year, and the vertical axis relates the initial immunity index of the simulated year, both defined at the beginning of the wet season. Each dot shows the results of one simulation.

In order to accurately simulate malaria transmission, initial conditions as well as the interaction between the climate forcing and initial conditions should be considered. These findings have important implications for studies that aim to link malaria infection rates to environmental drivers, particularly in the context of early warning systems, or longer term climate change projections. They can also be important when evaluating malaria control interventions, as prevalence levels will be affected by both sets of factors.

Future research should further investigate the interactions between the climate forcing and initial conditions. For example, it would be beneficial to explore to what extent initial prevalence and the immunity level would buffer the influence of climate forcing at a wider range of transmission levels. Further research is also needed on how to best incorporate the uncertainty due to initial conditions in current efforts to produce environmentally driven early warning systems or climate change projections of future malaria transmission. When historical environmental and epidemiological data are available, they could be used to inform initial conditions, or to initialize the model by simulated several years prior to the year of interest. If historical information is limited, ensemble-based methods can be used to simulate malaria transmission spanning a range of initial conditions to incorporate the uncertainty due to initial conditions. Bayesian inference methods can be used to estimate initial infection and immunity levels of an outbreak (Shaman and Karspeck, 2012).

4. Conclusion

In the context of a field-tested mechanistic model of malaria transmission, we tested the sensitivity of simulated malaria prevalence to initial conditions in prevalence and immunity level, reflecting the memory of the system. We found these effects to be of comparable magnitude to the effects of interannual variability in environmental conditions, suggesting that both the history of the system as well as concurrent climate conditions are important in shaping seasonal malaria transmission. The memory of this complex malaria system is longer in high transmission settings than in low transmission settings. As such, it is important to include the effects of immunity in models of malaria transmission. Our focus on hysteresis in malaria transmission sheds light on another dimension of complexity in this important system. In order to accurately simulate and forecast malaria transmission, initial conditions describing prevalence and human immunity as well as the

Please cite this article as: T.K. Yamana et al., Hysteresis in simulations of malaria transmission, Advances in Water Resources (2016), http://dx.doi.org/10.1016/j.advwatres.2016.10.003

interaction between the climate forcing and these initial conditions must be considered.

Acknowledgment

This work was funded by the U.S. National Science Foundation grant EAR- 0946280.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.advwatres.2016.10.003.

References

Babiker, H.A., Abdel-Muhsin, A., Ranford-Cartwright, L.C., Satti, G., Walliker, D., 1998. Characteristics of Plasmodium falciparum parasites that survive the lengthy dry season in eastern Sudan where malaria transmission is markedly seasonal. Am. J. Trop. Med. Hyg. 59 (4), 582–590.

Bomblies, A., 2014. Agent-based modeling of malaria vectors: the importance of spatial simulation. Parasites Vectors 7, 1–10.

Bomblies, A., Duchemin, J.B., Eltahir, E.A.B., 2008. Hydrology of malaria: model development and application to a Sahelian village. Water Resour. Res. 44, W12445. http://dx.doi.org/10.1029/2008WR006917.

Bomblies, A., Duchemin, J.B., Eltahir, E.A.B., 2009. A mechanistic approach for accurate simulation of village-scale malaria transmission. Malar. J. 8 (1), 223.

Bousema, T., et al., 2012. Hitting hotspots: spatial targeting of malaria for control and elimination. PLoS Med. 9 (1), e1001165.

Childs, D.Z., Boots, M., 2010. The interaction of seasonal forcing and immunity and the resonance dynamics of malaria. J. R. Soc. Interface 7 (43), 309–319.

Chitnis, N., Hyman, J.M., Cushing, J.M., 2008. Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model. Bull. Math. Biol. 70 (5), 1272–1296.

Dobson, A., 2009. Climate variability, global change, immunity, and the dynamics of infectious diseases. Ecology 90 (4), 920–927.

Ebi, K.L., et al., 2005. Climate suitability for stable malaria transmission in Zimbabwe under different climate change scenarios. Clim. Change 73 (3), 375–393.

Gambhir, M., Michael, E., 2008. Complex ecological dynamics and eradicability of the vector borne macroparasitic disease, lymphatic filariasis. PLoS One 3 (8), e2874.

Gianotti, R.L., Bomblies, A., Eltahir, E.A.B., 2009. Hydrologic modeling to screen potential environmental management methods for malaria vector control in Niger. Water Resour. Res. 45 (8), W08438.

