The malaria transmission in Anhui province China

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A B S T R A C T

Plasmodium vivax and Plasmodium falciparum cases have opposite trends in Anhui China in the past decade. Long term and seasonal trends in the transmission rate of P. falciparum in Africa has been well studied, however that of P. vivax transmitted by Anopheles sinensis in China has not been investigated. There is a lot of work on the relationship between P. vivax cases and climatic factors in China, with sometimes contradicting results. However, how climatic factors affect transmission rate of P. vivax in China is unknown. We used Anhui province as an example to analyze the recent transmission dynamics where two types of malaria have been reported with differing etiologies.

We examined breakpoints of the P. vivax and P. falciparum malaria long term dynamics in the recent decade. For locally transmitted P. vivax malaria, we analyzed the transmission rate and its seasonality using the combined human and mosquitos SIR-SI model with time-varied mosquito biting rate. We identified the effects of meteorological factors on the seasonality in transmission rate using a GAM model. For the imported P. falciparum malaria, we analyzed the potential reason for the observed increase in cases.

The breakpoints of P. vivax and P. falciparum dynamics happened in a same year, 2010. The seasonality in the transmission rate of P. vivax malaria was high (42.4%) and was linearly associated with temperature and nonlinearly with rainfall. The abrupt increase in imported P. falciparum cases after the breakpoint was significantly related to the increased annual Chinese investment in Africa.

Under the conditions of the existing vectors of malaria, long-term trends in climatic factors, and increasing trend in migration to/from endemic areas and imported malaria cases, we should be cautious of the possibility of the reestablishment of malaria in regions where it has been eliminated or the establishment of other vector-borne diseases.

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1. Introduction

Malaria is a vector-borne disease caused by parasites of the *Plasmodium* genus and primarily transmitted by *Anopheles* species. Four species of *Plasmodium* have been implicated in human malaria, including *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium falciparum* and *Plasmodium ovale*. *P. vivax* and *P. falciparum* are the primary causes; *P. vivax* has the widest spatial distribution and *P. falciparum* is associated with the highest mortality rates observed with malaria (Hay et al.,

2004). The mortality rate of *P. falciparum* was 71.9 per 100,000 in 2010 and 41 per 100,000 in 2018 in Africa, compared with the global mortality rate of malaria of 16.6 per 100,000 in 2010 and 10.2 per 100,000 in 2018 (WHO, 2019). *Anopheles gambia* spp accounts for major cases in parts of Africa, while *Anopheles sinensis* is the primary vector in over 29 provinces in central China and has been the only vector of *P. vivax* since 2010 (Feng et al., 2017). Starting in the 1950s, China gradually implemented comprehensive prevention measures to control malaria. Total malaria cases reported in China decreased from 40,036 in 2005 to 3299 in 2015 (Wang et al., 2014).

Anhui province has a population of 63.7 million (454 persons per square kilometer) in 2019 and is located in central China. In 2006, Anhui reported the highest incidence in the country, 57.2 per 10,000 (34,984 cases) which was 54.5% of all cases reported that year (Gao et al., 2012). The high incidence in 2006 was a result of the rebound starting in 1993 after nine years of low numbers of malaria cases (<10 cases/10,000 population) (Fig. 1a). The control measures after 2007 reversed this trend in reported malaria cases back to what was observed in the early 1990s. In 2019, Anhui, among other 13 provinces, passed the *P. vivax* elimination evaluation from the Malaria Elimination Assessment Group of the National Health Commission (2020 National Health Commission of the People's Republic of China) and have been malaria free under the World Health Organization (WHO) definition. According to the WHO, elimination of malaria is achieved when local transmission is interrupted and no incidence is reported for at least three consecutive years (WHO, 2017).

All reported cases of *P. vivax* malaria in Anhui province from 2004 to 2010 were locally acquired (Xu et al., 2015). In contrast, reported *P. falciparum* malaria cases in Anhui province were all imported and 80% of cases had travel history to Africa (Zhang et al., 2018, 2019). The two types of malaria cases in Anhui had opposite trends. Since 2006, *P. vivax* malaria cases have decreased significantly (Fig. 1b, Average Annual Percent Change: 46.7 CI: 52.1, −40.7, P < 0.01) while *P. falciparum* malaria cases increased significantly since 2004 (Fig. 1c, Average Annual Percent Change: 57.2 CI: 22.1, 102.4, P < 0.01; calculated using Joinpoint v. 4.7.0.0, NCI). Imported *P. falciparum* malaria in Jiangsu, Anhui's neighboring province, was related to Chinese laborers going to Africa (Liu et al., 2014). Studies also show that annual number of laborers to Africa from China is proportional to the amount of Chinese investment in Africa (Li et al., 2015). There are examples where imported cases may cause resurgence of malaria local transmission (Danis et al., 2013). Because of the entomologic risk in having vectors across many parts of China (Zhu et al., 2013) and because malaria continues to be imported from other countries, there is concern for the resurgence of malaria local transmission. To prepare for a possible resurgence of malaria, we should understand malaria transmission dynamics in China.

