Model-based risk assessment of dengue fever transmission in Xiamen City, China

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Abstract

Background: Quantitative assessment of the risk of local transmission from imported dengue cases makes a great challenge in China. The purpose of this study is to observe the risk of mosquito-borne transmission in Xiamen City through ecological and insecticide resistance monitoring. Quantitative evaluation of mosquito insecticide resistance, community population and the number of imported cases affecting the transmission of dengue fever in Xiamen was carried out based on transmission dynamics model to investigate the correlation between key risk factors and DF transmission.

Methods: Based on the epidemiological characteristics of DF in Xiamen City, a transmission dynamics model was built to simulate the secondary cases caused by imported cases to evaluate the transmission risk of DF, and to explore the influence of mosquito insecticide resistance, community population and imported cases on the epidemic situation of DF in Xiamen City.

Results: For the transmission model of DF, when the community population was between 10,000 and 25,000, the number of imported DF cases and the mortality rate of mosquitoes were associated with the spread of indigenous DF cases, however, the birth rate of mosquitoes could not gain more effect on the spread of local DF transmission.

Conclusions: Through the quantitative evaluation of the model, this study determined that the resistance of mosquito has an important influence on the local transmission of dengue fever caused by imported cases in Xiamen, and the Breteau index can also affect the local transmission of the disease.

Keywords: Dengue fever, Mathematical model, Risk assessment

Introduction:

Dengue fever (DF) is a viral infectious disease transmitted by *Aedes albopictus* and *Aedes aegypti*, which has four different genotypes (DENV-1, DENV-2, DENV-3, DENV-4) [1, 2]. People infected with dengue virus can have fever, dengue hemorrhagic fever and other clinical symptoms. For severe cases, people suffer from dengue shock syndrome and death[3, 4]. One recent research indicates that there are 390 million (95% confidence interval 284~528 million) new DF cases per year in the world, of which about 12,000 death per year?[1, 5]. Researches have estimated that the incidence of DF had increased nearly 30 times from 1970s? and about one third of the world's population are at risk of DF infection now?[6, 7, 8]. At the same time, due to the lack of effective treatment and vaccination against DF, the epidemic of DF has become one of the major global public health problems, causing serious disease burden to many countries and regions.[2].

In recent years, the annual reported incidence of DF in China has shown an upward trend[9]. In China, Guangdong, Guangxi, Hainan and other areas, have high incidences of DF, the central and northern regions of China also have reported cases of DF[10, 11]. Xiamen City, as a special economic zone in China, has frequent personnel exchanges with countries and regions in Southeast Asia with high incidence of DF cases. Meanwhile, located in the subtropical maritime monsoon climate zone, Xiamen City has suitable temperature and humidity for mosquito-borne transmission. Thus, when dengue virus is imported in the summer, the risk of disease transmission was higher.

Prior to this study, there have been many researches on DF by using mathematical models[12, 13, 14]. A study established a human-vector coupled dynamic model to evaluate the effect of intervention measures taken in DF outbreak[12]. In another study, the generalized mixed linear equation was introduced into the SIR dynamics model, which emphasized the influence of meteorological conditions on *Ae. albopictus* and discussed the influence of meteorological factors on DF propagation[13]. Another study using the time series regression tree analysis have found that the timeliness of DF monitoring system in DF transmission in Zhongshan City, China and meteorological factors have influenced the local DF incidence[14]. Nevertheless, in the research of potential factors affecting DF communication, there is no quantitative evaluation of DF potential communication risk factors based on communication dynamics model in China.

In this paper, we developed a Hosts-Vectors Susceptible–Exposed–Infectious–Asymptomatic–Recovered (SEIAR) transmission dynamics model to quantitatively evaluate the influence of mosquito insecticide resistance and imported cases on DF transmission in Xiamen City. In addition, the SEIAR model could provide with an early warning and forecasting system for controlling DF transmission for public health professionals.

Methods:

Study Area

Xiamen (118°04’04”E, 24°26’46”N), located in the southeast of China, is a coastal city with a population of 4.29 million. It is an important city in Fujian Province and occupies an area of 1700.61 square kilometres. The city has six districts, 26 streets, 12 towns, 361 communities and 147 villages. The city belongs to is subtropical monsoon climate with a yearly average temperature of 21℃ and an average annual rainfall of about 1315mm, from May to August. According to the dengue surveillance data from 2005 to 2019 in Xiamen City, *Ae. Albopictus* was the only vector species in the city, and imported DF cases were accounted for the majority cases[15].

Case definition and case-finding

In the study, an indigenous case was defined as an individual who are infected with DF and have not left this city (current address) within 14 days before the onset of disease. An imported DF cases was defined as an infected patient who had been to DF epidemic regions within 14 days after the onset of disease.

All the DF cases were identified following the diagnostic criteria announced by National Health Commission of the People's Republic of China (WS216-2008) [16]:

a) Suspected case: an individual who had been to DF epidemic regions within 14 days or there has been a DF case around his/her residence or workplace (within a radius of 200m) within one month, along with having one or more symptoms, and no specific diagnosis has been confirmed as other diseases.

b) Clinically diagnosed case: a suspected case with leucopenia or thrombocytopenia, or a suspected case whose serum specific immunoglobulin IgG or IgM test is positive.

c) Laboratory-confirmed case: a clinically diagnose case has one or more of the following test results:

I. Serum tested positive for DENV RNA by real-time PCR;

II. An IgG titer in the recovery period is fourfold higher than that in the acute period;

III. Isolation of the DENV from the blood, tissue or cerebrospinal fluid of a patient with acute infection.

Vector investigation and insecticide resistance monitoring

In order to obtain the relevant parameters in the model, we have assessed the density of *Ae. albopictus* in Xiamen City by three ecological monitoring methods: Breteau index method, Container index method and Human-baited double net trapping method. And mosquito surveillance was performed twice a month in two districts (Huli and Xiang'an) of Xiamen City from May to November in 2020.

