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Seasonality of *Plasmodium falciparum* transmission: a systematic review

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Abstract

Although *Plasmodium falciparum* transmission frequently exhibits seasonal patterns, the role and drivers of malaria seasonality are unclear. Given the massive variation in the landscape upon which transmission acts, intra-annual fluctuations are likely influenced by different factors in different settings. Further, the presence of potentially substantial inter-annual variation can mask the seasonal patterns; it may be that a location has "strongly seasonal" transmission and yet no single season ever matches the mean, or synoptic, curve. Accurate accounting of the extrinsic factors of malaria transmission for a given location can inform efficient control and treatment strategies. In spite of the demonstrable importance of accurately capturing the seasonality of malaria, as well as the strength of the seasonal pattern, data required to describe these patterns is not universally accessible and as such localized and regional efforts at quantifying malaria seasonality are disjointed and not easily generalized. The purpose of this review is to audit the extant literature on seasonality of *P. falciparum* and quantitatively summarize the collective findings. The contradicting results of studies using similar but not identical data and modeling approaches from similar but not identical locations as well as the confounding nature of climatological covariates underlines the importance of a multi-faceted modeling approach that attempts to capture seasonal patterns at both small and large spatial scales - 215 words (needs to be 200).

Index terms— keyword, keyword

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1 Introduction

Like many infectious diseases, malaria incidence often displays seasonal variation. The nature and extent of the seasonality varies enormously from place-to-place and from year-to-year. Temporal variation in malaria transmission is, along with its spatial distribution, among the most basic aspects of its epidemiology. Knowledge of the main drivers of seasonality, their timing, and interaction with malaria transmission in a given location can facilitate effective planning and implementation of routine control and treatment activities. Some interventions can be more effective if deployed at seasonally optimal times. Seasonal malaria chemoprevention, for example, which involves the preventative administration of antimalarial drugs to young children [Organization, 2013], is optimally targeted at regions with a short, intense, malaria transmission season, and requires accurate timing within that season [Cairns et al., 2012]. An understanding of seasonality is also important when measuring and describing geographical patterns of malaria risk [Gething et al., 2011]: observations made at different months in the year are difficult to compare without reference to a known underlying seasonal signal. Similarly, seasonality affects interpretation between different types of malaria data: the overall and age-specific relationships between vector population density, the entomological inoculation rate (EIR), the force of infection, infection prevalence or parasite rate (PR), disease incidence and mortality all differ in non-linear ways in areas of differing seasonality [Carneiro et al., 2010, Roca-Feltrer et al., 2010].

Despite the clear importance of quantifying the seasonality of malaria, data describing it are not widely available. While those involved in day-to-day disease control and treatment may harbor detailed knowledge of local seasonal patterns, there remains no single resource providing consistent and comparable data on the extent, timing, and determinants of seasonality at regional to global scales. The first challenge is one of definition. In a malaria context, the term seasonality encapsulates a complex and multi-faceted phenomenon which remains inconsistently defined, described, and interpreted. A basic description of seasonality in a location would include the relative magnitude, timing of onset, and duration of different seasons. These attributes must be characterized separately for each malaria metric of interest. Crucially, characterization of the "typical" seasonal pattern is likely to differ from that observed in any single year, since inter-annual variation is often substantial. Malaria seasons often start earlier or end later, last for a longer or shorter duration, or are more or less pronounced from one year to the next, and so this year-to-year variation around an average pattern must be captured and described.

A second challenge, leading directly from the first, is the availability of standardized and geolocated data describing patterns of seasonality that can be compared across a wide set of locations. While there is a degree of consensus on the broad global patterns of seasonality, this falls considerably short of a geographically detailed, quantitatively rich characterization that could support in-depth control planning. Our understanding of the geographical distribution of malaria has benefited enormously from the proliferation of standardized [Hou, 2013], often nationally representative [DHS, , MIS,] cross-sectional parasite rate surveys, and their assimilation into geospatial models [Gething et al., 2011, Gething et al., 2012], but such data are not well suited to capturing seasonal variation. Conversely, longitudinal or other time-series data that are ideal for analysing temporal patterns are less commonly obtained, address a disparate set of malaria metrics, tend to be unevenly distributed geographically [Gething et al., 2014] and can be prone to biases and missing data [Rowe et al., 2009].