Focusing on transmission dynamics allows us to capture the complexity of the vector-host-environment interaction of a vector borne disease system. In addition to the decreasing trend, cases of *P. vivax* malaria in Anhui show a cyclic pattern. There are two tendencies in studying the cyclic pattern of locally acquired malaria cases and the factors driving the trend. One is in how climatic factors such as temperature and rainfall patterns affect malaria transmission dynamics through their impact on mosquito population dynamics, mosquito biology, and the transmission intensity (Beck-Johnson et al., 2013; Paaijmans et al., 2010). This is the primary mode of studying *P. falciparum* transmission in Africa, and is well studied (Pascual et al., 2008). The other is the use of statistical models to evaluate the effect of meteorological factors on malaria cases. For malaria in China, most researchers focus on the latter, statistical approach, finding trends where temperature or rainfall have a positive effect on disease incidence (Guo et al., 2015; Huang et al., 2011). To date, there has not been enough work in China to fully understand the complex transmission dynamics of malaria.

In this paper, Anhui province is used as a case study to analyze recent epidemic trends and transmission dynamics of malaria in China. We examine whether significant changes occurred in the malaria dynamics in recent decades in Anhui. For *P. vivax* malaria, we analyze the transmission rate and the seasonality in the transmission rate, and identify the influential effects of meteorological factors including rainfall and temperature on the seasonality in transmission. For *P. falciparum* malaria that is primarily imported, we assess the relationship between the number of *P. falciparum* malaria cases in Anhui and annual Chinese investment in Africa.

2. Methods

2.1. Data

The number of cases of *P. falciparum* malaria and *P. vivax* malaria in Anhui from 2004 to 2016 were downloaded from the Chinese Center for Disease Control and Prevention (www.phsciencedata.cn). Demographic data including birth rate, death rate, and total population of Anhui from 2004 to 2016 were obtained from the Statistics Bureau of Anhui (http://tjj.ah.gov.cn/tjjweb/web/index.jsp). The meteorological data in the form of monthly average temperature and total rainfall for 17 meteorological stations from 2004 to 2009 in Anhui was downloaded from the China Meteorological Data Network (http://data.cma.cn). The meteorological data from 17 stations was then averaged. Herein, we study the relationship of temperature trends and the seasonality in transmission, hence we only consider the average temperature. Total annual Chinese investment in Africa was downloaded from the Ministry of Commerce of the People's Republic of China (fec.mofcom.gov.cn/).
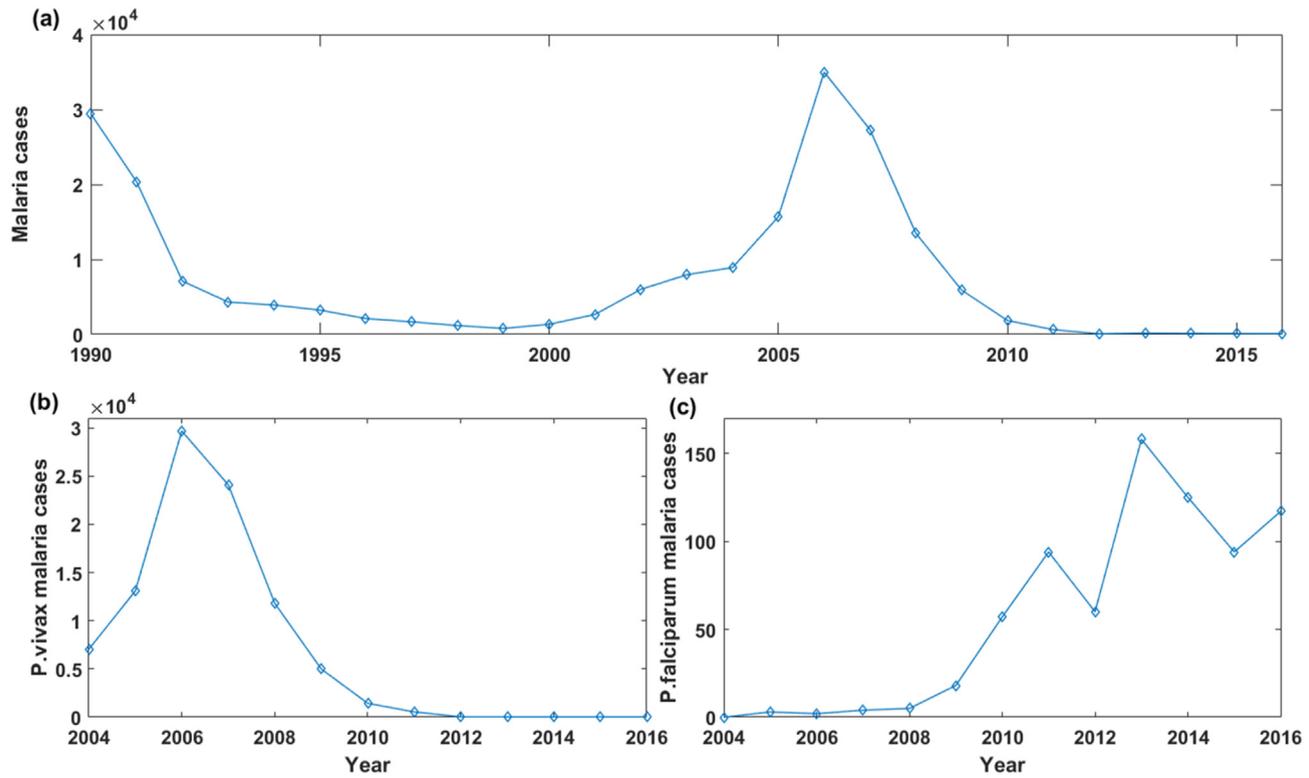
Fig. 1. The reported malaria cases in Anhui province. (a) Reported cases of malaria in Anhui province from 1990 to 2016; Time series of the number of cases of *P. vivax* (b) and *P. falciparum* (c) malaria in Anhui from 2004 to 2016.