Breteau index (BI)

An investigation of BI was conducted from May 1st to November 1st in Xiamen City. In four residential areas of different geographical locations, there were no less than 100 households selected in each monitoring district. For other habitats, such as park, bamboo forests, old tire dumps, waste collecting stations, 50 households need to be collected. Then we recorded the occurrence of *Ae.albopictus* larvae in all indoor and outdoor water containers[17]. For identifying the species, we collected the larvae and brought them back to Center for Disease Control and Prevention (CDC) laboratory for breeding to adult mosquitoes and thereby making the identification (S1 Text p. 1). Finally, we use the following formula to calculate the BI:

$$\mathrm{BI} = \frac{\text{Number of positive containers of } Ae.albopictus}{\text{Number of households surveyed}} \times 100\%$$

Container index (CI)

The site selected for monitoring Container index is consistent with the above-mentioned site, and should be used to monitoring the CI first. In each monitoring district, it has to be no less than 100 containers in four residential areas for 4 days, and the distance between each container is 25~30m. On the fourth day, the adult mosquitoes were monitored, and the species were identified after larvae grew up (S1 Text p. 1,2). We used the following formula to calculate the CI:

$$\mathrm{CI} = \frac{\text{Number of positive containers}}{\text{Number of effective containers}} \times 100\%$$

Human-baited double net trapping（HDN）

Adult mosquito monitoring mainly adopts the method of human-baited double net trapping. We have selected four different habitats, each with two nets more than 100 meters apart. In the afternoon (15:00-18:00), when the vector activity was at its peak, the attractor had both legs exposed in an internal closed mosquito net, and the collector was in trousers[18]. Mosquito repellent was not used during the monitoring process. An electric mosquito absorber was used to collect vector Aedes that fell on the mosquito net, then then leave as soon as possible. The monitoring lasted for 30 minutes and the vector Aedes were collected from each mosquito net (S1 Text p. 2). We use the formula to calculate the inducement index:

$$\mathrm{HDN} = \frac{\text{Number of female mosquitoes captured}}{\text{Number of mosquito nets} \times 30\text{minutes}} \times 60\text{minutes/hours}$$

Insecticide resistance monitoring

It was from the end of 3rd instar to the beginning of 4th instar larvae that were chosen to monitor the insecticide resistance. And we adopted the impregnation technique recommended by WHO (refer to GB/T26347-2010) to determine LC50 and calculate

RR[17]. In the meantime, the WHO recommended contact tube method (refer to GB/T26347-2010) was used to monitor the resistance of adult mosquitoes to insecticides, and thereby the mortality of adult mosquitoes at diagnostic dose was determined. We selected 11 different types of pesticides, namely: 0.2% bendiocarb, 0.2% fenitrothion, 0.03% deltamethrin, 0.04% permethrin, 0.5% propoxur, 0.5% malathion, 0.08% beta-cypermethrin, 0.07% lambda-cyhalothrin, 2% chlorpyrifos, 0.4% beta-cypermethrin. See S1 Text p. 3~6 for specific experimental methods.

Dynamic model of DF transmission

In this study, we built a dynamics model based on SEIAR to simulate the transmission of the dengue virus [12, 19, 20]. And in this model, people were divided into the following five compartments: susceptible (S_p), exposed (E_p), infectious (I_p), asymptomatic (A_p), removed (R_p). Vectors were divided into the following three compartments: susceptible (S_p), exposed (E_p), infectious (I_p). And the interaction between the human and vector is presented in Fig.1.

This model is based on the following assumptions:

(1) The model assumes that the propagation coefficient of S_p and I_m after effective propagation is β_{mp}, the transmission rate from I_i to S_m is β_i, and the transmission rate from S_m to I_p and A_p is β_{pm}. Therefore, at time t, the number of newly infected DF is $\beta_{pm}S_pI_m$, and the number of newly infected vectors is $\beta_iS_mI_i+\beta_{pm}S_m(A_p+I_p)$.

(2) The model assumes that the proportion of recessive infection is q and the latency is $\frac{1}{\omega}$, So at time t, the number of individual who changed from E_p to A_p and I_p were $q\omega_pE_p$ and $(1\text{-}q)\omega_pE_p$.

(3) The model assumes that the time interval from onset to first diagnosis of case I_p was $\frac{1}{\gamma}$, so at time t, the number of people who changed from I_p to R_p is γI_p. In addition, we assume that the infection period of asymptomatic infected person A is $\frac{1}{\gamma'}$, so at time t, the number of people who changed from A to R is $\gamma' A_p$.

(4) The model assumes that the natural vectors mortality rate is b, the natural birth rate is a, and the vertical transmission ratio of dengue virus by mosquitoes is n.