This scarcity of robust and comparable data means the empirical evidence base on patterns of seasonality remains unconsolidated. The purpose of this review is to audit the extant literature on seasonality of *Plasmodium falciparum*, and to provide a quantitative summary in terms of: (i) the geographical regions represented; (ii) the type of malaria metrics measured; (iii) the climatic drivers identified; and (iv) the analytical approach taken to explore seasonal dynamics, which include a broad class of both statistical and mechanistic modeling approaches.

2 Methods

2.1 Constructing a Systematic Bibliographic Database

The intended scope of this review was all studies in the scientific literature that have either explicitly or implicitly observed, described, or modeled malaria seasonality and its drivers. Hundreds of such studies exist from sites around the world, fostered in part by the increasing diversity and availability of environmental and climatic covariates arising from both satellite imagery and improved on-the-ground data collection techniques. Six search terms were selected to systematically compile a list of papers relevant to the seasonality of *P. falciparum*transmission. These terms were then entered into the academic search engine Web of Knowledge [WoK,] and new papers from each search term added to the list each time (Table 1). These search terms were deliberately broader than the scope of this review to capture as many potentially relevant papers as possible, with the large set of returned studies then successively screened for inclusion according to a set of criteria described below.First, the abstract and titles of each paper were checked to identify papers with a focal subject that was not malaria seasonality. These papers were removed from consideration at this stage (471 papers). To systematically quantify the remaining broad assembly of literature, we designed and implemented a classification questionnaire that we applied to every publication. The 'questionnaire' was structured as follows:

i) Does the paper try to understand malaria seasonality or produce a model of the relationship between malaria and environmental variables?

ii) Does the paper include environmental or climatic variables and, if so, which variables are considered?

iii) Are the data used by the authors new and if so what type of data is used to represent malaria?

iv) In which locations is the study based?

v) What time periods does the paper cover?

vi) Is the analysis primarily mechanistic or statistical in nature and what are the main methods?

vii) What aspects of seasonality does the paper consider (e.g. timing of malaria peaks, difference between minimum and maximum, environmental drivers)?

viii) Is the paper primarily concerned with climate change?

ix) Is the method of particular interest because of its novelty or because it creates a solution to a particular problem?

x) Does the paper call for work on this issue?

The answers to these questions were recorded systematically to produce a reference for the comparison of approaches to investigating malaria seasonality as well as the global coverage of these attempts.

3 Results

Classifying each manuscript using the above questionnaire generated a considerable amount of detailed information. For brevity, we summarize this information in general terms below. To provide readers with increasing levels of detail, we include 6 supplemental tables in the SI, and finally provide the raw database as an additional supplemental file.

3.1 Regions

In total, we identified 159 manuscripts that satisfied our criteria for inclusion (Flowchart 1). Across these papers, the vast majority (74.2%, 118/159) concerned the effects of climate and seasonality on malaria in Africa (see Figure 1). 5 studies covered all of Africa, while 9 focused on regions of Africa (Table S1). Excluding these regional and continent-wide studies, there were 104 studies of 26 African countries. Outside Africa, there were 28 studies within Asia, with China (8) and India (4) being the two most studied countries (Figure 1). Beyond these locations, there were 11 studies in South and Central America, 2 studies in Iran and 2 studies in Europe (1 each in Portugal and Poland). Some studies attempted to analyze single locations within the countries of interest, while others utilized data from numerous locations within the country. For complete classification of the frequency of location utilization, see Table S1.

3.2 Malaria Metrics

Malaria transmission has historically been evaluated using various metrics. Abundances or frequency of blood feeding by *anophelene* mosquitoes, the vectors of malaria, have been used as a proxy for transmission, and a measure of transmission potential . EIR, which is the product of the number of vectors attempting to feed and the percent of mosquitoes actively infective, gives quantitative estimates of the number of infective bites per person per unit time. Prevalence of infections or incidence of clinical cases, detected actively in the community or passively at health facilities provide direct measures of the current level of transmission and disease within human hosts. Different metrics of malaria are representative of different aggregated temporal windows of transmission, which complicates attempts to link the environmental drivers and malariometric outcomes of seasonal transmission.