Griffin, J.T., et al., 2016. Potential for reduction of burden and local elimination of malaria by reducing Plasmodium falciparum malaria transmission: a mathematical modelling study. Lancet Infect. Dis. 16 (4), 465–472.

Kilian, A.H.D., Langi, P., Talisuna, A., Kabagambe, G., 1999. Rainfall pattern. El Niño and malaria in Uganda. Trans. R. Soc. Trop. Med. Hyg. 93 (1), 22–23.

Koelle, K., Pascual, M., 2004. Disentangling extrinsic from intrinsic factors in disease dynamics: a nonlinear time series approach with an application to cholera. Am. Nat. 163 (6), 901–913.

Lal, A.M.W., 1998. Performance comparison of overland flow algorithms. J. Hydraul. Eng. 124 (4), 342–349.

Laneri, K., et al., 2015. Dynamical malaria models reveal how immunity buffers effect of climate variability. Proc. Nat. Acad. Sci. 112 (28), 8786–8791.

Langhorne, J., Ndungu, F.M., Sponaas, A.M., Marsh, K., 2008. Immunity to malaria: more questions than answers. Nature Immunol. 9 (7), 725–732.

Nassir, E., et al., 2005. Impact of genetic complexity on longevity and gametocytogenesis of Plasmodium falciparum during the dry and transmission-free season of eastern Sudan. Int. J. Parasitology 35 (1), 49–55.

Rodó, X., et al., 2013. Climate change and infectious diseases: can we meet the needs for better prediction? Clim. Change 118 (3-4), 625–640.

Schwinning, S., Sala, O.E., Loik, M.E., Ehleringer, J.R., 2004. Thresholds, memory, and seasonality: understanding pulse dynamics in arid/semi-arid ecosystems. Oecologia 141 (2), 191–193.

Shaman, J., Karspeck, A., 2012. Forecasting seasonal outbreaks of influenza. Proc. Nat. Acad. Sci. 109 (50), 20425–20430.

Thomson, M.C., et al., 2006. Malaria early warnings based on seasonal climate forecasts from multi-model ensembles. Nature 439 (7076), 576–579.

Thomson, M.C., Mason, S.J., Phindela, T., Connor, S.J., 2005. Use of rainfall and sea surface temperature monitoring for malaria early warning in Botswana. Am. J. Trop. Med. Hyg. 73 (1), 214–221.

Tonnang, H.E., Kangalawe, R.Y., Yanda, P.Z., 2010. Predicting and mapping malaria under climate change scenarios: the potential redistribution of malaria vectors in Africa. Malar. J. 9, 111.

Van Lieshout, M., Kovats, R.S., Livermore, M.T.J., Martens, P., 2004. Climate change and malaria: analysis of the SRES climate and socio-economic scenarios. Global Env. Change 14 (1), 87–99.

Who (2001) Malaria Early Warning Systems: concepts, indicators and partners: A framework for field research in Africa. *Malaria Early Warning Systems: concepts, indicators and partners: A framework for field research in Africa. WHO/CDS/RBM/2001.32*.

Yamana, T.K., et al., 2013. Incorporating the effects of humidity in a mechanistic model of Anopheles gambiae mosquito population dynamics in the Sahel region of Africa. Parasites Vectors 6, 235.

Yamana, T.K., Bomblies, A., Eltahir, E.A.B., 2016. Climate change unlikely to increase malaria burden in West Africa. Nature Climate Change. Advance Online Publication. 10.1038/nclimate3085.

Yamana, T.K., Bomblies, A., Laminou, I.M., Duchemin, J.-B., Eltahir, E.A., 2013. Linking environmental variability to village-scale malaria transmission using a simple immunity model. Parasites Vectors 6, 226.

Yamana, T.K., Eltahir, E.A., 2010. Early warnings of the potential for malaria transmission in rural Africa using the hydrology, entomology and malaria transmission simulator (HYDREMATS). Malar. J. 9, 323.

Yamana, T.K., Eltahir, E.A.B., 2013. Projected impacts of climate change on environmental suitability for malaria transmission in West Africa. Environ. Health Perspect. 121 (10), 1179–1186.

Zhou, G., Minakawa, N., Githeko, A.K., Yan, G., 2004. Association between climate variability and malaria epidemics in the East African highlands. Proc. Nat. Acad. Sci. U.S.A. 101 (8), 2375.