The mathematical model is described by the following ordinary differential equations （ODE）：

$$\frac{dS_p}{dt} = -\beta_{mp} S_p I_m$$

$$\frac{dE_p}{dt} = \beta_{mp} S_p I_m - \omega_p E_p$$

$$\frac{dI_p}{dt} = (1-q)\omega_p E_p - \gamma I_p$$

$$\frac{dA_p}{dt} = q\omega_p - \gamma' A_p$$

$$\frac{dR_p}{dt} = \gamma' A_p + \gamma I_p$$

$$\frac{dS_m}{dt} = ac(N - nI_m) - \left[\beta_i I_i + \beta_{pm}\left(A_p + I_p\right)\right] S_m - b_m$$

$$\frac{dE_m}{dt} = \left[\beta_i I_i + \beta_{pm}\left(A_p + I_p\right)\right] S_m - (\omega_m + b) E_m$$

$$\frac{dI_m}{dt} = \omega_m E_m + acnI_m - bI_m$$

$$\frac{dI_i}{dt} = -\varepsilon I_i - \beta_i S_m I_i$$

$$N_m = S_m + E_m + I_m$$

$$N_p = S_p + E_p + I_p$$

where the seasonality parameter can be modelled by a trigonometric function, according to existing studies. We assume the following function for the parameter c:

$$c = \cos[\frac{2\pi(t-\tau)}{T}]$$

Parameter estimation

There are fifteen parameters in this model (β_i, β_{pm}, β_{mp}, ω_m, ω_p, ε, γ, γ', a, b, c, q, n) according to the literature , see Table 1. The incubation period of dengue virus in human body is usually 4-8 days[20], therefore we selected the value of 6 days as the average, with ω_p =0.1667. It usually takes 8~12 days for imported dengue virus to enter mosquito host and cause its onset.[19], thus the value of 10 days was chosen in the model, with ω_m=0.1000 per day. The proportion of asymptomatic infections is usually 68.75%[21], so q=0.6875. The infectious period is 3~14 days[19, 22], we selected 7 days in the simulation, thus $\gamma=\gamma'$=0.1429. Based on a previous study, the initial values of birth and mortality rate of mosquitoes was set as a=b=0.0714[19]. In addition, with the constant change of resistance to mosquito-borne insecticide, we set the value range of a and b to 1/50~1/14 according to our study. The vertical transmission rate of dengue virus DENV-1 through vertical infection ranged from 1.4% to 17.4%[23], which was assumed it to be 10.0%, so n=0.1000.

Evaluate the risk of DF transmission in different conditions

We assessed the transmission risk of DF in Xiamen City through SEIAR model. According to practical experience and previous studies, we included the following factors as transmission risk factors into our research: community population, the number of imported cases, larvae density, adult vector density, mosquito insecticide resistance. Consequently, in this study, BI method was used to assess the larvae density of the vector and light-trap method was used to measure assess the adult vector density. The changes in mosquito mortality reflect the intensity of mosquito-borne insecticide resistance.

According to the community situation of indigenous cases in Xiamen City in 2019, the community population was set as 10000, 15000 20000 and 25000, and the parameter of imported cases were 1 to 60. Our previous studies on insecticide resistance have determined that the mosquito birth and mortality rate would be set as 1/50, 1/38, 1/26 and 1/14. Simultaneously, the number of susceptible mosquito-borne could be reflected by changing the mosquito density, which was 1, 2, 3, 4 and 5, respectively, in BI. Therefore, we have set the following scenarios to quantitatively assess the transmission risk of DF in Xiamen City:

Scenario1: We set the community population as 10,000, and BI values were 1, 2, 3, 4, and 5. The mortality rates of mosquitoes were set as 1/50, 1/38, 1/26 and 1/14 respectively. We would like to see how many dengue cases were imported, and which could cause the spread of indigenous secondary cases.

Scenario2: We set the community population as 15,000, BI values were 1, 2, 3, 4, and 5, respectively; The mortality rates of mosquitoes were set as 1/50, 1/38, 1/26 and 1/14, respectively. And to see how many dengue cases were imported, which could cause the spread of indigenous secondary cases.

Scenario3: We set the community population as 20,000, BI values were 1, 2, 3, 4, and 5 respectively; The mortality rates of mosquitoes were set as 1/50, 1/38, 1/26 and 1/14 respectively. And to see how many dengue cases were imported, which could cause the spread of indigenous secondary cases.

Scenario4: We set the community population as 25,000, BI values were 1, 2, 3, 4, and 5 respectively; The mortality rates of mosquitoes were set as 1/50, 1/38, 1/26 and 1/14 respectively. And to see how many dengue cases were imported, which could cause the spread of indigenous secondary cases.

Simulation and statistical analysis

We used Berkeley Madonna ver.8.3.18 (developed by Robert Macey and George Oster of the University of California at Berkeley, CA, USA) for parameter fitting and model simulation. The goodness-of-fitting was assessed by least root-mean-square error between simulated and observed number of new indigenous cases per day between August 24th and November 5th. The simulation method was the Runge–Kutta method of order four. Differential equations were solved by the step of 0.02. Meanwhile, the goodness of fit was judged by the coefficient of determination (R^2) value.