Across the 159 manuscripts, 21 used mosquito abundance as a malaria metric (Fig. S1 a). The majority of these studies concerned regions of Africa. Incidence of clinical disease was the most frequently investigated malaria metric (62 papers), and most of the regions of the globe with malaria were represented by studies using this metric (Fig. S1 b). EIR and infection prevalence were only investigated in regions of Africa (Fig. S1 b, c respectively). As with mosquito abundance, EIR and prevalence were far less frequently studied relative to incidence (6 and 18 studies respectively).

3.3 Climatic Drivers

The most commonly reported aspect of malaria seasonality was observed temporal relationships between a given malaria metric and a given putative environmental or climatic driver of that seasonality. The most direct method of obtaining data in specific locations is to take on-site measurements of variables of interest or to use local weather stations. However, accurate and complete records of all variables of interest across space and time may be lacking, particularly in many of the resource-poor locations of interest for malaria transmission. Over wider areas the use of nationally collected data from weather station networks may be more appropriate (e.g. National Meteorological Services Agency in Ethiopia, Islamic Republic of Iran Meteorological Organisation, and China Meteorological Administration). A common source of global climatic data is WORLDCLIM which, by interpolating data to cover areas away from initial weather station locations, has made available fine resolution interpolated surfaces from several trusted weather databases over a 50 year time period [Hijmans et al., 2005]. An alternative to terrestrial weather and climate data is provided by satellite sensor such as Moderate-resolution Imaging Spectroradiometer (MODIS) on the Terra and Aqua satellites; [King et al., 2003]. Unlike data from weather stations which can be patchy in their coverage, satellite sensors can achieve complete global coverage, and data from satellite mounted sensors such as the Advanced Very High Resolution Radiometer can be used to infer variables such as sea surface temperature [McClain, 1983], water vapour levels [King et al., 2003], atmospheric gas concentrations [Thies & Bendix, 2011] and precipitation [Kidd & Levizzani, 2011] as well as compute vegetation indices such as the normalised difference vegetation index (NDVI) which measures the "greenness" of vegetation based on its reflectance. The choice of data source on climatic drivers of malaria metrics will depend on various factors such as the spatial and temporal resolutions, time period and location of the study in question.

The majority of papers analyzed the relationship between malaria metrics and temperature or rainfall (40.3%, 64/159 and 34%, 54/159, respectively; Figure 2 a,b). Satellite-derived indices quantifying vegetation coverage were also frequently investigated (11.3%, 18/159; Figure 2c), often in conjunction with temperature and/or rainfall. All other potential drivers (e.g., relative humidity, wind speed and direction, sunspots) were either used rarely (2.5%, 4/159; Figure 2d) or in conjunction with a subset of the three main drivers (12.6%, 20/159). Here we summarize findings from those studies that used statistical methods to investigate seasonal drivers.

3.3.1 Temperature

Temperature covariates were found to be a significant driver of malaria seasonality in statistical models more frequently than any other climatological drivers (64). Amongst temperature-based variables, minimum monthly temperature was most frequently found to have a significantly relationship with temporal malaria metrics (24 analyses), followed by maximum monthly temperature (19 analyses) and mean monthly temperature (12 analyses). The range of significant time lags between monthly temperature and malaria metrics varied by both region and, as expected, malaria metric. As with all analyses, the dominance of malaria incidence-based investigations within the literature was again evident. However, as is evident by the history of lab and field-based experiments correlating temperature with mosquito population dynamics [Craig et al., 1999], it is not surprising that 14 papers found a significant relationship between some measure of monthly temperature and vector abundance (Fig. S2). All but one of these was a zero-month lag, with a single study lagging temperature by two months and all but one of the studies concerned regions in Africa (one was in Portugal). Incidence was the most frequently investigated malaria metric, and of the 62 statistical analyses that correlated climatological drivers with incidence, 28 found a significant relationship between monthly temperature and incidence.

Temperature was a significant driver in incidence studies throughout the Old World, with lags ranging from 0 to 9 months (Fig. 3). EIR, the other direct measure of current transmission activity within a region, was found to be significantly related to temperature in 4 studies, at lags from 0 to 5 month, all within Africa (Fig. S3). Finally, across the 4 papers that found significant relationships between monthly temperature and prevalence, all again occurred in Africa and most found a maximum lag of 2 months significant (Fig. S4c). A more detailed break-down of the number of times a specific temperature variable was found to be a significant driver of a specific malaria metric in a specific region can be found in the SI.