2.2. Wavelet power spectrum

We use wavelet analysis to estimate the periodicity of *P. vivax* malaria and *P. falciparum* malaria in Anhui province. In contrast to Fourier analysis, the wavelet analysis is well suited for the study of signals whose spectra change with time. This time-frequency analysis of the signal provides information on the different frequencies as time progresses (Cazelles et al., 2013; Chazelles et al., 2007).

2.3. Breakpoints

By identifying breakpoints, we examine when significant changes occurred in the malaria dynamics in Anhui from 2004 to 2016. The significant change we are focused on is known as a regime shift and the change point is called breakpoint (Pascual et al., 2008; Solow & Beet, 2005).

We use hypothesis testing for the breakpoint of *P. vivax* malaria, whose time series contains both a long term trend and a within year seasonal trend. We examine only one breakpoint assuming there are different qualitative dynamics before and after the breakpoint. The null hypothesis (H_0) is: there is no breakpoint and one model could describe the *P. vivax* malaria dynamic from 2004 to 2016. The alternative hypothesis (H_0) is: two models (one for time series before and one for after the breakpoint) are needed to describe *P. vivax* dynamics during this time period. Because there is significant cyclic change in the *P. vivax* time series, the Seasonal Autoregressive Integrated Moving Average (SARIMA) model is used. The parameters of the auto-regressive and seasonal parts in SARIMA model (ARMA (p,q) $\times$ (P,Q)s), where P,Q,s represent the components of the seasonal part, are selected by using R (R Core Team, 2013).

Under $H1$, the breakpoint is assumed to occur in any possible month, and two SARIMA models are fit for two time series before and after the month, and the log likelihood values of the two SARIMA models are added. By comparing the maximum log likelihood values for the two hypotheses, the breakpoint can be identified.

Since *P. falciparum* malaria cases in Anhui province during the study period were all imported with strong independence and randomness (Xu et al., 2015), we use Bayesian Gibbs sampling to find the breakpoint (Christensen et al., 2010). We analyze the number of *P. falciparum* malaria cases in Anhui for 144 months from 2005 to 2016 (there were no reported cases in 2004). For a breakpoint k, the *P. falciparum* malaria cases in the ith month ($i = 1$ to k) y_i, is assumed to have a Poisson distribution with mean θ. Then cases in month j ($j = k+1$ to 144) y_j have a Poisson distribution with mean λ. The Poisson process with a breakpoint at k is given by

$$y_i \sim \text{Poisson}(\theta), i = 1, …, k \; y_j \sim \text{Poisson}(\lambda), j = k+1, …, n \; n = 144$$

Conditional conjugate priors are for θ and λ are

$$\theta \sim \text{Gamma}(a_1, b_1) \; \lambda \sim \text{Gamma}(a_2, b_2)$$

We ran a Markov chain for 25,000 iterations and calculated the posterior distribution of θ/λ based on the last 2000 iterations.

2.4. Epidemic model of P. vivax malaria in anhui province

P. vivax malaria cases reported in Anhui from 2004 to 2010 were all locally acquired cases (Xu et al., 2015). To further study the transmission characteristics of *P. vivax* malaria in Anhui province, we use a model that follows the Ross-McDonald framework (Keeling & Rohani, 2008), however we utilize a seasonal transmission rate.