Results

Epidemiological characteristics of DF in Xiamen City

In 2019, a total of 138 cases of DF were reported in Xiamen City, and there were 19 indigenous cases and 119 imported cases. The distribution of all DF cases in Xiamen City is shown in Fig.2, among which indigenous cases were mainly reported in Huli District, Siming District and Jimei District. The imported cases were reported in all districts of Xiamen City. The number of new cases in Xiamen City per month is shown in Fig.3. The first indigenous case was reported in the Jinshan community of Huli District on August 24th,2019. The peak of DF incidence was from July to October, and the number of DF cases reported in these four months accounts for 75% of the total reported cases in the whole year. The population distribution of DF cases in Xiamen

City in 2019 is shown in Table 2. Male patients were predominate in imported cases, while females outnumbered males in local cases. Meanwhile, most of the reported DF cases were adults aged between 20 and 50 years old, with no cases reported in people younger than 10 years old. In addition, a higher proportion of cases were reported in commercial services and domestic activities.

Investigation on mosquito-borne ecology and insecticide resistance monitoring

We conducted a household survey of *Ae. Albopictus* between May and October 2020. A total of 9060 *Ae. Albopictus* were captured, and 693 Aedes larvae were positive in water accumulation of Aedes larvae were found, see Fig.4(A). The average value of BI is 7.6, among which the average value of BI in Huli District is 9.3 and that in Xiang'an District is 6.1. The monitoring results of BI are shown in Table 3. It is noticeable that the BI index of Xiamen City is higher than the safety level of 5 from May to October 2020. Besides, from May to October 2020, we have placed a total of 9840 mosquito container in Xiamen City. Among them, 8893 were recovered with rate of 90.4%. The results showed that there were 518 positive traps, and the average index of CI was 5.8, which was higher than the safety level of 5 from June to October. Therefore, it can be found that the change of CI is similar to that of BI; and the value is generally lower than BI, see Fig.4(B).

For monitoring of adult mosquito, we used the Human-baited double net trapping technique. From May to October, a total of 276 double-layered accounts were deployed. Finally, it was calculated that 1.7 mosquito nets were detected per hour, of which the highest was 2.2 in July, and the safety level was higher than 2 in both June and July, see

Fig.4(B).

Therefore, we monitored the insecticide resistance of *Ae. albopictus* in Xiamen City, the results demonstrated that knock-down rate of mosquitoes at 1 hour, the corrected mortality rate for 24 hours and the insecticide resistance are shown in Table.3 below. Furthermore, the resistance times and resistance result of *Ae. albopictus* larvae exposed to parathion, prepoxur and pyriproxyfen are shown in Table.4 below.

Risk assessment of different transmission models

In this study, by adjusting different parameters in the model, we observed whether different imported cases can cause the transmission of indigenous DF cases, and quantitatively assessed the transmission risk of DF in Xiamen City， as shown in Fig.5. In scenario 1, we set the community population to 10,000. At this point, by changing BI value, birth rate and mortality rate of mosquitoes, we found that 58 DF cases imported from the community can cause indigenous DF cases when mosquito mortality rate is 1/14 and BI value is 1. With the BI values changing from 2, 3, 4 to 5, the imported case parameters are set to 29, 19, 14 and 11 cases respectively, which can generate indigenous secondary cases. On the other hand, when the BI value is fixed at 1, the mosquito mortality rate changes to 1/50, so it takes 10 imported cases to cause the spread of indigenous cases. However, when changing the birth rate parameters, the impact on the model is limited, and the input of dengue cases within the set range cannot produce local secondary cases. As mosquito mortality declines and BI value increases, so did the number of imported cases that can cause the spread of local dengue cases, see Fig.5(A).

In scenario 2, the community population is 15,000. At this time, the BI value is set to 1, the mosquito mortality rate is 1/14, and 25 imported cases are needed to produce local secondary cases. However, when the mortality rate is 1/14 and the BI value is 5, or when the mortality rate is 1/50 and the BI value is 1, only 5 imported cases are needed to produce local secondary cases. At the same time, we also found that when the BI value increased, the mortality dropped to a certain range, and only one imported case could cause local dengue fever cases, and the risk of DF transmission was relatively high at this time， see Fig.5(B).

In Scenario 3 and Scenario 4, the community population reaches 20,000 and 25,000 respectively. The results showed that under the same BI value and mosquito mortality conditions, the larger the community population, the smaller the number of imported cases needed to cause local dengue fever transmission, and the higher the transmission risk. Moreover, we changed the BI value and mosquito mortality, and found that the lower the mortality rate, the higher the BI, the higher the transmission risk of dengue fever. Especially when the BI value is above 3 and the mortality rate is less than 1/26, only one dengue fever case is needed to produce an indigenous DF case， see Fig.5(C) and Fig.5(D).

Discussion

DF cases were first reported in Foshan city, Guangdong province in China in 1978. The dengue virus then spreaded widely to Guangdong, Guangxi, Hainan and Fujian provinces, causing hundreds of thousands of cases[24]. As a main economic city in Fujian Province, Xiamen has a comfortable climate for DF and a large population mobility, resulting in a heavy public health burden caused by DF. In this study, we used the transmission dynamics model to quantitatively evaluate the influence of community population, mosquito density and mosquito-borne insecticide resistance on DF transmission in Xiamen City, so as to promote the formulation of more effective prevention and control strategies.