3.3.2 Rainfall

54 papers across the globe have found rainfall to be a significant predictor of malaria seasonality. Ten papers found a significant relationship between mean monthly rainfall and malaria metrics. Presumably driven by the non-linear relationship between rainfall and malaria, many investigators assessed specific statistics of rainfall other than mean monthly amount, such as seasonal rainfall [Mabaso et al., 2007], total rainfall during a set period (e.g., [Small et al., 2003]), and various other indices of variation. 2 papers (both based in Africa) found a significant relationship between rainfall and vector abundance (Fig. S5) with lagged relationships between 0 and 2 months. For both incidence and EIR, lags ranged from 0 to 4 months (33 papers, Fig. 4; 2 papers, Fig. S6 respectively). Across the 3 papers that found significant relationships between monthly rainfall and prevalence, all found a 0 month lag to be statistically significant (Fig. S7a). A more detailed regional break-down of the number of times a specific rainfall variable was found to be a significant driver of a specific malaria metric can be found in the SI.

3.3.3 Vegetation Indices

18 papers found a satellite-derived vegetation index to be a significant driver of malaria metrics; all but three used NDVI. Across various monthly vegetation indices, 4 papers found a significant correlations to vector abundance (Fig. S8). All of these were 0 month lags and located in

either Africa or Asia. Significant relationships between vegetation indices and incidence were found across the globe at 0 to 3 month lags (9 papers, Fig. S9). 2 papers found significant concurrent relationships between vegetation indices and EIR in Africa (Fig. S10) and across the 3 papers that found significant relationships between monthly vegetation indices and prevalence, also all in Africa, lags of 0.5 and 1 month were identified. (Fig. S11a). Again, more detailed break-downs of these results are provided in the SI.

3.4 Approaches - Statistical Methods

The database of seasonality studies included a wide range of different statistical modeling approaches to investigate empirical associations between malaria metrics an environmental drivers (116 papers). These ranged from descriptive approaches to fuzzy logic models and complex spatio-temporal methods. Thirteen studies used methods classified by the authors as 'simple.' This included descriptive methods and purely correlative approaches with no model fitting. The largest number of papers, 38, used classes of regression methods including both parametric and non-parametric. Some included residual error structures such as autoregressive terms. Logistic and Poisson regression were common approaches within this group along with several multivariate methods and mixed models. A further six studies used spatial methods, including spatial regression and spatial autocorrelation terms, along with geostatistical and niche modelling methods, and two additional studies used explicitly spatio-temporal methods. Ten of the papers using statistical methods used Bayesian approaches. Of these, two were spatial models and one used spatio-temporal methods.

The overall number of papers published per year increased towards the present (Fig. S12), although a clear trend of increasing modeling sophistication was evident, with a proportional decline in studies using simple statistical methods and non-spatial regression approaches whilst spatial and Bayesian approaches increased. Almost all of the descriptive papers concentrated on

Asia and Africa and were largely concerned with malaria cases or incidence. Rainfall and temperature predictors were commonly used within this group of papers. Among the models using regression methods the most common malaria metrics investigated were again number of cases and incidence. However, within this group the diversity of malaria metrics investigated was greater than for other approaches. The majority of papers using regression methods dealt with Africa but there were also examples in Asia, the Americas and Europe. Regression methods, perhaps due to the breadth of studies using these approaches, used the most diverse range of predictor variables. Malaria cases and prevalence were again well represented by studies using Bayesian methods. However, the two studies using spatio-temporal Bayesian models investigated environmental drivers of malaria prevalence [Gemperli et al., 2006] and vector abundance [Sogoba et al., 2007]. Similarly the spatio-temporal regression models were concerned with EIR, vector abundance and PR rather than number of cases and incidence [Amek et al., 2012, Mirghani et al., 2010]. Bayesian modelling approaches were most commonly associated with temperature as a predictor along with rainfall in many cases and were mostly focused on Africa.