In model (1), S_H and I_H are the numbers of susceptible, infected humans respectively, S_M and I_M are the numbers of susceptible and infected mosquitoes respectively. Mosquitoes never recover from the infection because their infected period ends with their death due to their relatively short lifecycle.

$$\frac{dSH}{dt} = \nu H - \frac{rTHMSHIM}{NH} - \mu HSH$$

$$\frac{dIH}{dt} = \frac{rTHMSHIM}{NH} - \mu HIH - \gamma HIH$$

$$\frac{dSM}{dt} = \nu M - \frac{rTMHSMIH}{NH} - \mu MSM$$

$$\frac{dIM}{dt} = \frac{rTMHSMIH}{NH} - \mu MIM \tag{1}$$

Where r is the biting rate, T_{HM} is the probability of transmission to human after being bitten by an infected mosquito, and T_{MH} is the probability of transmission to mosquito after a mosquito bite; ν_H and ν_M are births of humans and mosquitoes, μ_H and μ_M are death rates for humans and mosquitoes, γ_H is the human recovery rate. N_H is the total human population.

To model the seasonality in transmission rate, we consider the seasonality in the biting rate as a sinusoidal function:

$$r(t) = r_0(1 - r_1 \cos(2\pi t + \varphi)) \tag{2}$$

where r_0 is the average mosquito biting rate, and r_1 ($0 < r_1 < 1$) is the variation in the amplitude of biting rate around the average r_0 and is defined as the seasonality of the biting rate. The parameter φ is the phase shift of the function. Parameters and values are shown in Table 1.

The malaria transmission matrix can be further specified by the mosquito biting rate and the probability of transmission following a bite:

$$\boldsymbol{\beta}(t) = \begin{bmatrix} 0 & \beta 1(t) \\ \beta 2(t) & 0 \end{bmatrix}$$

$$= \begin{bmatrix} 0 & \dfrac{r_0 T_{HM}}{N_H}(1 - r_1 \cos(2\pi t + \varphi)) \\ \dfrac{r_0 T_{MH}}{N_H}(1 - r_1 \cos(2\pi t + \varphi)) & 0 \end{bmatrix} \tag{3}$$

where $\beta_1(t)$ and $\beta_2(t)$ are the transmission rates from mosquito to human and from human to mosquito respectively. Since elements of the transmission matrix are proportional to the biting rate, the amplitude of transmission seasonality is the same as that of the biting rate.

The method of least squares is used to estimate the biting rate parameters of *P. vivax* malaria in equations (1) and (2) fitting *P. vivax* malaria cases in Anhui from 2004 to 2009. The year of 2010 is not studied because our analysis result of breakpoint show that the breakpoint was in the middle of the year of 2010. The transmission matrix is then calculated from equation (3).

To understand *P. vivax* malaria transmission, we calculate the basic reproductive ratio, R_0, which quantifies the number of secondary infections that result from a single infected mosquito in a fully susceptible population. Basic reproductive ratio is an important indicator of transmission level, providing information for understanding disease transmission and control (Kammanee et al., 2001; Smith et al., 2007). For model (1), R_0 is given by (Keeling & Rohani, 2008):

$$R0 = \frac{r^2 TMHTHMNM}{\mu m(\mu H + \gamma H)NH} \tag{4}$$

2.5. Generalized additive model and pearson correlation coefficient

Using a generalized additive model (GAM), we analyze factors affecting the *P. vivax* malaria transmission rate; Pearson Correlation Coefficient was used to compare the factors influencing the increase in *P. falciparum* malaria incidence.

Because the malaria transmission rate is in the form of a matrix and each element is linearly proportional to the mosquito biting rate $r(t)$, the GAM quantifies the effects of rainfall and temperature on the mosquito biting rate of *P. vivax* malaria:

Table 1
Parameter descriptions and values.

Parameter	Value	Description	Reference
T_{HM}	0.1	The probability that an infected mosquito biting a susceptible human transmits the infection	Churcher et al. (2017)
T_{MH}	0.16	The probability that a susceptible mosquito bites an infected person and is transmitted	(Churcher et al., 2017; Keeling & Rohani, 2008)
γ_H	2	The recovery rate for humans (per month)	Duan (2012)
ν_H	3300	The recruitment rate of humans (per month)	(2019)Chinese National Bureau of Statistics
ν_{HM}	220,000	The recruitment rate of mosquitoes (per month)	Assumed
μ_H	0.0011	The mortality rate for humans (per month)	(2019)Chinese National Bureau of Statistics
μ_M	1.5	The mortality rate for mosquitoes (per month)	Feng et al. (2017)
$S_H(0)$	3,000,000	The number of initial susceptible humans	Assumed
$S_M(0)$	4,500,000	The number of initial susceptible mosquitoes	Assumed
$I_H(0)$	0	The number of initial infected humans	Assumed
$I_M(0)$	1	The number of infected mosquitoes	Assumed
R_H	0	The number of recovered humans	−
r_0	−	The average mosquito biting rate	Estimated
r_1	−	The seasonality in mosquito biting rate	Estimated

$$rb(t) = a + f1(temperature) + f2(rain) + \varepsilon \tag{5}$$

where the biting rate $r(t)$ is the dependent variable, the *temperature* and *rain* are independent variables representing climatic factors of average temperature and total rainfall, a is the intercept, and $\varepsilon \sim N(0, \sigma^2)$ is the error term.