Population risk assessment:

In 2019, the distribution of DF cases in Chinese mainland has expanded significantly, with 1066 regions reporting imported cases and 550 regions reporting indigenous cases[25]. From 2005 to 2019, the imported cases of DF in Xiamen City showed a rapid increasing trend. In 2019, Xiamen reported a total of 119 imported cases from multiple regions and countries, mainly distributed in Huli and Siming District. The public health and epidemic prevention departments of these two administrative districts need to pay extra attention to the transmission of imported cases to secondary cases in the local areas. The indigenous cases were reported mainly from August to October, for the main reasonthat the temperature and humidity in summer are suitable for mosquito-borne growth and reproduction, leading to the local spread of dengue virus[12, 26]. Imported cases have also been reported in 11 months except March. We believe that Xiamen City, as a coastal city, has frequent communication with Southeast Asian countries and regions, and there are many imported cases reported during the high incidence of DF in summer. Accordingly, the customs and epidemic prevention departments should pay attention to the movement of personnel from areas with high incidence of DF and do a good job of port education on DF prevention, which can effectively reduce the local spread and even outbreak of DF. The reported cases are mainly concentrated in the middle-aged and young people aged 21~50, and the majority are professional engaged in commercial services. According to the study, these people are more susceptible to DF infection due to their active work. Therefore, the education and medical investigation of these people should be strengthened as part of daily prevention work.

Mosquito vector risk assessment:

According to our research, we selected Huli District and Xiang 'an District of Xiamen City to investigate mosquito-borne ecology and monitor insecticide resistance. The results showed that the average value of BI and CI in Huli District were 9.3、5.3, then 6.1 and 6.4 in Xiang 'an District, all of which were higher than the safety level of 5. In these cases, larvae proliferated rapidly, increasing the risk of dengue virus transmission[26]. At this point, when imported cases occur in the jurisdiction, DF might spread or even spread locally. At the same time, we measured the number of adult mosquitoes by HDN method, and the results showed that the average of HDN in Huli District was 3.4, which gradually decreased after August, while the HDN in Xiang 'an District was always at a low level, just similar to the number of indigenous cases. As previously monitored, *Ae. albopictus* in Xiamen is sensitive to malathion and propoxur, and has high resistance to pyrethroid insecticides such as deltamethrin, beta-cypermethrin and beta-cypermethrin. Thus, we selected mosquitoes in two districts to carry out insecticide resistance tests. The results illustrated that *Ae. albopictus* in Huli District was sensitive to warfarin, fenitrothion, propoxur, malathion and chlorpyrifos, and had higher resistance to other insecticides. *Ae. albopictus* in Xiang 'an District was only sensitive to warfarin, fenitrothion and chlorpyrifos, showing different resistance scenarios? to other insecticides. Based on previous studies, mosquito resistance to chemical insecticides is inevitable, so we need to avoid using chemical insecticides blindly[27, 28]. The local public health authorities can scientifically assess the risk of mosquito-borne transmission on the basis of experiments, rationally select sensitive and low-resistance pesticides, and use them in crop rotation on an annual basis. This can effectively precent the increase of resistance and achieve the purpose of reducing mosquito density.

Model evaluation:

In this study, a dynamics model was used to investigate the impact of potential risk factors such as community population, number of imported cases, mosquito vector density and mosquito insecticide resistance on the local transmission of DF in Xiamen. We set up four scenarios with simulated community population of 10,000, 15,000, 20,000 and 25,000, and input different numbers of DF cases to quantitatively evaluate the spread of indigenous DF cases. In the model, the density of mosquito vectors is reflected by the change of BI index, while the insecticide resistance of mosquitoes is assumed to change the birth rate and mortality rate of mosquitoes. According to our simulation results, when the community population is 10,000, the mortality rate of mosquitoes is 1/14 of the highest value in the set range, and the BI index is 1, both insecticide resistance and mosquito vector density of mosquitoes are at the lowest value, so 58 imported DF cases are needed to cause the spread of indigenous DF cases. As the density of mosquito vectors gradually increases, the number of imported cases required for indigenous DF transmission gradually decreases. Similarly, when the mortality rate of mosquitoes is reduced to 1/50, that is, mosquito resistance to insecticide is very high, only 10 imported cases can result in secondary local cases. This result suggests that public health departments should pay attention in eliminating mosquito vectors and choose sensitive and low-resistance chemical. In addition, in the model, we found that the birth rate of mosquitoes has little influence on the model, when we change the birth rate parameters, a certain number of dengue cases are input within the set range, which cannot cause the spread of indigenous cases.

When the community population gradually increased to 15,000,20,000 and 25,000, and when the mosquito mortality rate was 1/14 and BI value was 1, the number of imported cases needed to cause indigenous DF cases was 25,14 and 9 respectively, that is, when mosquito-borne insecticide resistance and mosquito-borne density were consistent, the community population base had a great influence on local transmission of DF. Therefore, we should do well in health education and health prevention and control in large communities to effectively improve the prevention and control effect of DF. In the meantime, we found that when the community population is more than 20,000, the mosquito density is more than 3, and the mortality rate of mosquitoes is less than 1/38, only one case can be imported, which can cause the spread of indigenous DF. At this time, the risk of transmission is very high, so mosquito prevention and control work mainly in large communities is needed to prevent the synergistic effect of these key factors from causing the spread of indigenous DF.