3.5 Approaches - Mechanistic Models

31 publications investigated the possibility of incorporating seasonality, or seasonal drivers, into mechanistic models of malaria response variables. The majority of these studied malaria in Africa, but there have also been several investigations in Asia and South America (Fig. S13). From the initial models of Ross and then Macdonald [Smith et al., 2012], mechanistic models of malaria have, in general, not greatly deviated from the original framework [Reiner et al., 2013]. There have been a few exceptions to this general observation, and some of the most complex mechanistic modeling approaches have also been adapted to incorporate seasonal differences in malaria. As with the statistical models, there are stark differences in the modeling approach between models that attempt to model monthly malaria incidence data or parasite rate surveys and models that attempt to model mosquito abundance. However, as was true for the statistical

approaches, local rainfall and temperature were the most frequently used climatological covariates used to drive temporal variation in malaria.

3.5.1 Mosquito abundance

Anopheles abundance is known to have a non-linear relationship with temperature [Craig et al., 1999]. If the ambient temperature is too cold or too hot, vectors of malaria have a diminished probability of survival. Thus, considerable effort has gone into identifying the optimal temperature window for *Anopheles.* Incorporating temperature into an understanding of the suitable range of mosquitoes (and then further a suitable range of malaria) has resulted in global maps of malaria potential [Gething et al., 2011]. Additionally, the potential that the regions of the globe that are within the optimal temperature window for *Anopholes* may shift or expand with global climate change has resulted in numerous investigations and publications [e.g., [Mordecai et al., 2013]]. Although much of the work has concerned defining the spatial distribution of temperature that is ever in the suitable range for malaria, several efforts have further investigated the seasonality of mosquito abundance and climatic drivers' effect on abundance.

Martens, in 1999, modeled the death rate of mosquitoes as a function of temperature in Celsius, $g(T)$, as:

$$g(T) = \frac{1}{-4.4 + 1.31T - 0.3T^2} \tag{1}$$

From basic maps of climate suitability [Craig et al., 1999] to being used as an integral part of complex malaria models [Parham & Michael, 2010, Ermert et al., 2011a], this equation/functional form, or an approximation of it, has been used extensively. Other incorporations of temperature to identify climate suitability have either taken a simple approach of directly defining a window outside of which a mosquito population could not be sustained

[Goswami et al., 2012] or using a similar but mathematically different functional form such as the logistic equation used by Lourenço et al [Lourenço et al., 2011]. In addition to temperature, functional forms have been used to incorporate other climatological covariates such as rainfall and temperature into estimates of climate suitability for *Anopohles*. As with statistical models of mosquito abundance, there was no estimated lag between the climatological covariates and mosquito abundance.

Complex agent-based models whose primary focus is based on mosquito abundance that incorporate mosquito population ecology and impacts of multiple simultaneous interventions have also been built to accommodate multiple climatological drivers as well as some of their interactions. Eckhoff [Eckhoff, 2011] explicitly tracks cohorts of eggs through their life cycle using mechanistic relationships implemented on the individual level. Modelling local population dynamics (as opposed to well-mixed patches common to mechanistic models defined by differential equations) may allow for locally optimized control strategies once paramerterized for a specific location.

3.5.2 Malaria incidence

Several mechanistic models included within our review primarily concern the mathematical properties of models that permit intra-annual variation. Recent work by Chitnis et al [Chitnis et al., 2012] and Dembele et al [Dembele et al., 2009] have both analyzed periodically fluctuating parameters within a larger system of differential or difference equations. Chitnis et al incorporated considerable complexity, especially with respect to the life cycle of *Anopholes*, and both analyze the asymptotic stability of their system as well as investigate the effects of various control efforts. Although these models are not directly applied to data, they provide a rigorous framework within which seasonally fluctuating variables, driven by climate or otherwise, can be incorporated. As noted in a recent review of mechanistic models of mosquito-borne pathogens [Reiner et al., 2013], the complexity of a mechanistic model is typically determined by the exact purpose of the research.

A variety of compartmental models of malaria have incorporated temperature and rainfall to different ends. For example, Massad et al [Massad2009] incorporated both a seasonal sinusoidal driver of mosquito abundance and a second host population into their compartmental modeling approach to assess the risk of travelers to a region with endemic malaria but in doing so they ignored the incubation period for both host and mosquito. Conversely, Laneri et al [Laneri et al., 2010] used a single host population, but incorporated rainfall, incubation periods and secondary infection stages to separate the roles of external forcing and internal feedbacks in inter-annual cycles of transmission.