We use Pearson Correlation Coefficient to assess the relationship between total *P. falciparum* malaria cases and Chinese investment in Africa. Investment in Africa in 2008 is extremely high compared with subsequent and prior years. This is because the Industrial and Commercial Bank of China acquired the Standard Bank of South African that year and is not related to the number of laborers. Thus, 2008 is an outlier and was omitted from the analysis.

3. Results

3.1. Cyclic pattern and breakpoints of the two types of malaria

From 2004 to 2012, *P. vivax* malaria incidence in Anhui exhibits an annual cycle (Fig. 2a). In contrast, there is no seasonality in *P. falciparum* malaria incidence over the entire study period (Fig. 2b).

3.2. P. vivax malaria transmission rate seasonality and influencing factors

The average mosquito biting rate (r_0) per month in Anhui is estimated to be 64.5, with 42.4% variation in the biting rate (r_1 in equation (2)). Using this mosquito biting rate in the transmission matrix gives:

$$\beta(t) = \begin{bmatrix} 0 & 2.135 \times 10^{-6} \times 1 - 0.424 \cos(\pi t/6 + 0.0003) \\ 3.416 \times 10^{-6} \times 1 - 0.424 \cos(\pi t/6 + 0.0003) & 0 \end{bmatrix}$$

There is a quantitative and periodic consistency between the simulation results and the reported cases showing the peak season of July to October each year (Fig. 3a). The seasonality in transmission rate (or the variation in the transmission rate) of *P. vivax* malaria in Anhui is the same as the seasonality in biting rate. During 2004 to 2009, the biting rate is highest in June and lowest in December and January (Fig. 3b). Substituting the average mosquito biting ratio into equation, the basic reproduction number is 1.22 (Fig. 4).

The mean monthly temperature, total monthly rainfall in Anhui for 2004 to 2009 are shown in Fig. 3c to d, compared with seasonal biting rate in Fig. 3b. The GAM result reveals the non-linear relationship between biting rate and transmission rate (Fig. 3e). The transmission rate is linearly affected by temperature (Fig. 3f). Moreover, variations in temperature have a greater impact on the transmission rate than rainfall (Table 2).

3.3. The relationship between the number of P. falciparum malaria cases in anhui and Chinese investment in africa

From 2004 to 2016, Chinese investment in Africa shows an upward trend and is significantly associated with the number of malaria cases in Anhui (Pearson correlation coefficient = 0.91, $p < 0.001$).

4. Discussion

The epidemic dynamics of the two types of malaria have opposing trends in Anhui from 2004 to 2016. The opposing trends are due to the elimination efforts successfully suppressing locally acquired P. vivax malaria while increasing Chinese investment in Africa resulted in increased importation of *P. falciparum* malaria cases by way of returning laborers.

Between 2004 and 2012, *P. vivax* malaria incidence exhibited an obvious annual cycle, which is determined by the transmission rate seasonality. Seasonal transmission of *P. vivax* malaria is affected by temperature and rainfall changes. Other studies show that temperature affects many aspects of *Anopheles sinensis*'s life cycle, including breeding, survival, feeding habits and activity behaviors (Wang et al., 2010). Even a small change in temperature can result in large changes in the biting rate of *Anopheles sinensis* (Wang et al., 2010). Within the temperature range of malaria transmission by *Anopheles sinensis*, the higher the temperature, the more frequent the biting rate (Ding et al., 1991). Our finding is in line with these studies and shows that the seasonality in biting rate and transmission rate are linearly related to the variation in temperature for *P. vivax* malaria. Compared with rainfall, temperature has a larger effect on the *P. vivax* malaria transmission rate.