The prevention and control of dengue fever is a social work, which requires the participation of health and epidemic prevention departments and the public. For places where DF is less threatening, we can mobilize the masses to carry out environmental prevention and control measures through community departments, so as to reduce the mosquito density in the external environment. For places where DF is a great threat, we suggest that public health departments should adopt chemical control during the high incidence period of DF (July to October) to reduce the risk of DF transmission, and select sensitive and low-resistance chemical insecticides to reduce the risk of DF transmission.

Limitation

It is worth noting that there are some limitations to our research. First of all, infectious disease outbreak assessment includes three steps and two factors, but in this study, we did not discuss the impact of environmental factors on mosquito vectors. Secondly, because DF is transmitted through vest, we can't evaluate the transmission ability of dengue fever by calculating R_0 (the basic reproduction number) or R_{eff} (the effective reproduction number).

Conclusions

In this study, propagation dynamics model was used to assess and predict the risk of DF. We emphasize that imported cases, community population, mosquito density and insecticide resistance play a key role in local DF transmission. Mosquito insecticide resistance was identified as the most critical factor for evaluating DF communication risks and implementing management control measures. The change of mosquito-borne birth rate and mortality rate can be regarded as indicators of mosquito-borne insecticide resistance. We suggest that detection of threshold effects of the number of imported cases, mosquito density and the changes of birth rate and mortality rate of local mosquito vectors tested by the transmission dynamics model can be used to predict and evaluate the risk of dengue fever epidemic. The identified factors are beneficial to the establishment of early warning and monitoring system of infectious diseases.

Supplementary information

Additional file 1: Text S1 Vector investigation and insecticide resistance monitoring methods

Abbreviations

DF: Dengue fever; SEIAR: Susceptible–Exposed–Infectious–Asymptomatic–Recovered; SEI: Susceptible-Exposed-Infectious; CDC: Center for Disease Control and Prevention; BI: Breteau index; CI: Container index; HDN: Human-baited double net trapping; WHO: World Health Organization

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Availability of data and materials

Data supporting the conclusions of this article are included within the article.

Authors' contributions

Tianmu Chen, Zhinan Guo, Weikang Liu and Xingchun Liu designed research; Zhinan Guo, Weikang Liu, Xingchun Liu, Buasiyamu Abudunaibi, Sihan Wu, Bin Deng, Tianlong Yang, Jiefeng Huang, Lei Lei and Zeyu Zhao analyzed data, Weikang Liu, Zhinan Guo, Buasiyamu Abudunaibi, Li Luo and Sihan Wu completed the experiment; Tianmu Chen, Zhinan Guo, Weikang Liu, Xingchun Liu, Buasiyamu Abudunaibi, Bin Deng, Lei Lei, Zeyu Zhao, Zhuoyang Li, Peihua Li, Chan Liu and Li Luo conducted the research and analyzed the results; Tianmu Chen, Zhinan Guo, Weikang Liu, Xingchun Liu, Buasiyamu Abudunaibi and Li Luo wrote the manuscript. Qingqing Hu and Weikang Liu He revised the format and language. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Dengue fever disease control and mosquito vector monitoring are part of CDC's routine responsibility in Xiamen Province, China. Therefore, this study does not need institutional review and informed consent. All data analysed data are anonymous.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Reference

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496 7446:504-7; doi: 10.1038/nature12060. https://www.ncbi.nlm.nih.gov/pubmed/23563266.
2. Khetarpal N, Khanna I. Dengue Fever: Causes, Complications, and Vaccine Strategies. J Immunol Res. 2016;2016:6803098; doi: 10.1155/2016/6803098. https://www.ncbi.nlm.nih.gov/pubmed/27525287.
3. Murphy BR, Whitehead SS. Immune response to dengue virus and prospects for a vaccine. Annu Rev Immunol. 2011;29:587-619; doi: 10.1146/annurev-immunol-031210-101315. https://www.ncbi.nlm.nih.gov/pubmed/21219187.
4. Endy TP, Yoon IK, Mammen MP. Prospective cohort studies of dengue viral transmission and severity of disease. Curr Top Microbiol Immunol. 2010;338:1-13; doi: 10.1007/978-3-642-02215-9_1. https://www.ncbi.nlm.nih.gov/pubmed/19802574.
5. Lee HS, Nguyen-Viet H, Nam VS, Lee M, Won S, Duc PP, et al. Seasonal patterns of dengue fever and associated climate factors in 4 provinces in Vietnam from 1994 to 2013. BMC Infect Dis. 2017;17 1:218; doi: 10.1186/s12879-017-2326-8. https://www.ncbi.nlm.nih.gov/pubmed/28320341.
6. Chen Y, Zhao Z, Li Z, Li W, Li Z, Guo R, et al. Spatiotemporal Transmission Patterns and Determinants of Dengue Fever: A Case Study of Guangzhou, China. Int J Environ Res Public Health. 2019;16 14; doi: 10.3390/ijerph16142486. https://www.ncbi.nlm.nih.gov/pubmed/31336865.

7. Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, Hoen AG, et al. Refining the Global Spatial Limits of Dengue Virus Transmission by Evidence-Based Consensus. Plos Neglect Trop D. 2012;6 8; doi: ARTN e1760
10.1371/journal.pntd.0001760. <Go to ISI>://WOS:000308497100009.

8. Chen R, Vasilakis N. Dengue--quo tu et quo vadis? Viruses. 2011;3 9:1562-608; doi: 10.3390/v3091562. https://www.ncbi.nlm.nih.gov/pubmed/21994796.