In general, the vast majority of mechanistic models of malaria incidence that incorporate seasonality or climate are bespoke to address a specific concern. There are, however, several important exceptions. Several research groups have spent the last decade (or more) developing extremely complex and detailed models of malaria. Combining statistical approaches, mechanistic models and in some cases fuzzy logic, these models attempt to recreate transmission patterns at large scales. Amongst these approaches, the utilization of climate and climatic drivers differs. Researchers from Imperial College and the London School of Hygiene & Tropical Medicine built an agent-based simulation model of malaria transmission fitted to 34 transmission settings across Africa [Griffin et al., 2010]. Using seasonal profiles of EIR fit to different regions they categorize transmission settings into different intensities and identify those locations where reasonable control efforts would have the largest impact. The Liverpool Malaria Model [Hoshen & Morse, 2004] models both malaria and the climatic drivers themselves and incorporates rainfall and temperature to drive the vector population. This complex model has been updated to incorporate further complexities [Ermert et al., 2011a] and then calibrated and validated on data from West

Africa [Ermert et al., 2011b]. Quantities such as the "start" and "end" of the malaria season were simulated and compared well with observed values where applicable. This model, as noted in [Ermert et al., 2011b], does not incorporate fine-scale hydrologic variability (since there is not extensive data to support its inclusion). This has been proposed as an explanation as to why year-to-year comparisons between simulations and observations at single locations are generally only weekly correlated.

Bomblies and colleagues [Bomblies et al., 2008] have introduced a modelling approach that explicitly incorporates hydrologic variability into vector abundance and then malaria incidence. In direct response to the typical mismatch of scales between the resolution of climatic drivers and the scale of vector population dynamics, the Hydrology, Entomology and Malaria Transmission Simulator (HYDREMATS) uses soil moisture and local hydrology to calibrate a model that captures mosquito abundance at a scale much closer to what is seen in the field, and has been used in several small scale validation and calibration studies [Bomblies et al., 2009, Yamana & Eltahir, 2011]. The inclusion of hydrology implicitly incorporates a lag between rainfall and malaria that is non-linearly determined based on ground cover, control practices and size of natural pools within the community. This level of high-resolution hydrological detail is difficult to obtain, or accurately simulate for entire regions or countries.

4 Discussion/Conclusion

Following an exhaustive literature search, we categorized 159 studies that either explicitly or implicitly addressed the seasonality of malaria. The vast majority of these efforts did not in fact attempt to quantify or describe the patterns of seasonality per se, but instead associated malaria data with climatic data. However, because the climatological covariates themselves follow seasonal patterns (some more strongly than others), linking climate with malaria, even at a lag, indicates the potential presence of seasonality. The two clearest aspects of these studies that partitioned the existing literature, somewhat predictably, were the types of data (both explanatory and response) and the types of analyses (generally speaking, statistical versus mechanistic). In every combination, although the limitations of available data soften the conclusions, the presence of variation in 'seasonality' seems to be both conditioned and driven by location and climate.

As discussed above, the increase in resolution (both spatially and temporally) of satellite-based climatological covariates has greatly contributed to the analyses performed and, in many cases, the amount of the variation in malaria explained. Additionally, improved data collection and data maintenance from existing weather stations, has provided ground reference data with which the satellite sensor data can be validated. Due to the necessary transmission steps that occur within the mosquito, it is not surprising that climatological covariates that are most clearly associated with mosquito ecology have been linked to malaria metrics. Rainfall and temperature, measured in a variety of ways, have been found to be significant drivers of malaria considerably more than any other covariate (34%, 54/159 and 40.3%, 64/159, respectively). Although there is an increase in the spatial and temporal resolution of explanatory covariates, as noted previously, existing data are often inadequate to predict mosquito abundance at the fine spatial scale upon which mosquito population dynamics occur [Ref]. For example, measured either at a local weather station or through satellite derived metrics, it is unclear how to translate a single 'rainfall' data location to predict the presence and quantity of larval breeding sites. Satellite-derived vegetation indices, such as NDVI, have been demonstrated to be useful to measure landscape suitability for mosquitoes (19%, 4/21) but they have only been shown in the literature to correlate concurrently to abundance (or at most lagged one month). In general, remotely sensed climate data provide an opportunity for increased understanding, but their utility (and accuracy) must be tempered by complex confounding variables such as land-type. For example, high NDVI values can indicate very different climates depending if the region measured has irrigation, is heavily forested or is on the desert fringe. Likewise, due to small-scale variation in land-type, the same amount of rainfall can have a very different impact on mosquito larval sites depending on where it is measured.