After 2013, there were no recorded cases of local transmission of *P. vivax* malaria in Anhui (Zhang et al., 2018). That the breakpoint for *P. vivax* malaria cases occurs in 2010 indicates that control measures were successful more than two years before case counts were brought to zero. It is interesting to note that the breakpoint for *P. vivax* malaria cases estimated in our study coincides with China's issuing of the document "China's Action Plan for Malaria Elimination (2010—2020)" in May 2010, which explicitly proposed the adoption of strengthened control strategies and measures to improve policies and guarantees related to malaria.
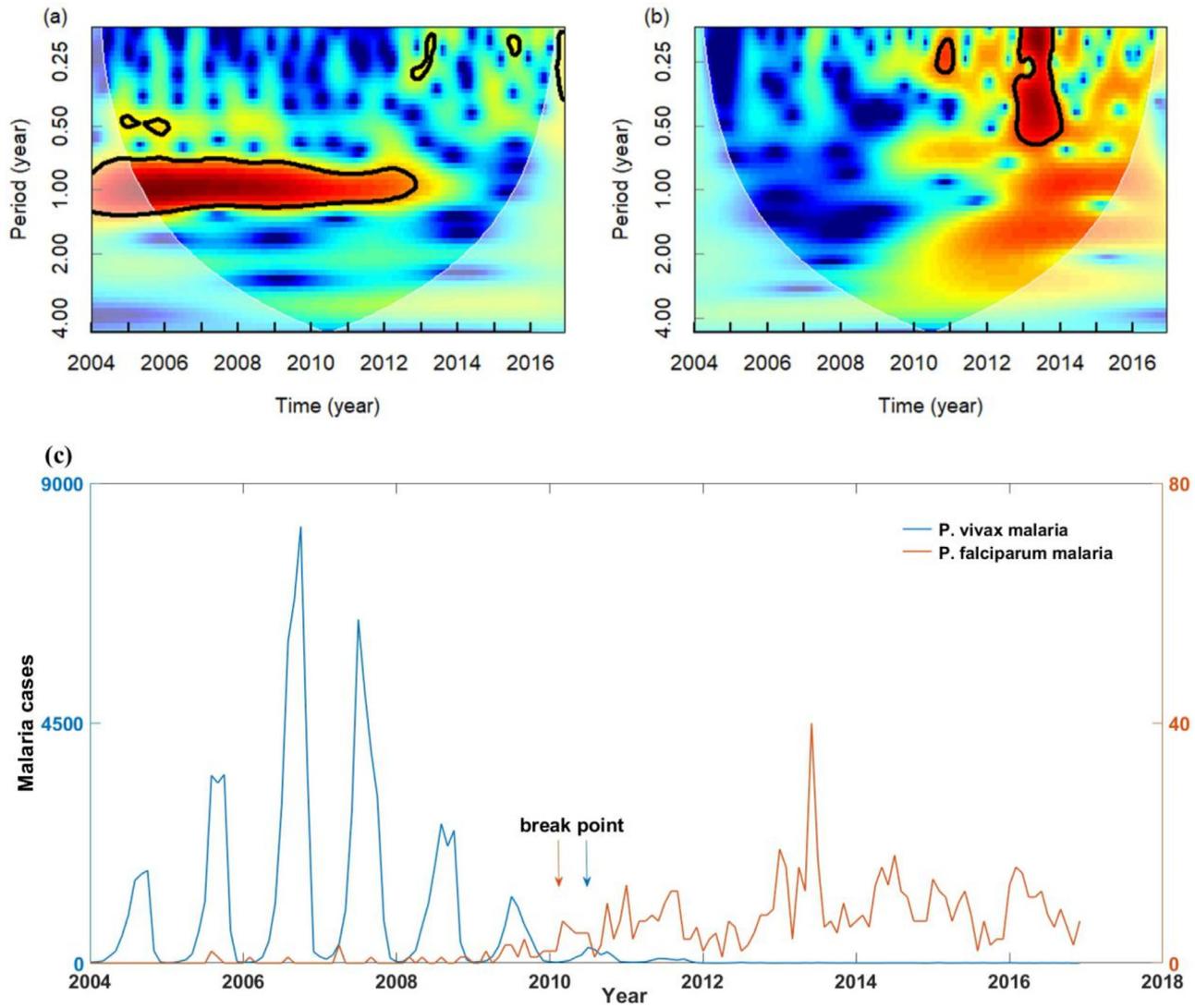
Fig. 2. Cases patterns of malaria in Anhui. The wavelet spectrum in Anhui province for the incidence of *P. vivax* malaria (a) and incidence of *P. falciparum* malaria (b). (c) Monthly *P. vivax* malaria (blue) and *P. falciparum* malaria (orange) cases in Anhui province with the breakpoints marked.

Table 2
The effect of variable(s) on the transmission rate of *P. vivax* malaria in Anhui.

	Variables	edf	Ref.df	F-statistic	*p*-value	R-Squared
Univariate model	Rainfall (mm)	2.374	2.952	29.03	<0.001	0.55
Univariate model	Temperature (°C)	1	1	159.1	<0.001	0.69
Multivariate model						
	Rainfall (mm)	2.203	2.744	6.281	0.00168	0.75
	Temperature (°C)	1	1	58.391	<0.001	

Abbreviationsedf − effective degrees of freedom; Ref.df − reference degree of freedom.