9. Cheng Q, Jing Q, Spear RC, Marshall JM, Yang Z, Gong P. Climate and the Timing of Imported Cases as Determinants of the Dengue Outbreak in Guangzhou, 2014: Evidence from a Mathematical Model. PLoS Negl Trop Dis. 2016;10 2:e0004417; doi: 10.1371/journal.pntd.0004417. https://www.ncbi.nlm.nih.gov/pubmed/26863623.

10. Li C, Lu Y, Liu J, Wu X. Climate change and dengue fever transmission in China: Evidences and challenges. Sci Total Environ. 2018;622-623:493-501; doi: 10.1016/j.scitotenv.2017.11.326. https://www.ncbi.nlm.nih.gov/pubmed/29220773.

11. Lai S, Huang Z, Zhou H, Anders KL, Perkins TA, Yin W, et al. The changing epidemiology of dengue in China, 1990-2014: a descriptive analysis of 25 years of nationwide surveillance data. BMC Med. 2015;13:100; doi: 10.1186/s12916-015-0336-1. https://www.ncbi.nlm.nih.gov/pubmed/25925417.

12. Yi B, Chen Y, Ma X, Rui J, Cui JA, Wang H, et al. Incidence dynamics and investigation of key interventions in a dengue outbreak in Ningbo City, China. PLoS Negl Trop Dis. 2019;13 8:e0007659; doi: 10.1371/journal.pntd.0007659. https://www.ncbi.nlm.nih.gov/pubmed/31415559.

13. Li R, Xu L, Bjornstad ON, Liu K, Song T, Chen A, et al. Climate-driven variation in mosquito density predicts the spatiotemporal dynamics of dengue. Proc Natl Acad Sci U S A. 2019;116 9:3624-9; doi: 10.1073/pnas.1806094116. https://www.ncbi.nlm.nih.gov/pubmed/30808752.

14. Liu KK, Wang T, Huang XD, Wang GL, Xia Y, Zhang YT, et al. Risk assessment of dengue fever in Zhongshan, China: a time-series regression tree analysis. Epidemiol Infect. 2017;145 3:451-61; doi: 10.1017/S095026881600265X. https://www.ncbi.nlm.nih.gov/pubmed/27873572.

15. Lambrechts L, Scott TW, Gubler DJ. Consequences of the expanding global distribution of Aedes albopictus for dengue virus transmission. PLoS Negl Trop Dis. 2010;4 5:e646; doi: 10.1371/journal.pntd.0000646. https://www.ncbi.nlm.nih.gov/pubmed/20520794.

16. Peng HJ, Lai HB, Zhang QL, Xu BY, Zhang H, Liu WH, et al. A local outbreak of dengue caused by an imported case in Dongguan China. BMC Public Health. 2012;12:83; doi: 10.1186/1471-2458-12-83. https://www.ncbi.nlm.nih.gov/pubmed/22276682.

17. Liu H, Liu L, Cheng P, Yang L, Chen J, Lu Y, et al. Bionomics and insecticide resistance of Aedes albopictus in Shandong, a high latitude and high-risk dengue transmission area in China. Parasit Vectors. 2020;13 1:11; doi: 10.1186/s13071-020-3880-2. https://www.ncbi.nlm.nih.gov/pubmed/31918753.

18. Tangena JA, Thammavong P, Hiscox A, Lindsay SW, Brey PT. The Human-Baited

Double Net Trap: An Alternative to Human Landing Catches for Collecting Outdoor Biting Mosquitoes in Lao PDR. PLoS One. 2015;10 9:e0138735; doi: 10.1371/journal.pone.0138735. https://www.ncbi.nlm.nih.gov/pubmed/26381896.

19. Andraud M, Hens N, Marais C, Beutels P. Dynamic epidemiological models for dengue transmission: a systematic review of structural approaches. PLoS One. 2012;7 11:e49085; doi: 10.1371/journal.pone.0049085. https://www.ncbi.nlm.nih.gov/pubmed/23139836.

20. Cheng Q, Jing QL, Spear RC, Marshall JM, Yang ZC, Gong P. Climate and the Timing of Imported Cases as Determinants of the Dengue Outbreak in Guangzhou, 2014: Evidence from a Mathematical Model. Plos Neglect Trop D. 2016;10 2; doi: ARTN e0004417

10.1371/journal.pntd.0004417. <Go to ISI>://WOS:000372567300034.

21. Wang T, Wang M, Shu B, Chen XQ, Luo L, Wang JY, et al. Evaluation of inapparent dengue infections during an outbreak in Southern China. PLoS Negl Trop Dis. 2015;9 3:e0003677; doi: 10.1371/journal.pntd.0003677. https://www.ncbi.nlm.nih.gov/pubmed/25826297.

22. Tang B, Xiao Y, Tang S, Wu J. Modelling weekly vector control against Dengue in the Guangdong Province of China. J Theor Biol. 2016;410:65-76; doi: 10.1016/j.jtbi.2016.09.012. https://www.ncbi.nlm.nih.gov/pubmed/27650706.

23. Bosio CF, Thomas RE, Grimstad PR, Rai KS. Variation in the efficiency of vertical transmission of dengue-1 virus by strains of Aedes albopictus (Diptera: Culicidae). J Med Entomol. 1992;29 6:985-9; doi: 10.1093/jmedent/29.6.985. https://www.ncbi.nlm.nih.gov/pubmed/1460640.