There are (at least) three different time-scales of malaria metrics, as described below. As the time-scale of the metric increases, and the lag between occurrence of a driver of transmission and the time its effect is felt upon the given metric increases, the complexity of the relationship likewise increases. First, mosquito population dynamics are essentially instantaneously responsive to climatological forcing. In addition to a non-linear relationship to temperature, the necessity of rainfall for larval sites combined with the hazard of flushing of these sites by flooding associated with heavy rainfall introduces a second non-linear relationship between climate and 'malaria' vis-à-vis mosquito density. Translating the climatic effects through mosquito density, two blood meals (one infecting the mosquito and a second infecting a susceptible host) and the IIP clearly temporally separates human incidence and climate drivers. Adding to this complexity, climatic drivers such as temperature have been shown to influence incubation periods. Thus, the second scale of drivers is based on malaria data associated with incidence (e.g. case data, death, etc). The longest scales of metrics are associated with prevalence. Integrating the amount of incidence across an entire transmission season, and then incorporating the waning of immunity that will slowly decrease the contribution of early infections to later prevalence surveys, these malaria variables are the least immediately influenced by season. Beyond the expectation of three different temporal scales of climate influence on malaria, different challenges are involved with measuring each of these malaria metrics. Those most likely to be greatly influenced by climate (e.g., mosquito abundance) are also the most stochastic and require the most serial samples to accurately account for measurement noise.

Perhaps due to the relative simplicity of the corresponding data analysis, or perhaps due to the noise reduction that occurs when taking means, synoptic data have been used extensively to assess both seasonal patterns of malaria as well as the effects of climatological covariates on malaria data. In a sense, the synoptic curve of incidence in a location is a close proxy to the seasonal pattern of malaria within the region. Were there to exist no inter-annual variation in incidence (or drivers) these two quantities would be comparable. As such, to infer a basic level of understanding of seasonal patterns, synoptic data can be a useful tool. However, in reality the previous premise is demonstrably false. Natural, intrinsic periodicity in malaria transmission suggests that averaging over years to produce a single value for expected incidence on a given day (or, more commonly, in a given month) obfuscates the truth and may bias inference [Ref]. Further, if climate is closely linked to incidence, averaging incidence across years with vastly different rainfall or temperature may result in producing seasonal signatures that in practice never occur themselves. Finally, global climatological drivers of climate like ENSO have multi-year cycles and synoptic data implicitly ignore any potential impact of these sorts of covariates.

The analysis conducted by a paper is typically strongly driven by the question the study is designed to address. Because most of the studies included in this review were not focused on assessing the strength and signal of seasonality, it is not surprising that the types of analyses were not appropriate for those questions. The vast majority of statistical approaches were a variation of regression. The most frequent purpose of a study was to link climatological covariates to temporal variation. This variation was acknowledged to occur at both intra- and inter-annual scales, but beyond fine-scale temporal variation, the papers most frequently focused on inter-annual scales. For the mechanistic approaches, except for a few that investigated the intrinsic periodic properties of their system, seasonality was incorporated by including relationships between parameters and climatological and temporal covariates. The most frequent driver of temporal variation in these studies concerned the daily survival rate of the mosquito. A non-linear relationship [Martens] has been identified in lab and field studies, where mosquitoes are more likely to die at both extremely cold and extremely hot temperatures.

The scope of this review concerns the current seasonal patterns of malaria across the globe. Although it is, thus, outside the purview of this review, the growing literature assessing the potential changes in the range and incidence of malaria in the face of potential changes in local and global climate must be noted. Within our review, 51 publications were excluded from further analysis because they were identified as being solely concerned with assessing some aspect of the impact of climate change on malaria. Many of these works have combined the predicted climate maps produced by WorldClim or ClimMond with the mosquito daily survival rates identified by Martens and others to predict either changes in range of climate suitability (which does not always imply 'increases' in range) or changes in incidence vis-à-vis changes in the length of the year for which transmission is possible. Given the extremely complex interplay between the natural transmission dynamics of malaria and the impact that humans and economic development exert on the system (either positively or negatively), understanding the consequences of a 5° C increase in local temperature on malaria remains a pertinent, but poorly understood problem.