There was no periodicity in *P. falciparum* malaria cases in Anhui because cases were imported. We found the increase in *P. falciparum* malaria cases after the breakpoint was related to a significant increase in Chinese investment in Africa. Since the
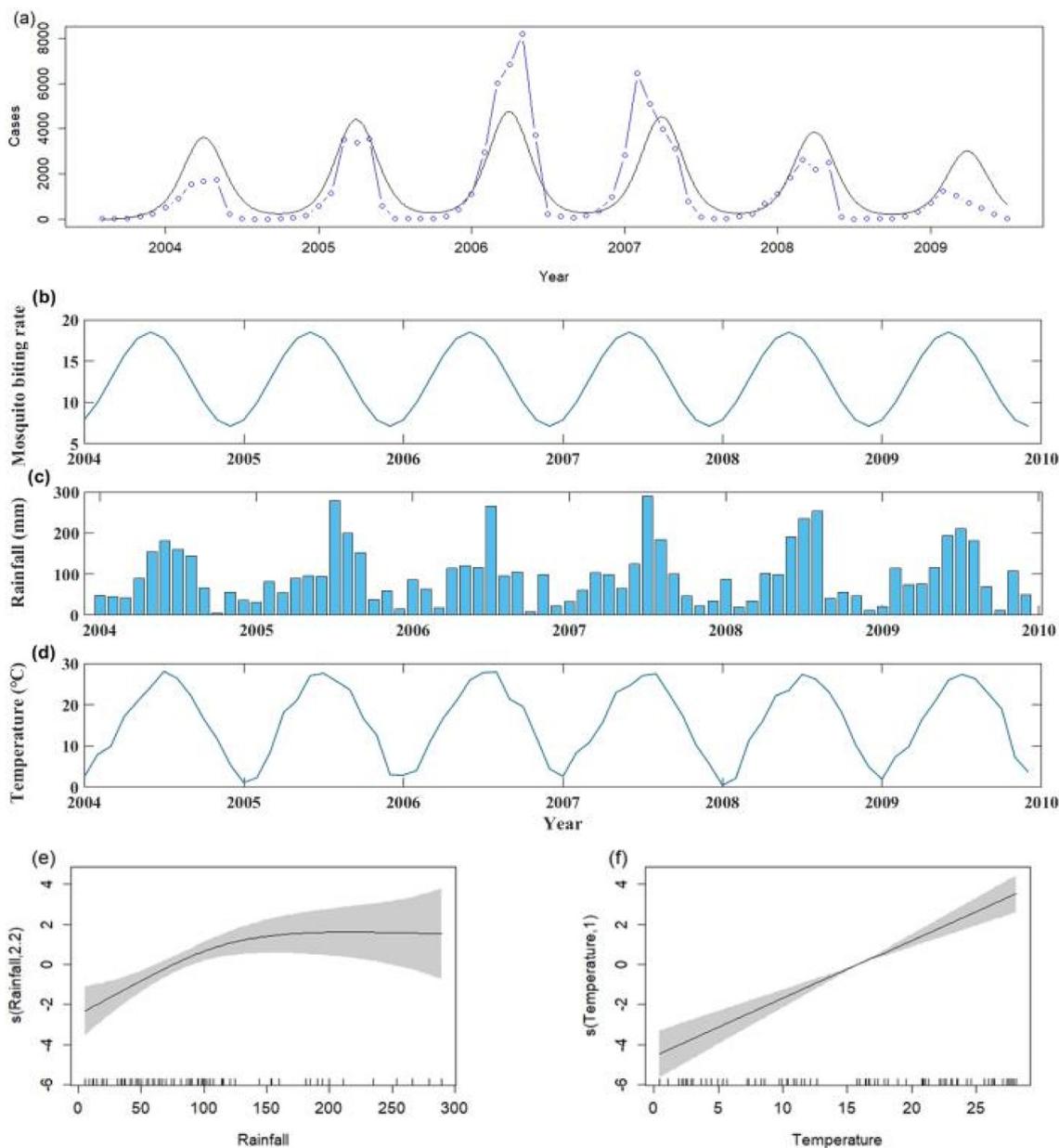