It is important to note that several previous studies have paved the way for this comprehensive review and have, themselves, begun the effort in earnest to quantify seasonal patterns either on small scales or in large regions across the globe. Mabaso et al [Mabaso et al., 2005] applied Markham's concentration index [Markham, 1970] to data from Zimbabwe. They identified significant effects of both temperature and rainfall in determining the strength and timing of seasonal outbreaks. Roca-Feltrer et al [Roca-Feltrer et al., 2010] conducted a systematic literature review of studies concerning the age of paediatric hospital admissions with sever malaria syndromes. This was followed by estimations of the potential impact of seasonal malaria chemoprevention on children across Africa [Cairns et al., 2012], work which suggested that seasonal prevention strategies could avert millions of malaria cases and tens of thousand childhood deaths every year. Ermert et al [Ermert et al., 2011b] utilized the Liverpool model [Ermert et al., 2011a] to approximate seasonality by identifying when the estimated EIR in a location first exceeded 0.1. They also were able to reliably recreate seasonal quantities such as the beginning and end of the 'season' with their model when applied to West Africa. Gemperli et al [Gemperli et al., 2006] used a seasonality map derived from climatological covariates (rainfall, temperature and NDVI, Ref) within a mechanistic modeling framework to estimate the length of the malaria season. Each of these studies, as well as several others, has indicated that there appears to be some level of predictability of malaria seasonality in endemic settings.

While these and other studies have investigated aspects of seasonality, either synoptically at a large spatial scale or in depth at a small spatial scale, the drivers and patterns of seasonality at the global level remain poorly understood. Malaria seasonality, though difficult itself to fully describe quantitatively, is not measurable from a single years' transmission patterns. The confounding and driving nature of climatological covariates requires a multi-faceted modeling approach. Both statistically and mechanistically, parsing the relative contribution of climate and an underlying seasonal pattern to observed data requires acquiring data with a minimal amount of measurement error or in sufficient quantities to reduce prediction error. Further, linking the patterns observed or identified in one specific location to the surrounding area and understanding the uncertainty in the extrapolated patterns of seasonality in the locations where data are scarce is critical. Both statistical and mechanistic approaches provide useful (and different) information and, thus, both should be used in concert to most adequately exploit the available data. We believe that only by modeling seasonal patterns at both small and large spatial scales while incorporating the inter-annual variability introduced by capricious climatological drivers can a clear picture of malaria seasonality be understood.

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Figure Captions

Figure 1: **Global distribution of malaria seasonality papers.** The frequency various countries across the globe are the focus of malaria seasonality papers is plotted with an exponential color scale. Studies that considered individual locations are indicated by grey points on the map.

Figure 2: **Distribution of malaria seasonality papers by climatological driver.** The frequency that climatological covariates are identified as significant drivers of malarial metrics is plotted for rainfall (panel A), temperature (panel B), vegetation indices (panel C) and all other covariates (panel D). Studies that considered individual locations are indicated by grey points on the maps.

Figure 3: **Reported relationships between temperature and malaria incidence.** In panel A, the distribution of significant temperature lags to incidence is plotted. Different approaches used different forms of monthly temperature in their model. In panels B, C, and D, the maximum significant temperature lag is plotted by country in South America, Africa and Asia respectively.

Figure 4: **Reported relationships between rainfall and malaria incidence.** In panel A, the distribution of significant rainfall lags to incidence is plotted. Different approaches used different forms of monthly rainfall in their model. In panels B, C, and D, the maximum significant rainfall lag is plotted by country in South America, Africa and Asia respectively.

Search Term	Hits	Cumulative total papers
Malaria & Seasonality & Model	74	74
Malaria & Seasonality & Mathematical	47	100
Malaria & Season & Mathematical	121	207
Malaria & Season & Model	181	325
Malaria & Climate & Model	376	640
Malaria & Climate & Mathematical	116	653

Table 1: **Summary of systematic search.** Number of papers returned by each of the six search terms selected to systematically compile a list of papers, from the academic search engine Web of Knowledge, relevant to the seasonality of *Plasmodium falciparum* transmission.