Fig. 3. Simulation results (solid line) and reported cases (circles) from 2004 to 2009 for *P vivax* malaria cases (a). Mosquito biting rate (b), monthly rainfall (c) and monthly mean temperature (d) in Anhui province. The GAM results of effect on transmission rate from rainfall (e) and temperature (f).
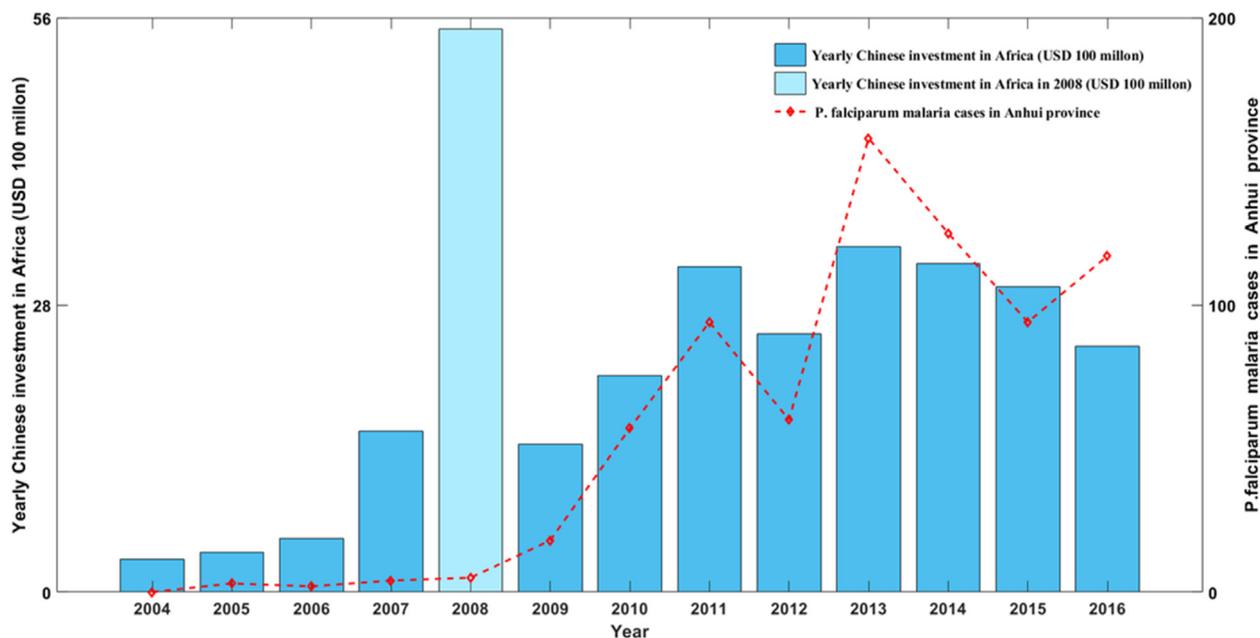
Fig. 4. The number of cases of *P. falciparum* malaria in Anhui province and yearly Chinese investment in Africa.

establishment of the Forum on China-Africa Cooperation (FOCAC) in 2000, Chinese investment to Africa has been on the rise and was at 4.11 Billion Yuan annually in 2017 (Doku et al., 2017; Kolstad & Wiig, 2011). This investment in Africa reflects laborers going to Africa for work and returning, sometimes as *P. falciparum* malaria cases. A similar situation happened in Jiangsu province, where there was a positive relationship between exported laborers to Africa and imported cases in Jiangsu (Liu et al., 2014). We did not have specific data on exported laborers from Anhui, so we used investment in Africa as a proxy. For provinces such as Yunnan where there is local transmission of *P. falciparum* malaria, imported *P. falciparum* malaria cases could further hamper elimination efforts.

This study has important implications for the potential re-introduction of malaria to Anhui province, and other provinces like Anhui. Although *P. vivax* malaria in Anhui has been eliminated, the vector *Anopheles sinensis* is still present. Studies show that imported cases of *P. vivax* increased in the past years with the extensive communication of China with southeast Asia countries (Li et al., 2016). Imported cases could cause the resurgence of local malaria. For example, after malaria had been eliminated in Greece, imported cases was related to the *P. vivax* local resurgence (Danis et al., 2013). This also happened in Sihong, a county in Jiangsu province, China. Sihong experienced an outbreak of *P. vivax* malaria in 2000 after a long-term stable low number of cases (She et al., 2010). This outbreak was related to the imported cases of malaria from its nearby province. Under the condition that the vector *Anopheles sinensis* is still ubiquitous, and considering the situations of long-term trends in climatic factors and ever increasing trend in migration and imported cases in *P. vivax* from southeast Asia, our finding indicates a possibility for the resurgence of *P. vivax* malaria.

Using data from Anhui province we highlight the challenges to malaria elimination in China. While Anhui has been able to eliminate *P. vivax*, the risk of reestablishment by other malaria parasites is evident in a paradoxical negative consequence of economic success. While elimination of malaria caused by *P. vivax* in Anhui is a success achieved through human interventions, we show a risk for resurgence. Whether malaria or other mosquito-borne diseases will re-emerge or not depends on relative contributions of climate and non-climate effects on the transmission and the balance with human interventions. Future study should focus on assessments of relative contribution of impact of factors on malaria transmission that will help us understand the risk level of resurgence or reestablishment by other malaria parasites. Beside trends in climatic factors and imported cases, some other factors and their complex interaction, such as vector movement and possible increasing of mosquito abundance due to pesticide tolerance, should be considered in the future study. Future studies should also focus on malaria in provinces in southern China such as Yunnan province where is a warmer region and malaria is harder to be eliminated in warmer regions.

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Author contributions

EM and DB analyzed the data, conducted modeling and modeling analyses, interpreted results and wrote the first draft of the manuscript. HB interpreted results, helped draft the manuscript; JZ conceived the study, coordinated and designed the study and drafted the manuscript. All authors gave final approval for publication.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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