24. Mu D, Cui JZ, Yin WW, Li Y, Chen QL. [Epidemiological characteristics of dengue fever outbreaks in China, 2015-2018]. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41 5:685-9; doi: 10.3760/cma.j.cn112338-20190715-00523. https://www.ncbi.nlm.nih.gov/pubmed/32447907.

25. Li J, Xiong Y, Wu W, Liu X, Qu J, Zhao X, et al. Zika Virus in a Traveler Returning to China from Caracas, Venezuela, February 2016. Emerging infectious diseases. 2016;22 6:1133-6; doi: 10.3201/eid2206.160273. https://www.ncbi.nlm.nih.gov/pubmed/27070735.

26. Williams CR, Mincham G, Ritchie SA, Viennet E, Harley D. Bionomic response of Aedes aegypti to two future climate change scenarios in far north Queensland, Australia: implications for dengue outbreaks. Parasit Vectors. 2014;7:447; doi: 10.1186/1756-3305-7-447. https://www.ncbi.nlm.nih.gov/pubmed/25240382.

27. Dusfour I, Vontas J, David JP, Weetman D, Fonseca DM, Corbel V, et al. Management of insecticide resistance in the major Aedes vectors of arboviruses: Advances and challenges. PLoS Negl Trop Dis. 2019;13 10:e0007615; doi: 10.1371/journal.pntd.0007615. https://www.ncbi.nlm.nih.gov/pubmed/31600206.

28. Achee NL, Grieco JP, Vatandoost H, Seixas G, Pinto J, Ching-Ng L, et al. Alternative strategies for mosquito-borne arbovirus control. PLoS Negl Trop Dis. 2019;13 1:e0006822; doi: 10.1371/journal.pntd.0006822. https://www.ncbi.nlm.nih.gov/pubmed/30605475.

Figure legends

Fig.1 The flowchart of the development of the dengue fever transmission model

Fig.2 Geographical location of the study area and distribution of DF cases in Xiamen in 2019. Filled red circle represents the indigenous cases and filled green circle represents the imported cases.

Fig.3 Reported cases of DF in Xiamen City, P.R. China, in 2019.

Fig.4 Monitoring results of mosquito-borne ecology. (a) Breteau index; (b)Container index; (c) Human-baited double net trapping.

Fig.5 Quantitative assessment results of DF transmission risk in Xiamen City.

(a) 10000 population community; (b)15000 population community; (c) 20000 population community; (d) 25000 population community;

Notes: The vertical index represents the mortality of mosquitoes, and the value is 1/15, 1/26, 1/38 and 1/50 respectively, and the horizontal indicator represents the value of BI, which are 1,2,3,4,5 respectively. The values in each grid represent the number of dengue cases that need to be imported to cause local transmission, and the darker the grid, the more dengue cases need to be imported.

Tables

Table 1: Parameter definitions and values

Parameter	Description	Unit	Value	Range	Method
β_i	Transmission relative rate from input case to mosquitoes	1	5.11892×10^{-6}	≥0	Curve fitting
β_{pm}	Transmission relative rate from human to mosquitoes	1	8.01142×10^{-6}	≥0	Curve fitting
β_{mp}	Transmission relative rate from mosquitoes to human	1	1.24107×10^{-5}	≥0	Curve fitting
ω_m	Incubation relative rate of mosquitoes infection	day^{-1}	1/10	0.0833~0.1250	References[19]
ω_p	Incubation relative rate of human infection	day^{-1}	1/6	0.1250~0.2500	References[20]
ε	Input case recovery ratio	1	0.1429	0.0714~0.3333	Curve fitting
γ	Removed relative rate of infectious individuals	day^{-1}	1/7	0.0714~0.3333	References[19, 22]
γ'	Removed relative rate of asymptomatic individuals	day^{-1}	1/7	0.0714~0.3333	References[19, 22]
a	Daily birth rate of mosquitoes	day^{-1}	1/14	0~1/14	References[19, 22]
b	Daily mortality rate of mosquitoes	day^{-1}	1/14	0~1/14	References[19, 22]
c	Seasonality parameter of the mosquitoes population	1	See text	0~1	Curve fitting
τ	Simulation delay of the initial time in the whole season	day	242	≥0	Analysis on the reported data
T	Duration of the cycle	day	365	≥0	Analysis on the reported data
q	Proportion of human asymptomatic infection	1	0.6875	0~1	References[21]
n	Proportion of transovarial transmission	1	0.1	0.0140–0.1740	References[23]

Table 2: The population distribution of DF cases in Xiamen City in 2019

		Indigenous cases	**Imported cases**
Gender	Male	8	94
	Female	11	25
Age	≤10	-	-
	11~20	2	4
	21-30	6	39
	31-40	2	39
	41-50	5	34
	51-60	1	2
	≥61	3	1
Occupation	Commercial service	7	21
	Student	2	4
	Staff member	3	1
	Worker	2	2
	Housework and unemployment	4	18
	Farmer	-	1
	Catering food industry	-	7
	Others	1	64

Table 3: Insecticide resistance of *Ae. albopictus*

Pesticides	(Adjusted) mortality rate		Population determine	
	Huli	Xiang'an	Huli	Xiang'an
0.2% bendiocarb	100%	100%	Sensitive species	Sensitive species
0.2% fenitrothion	96%	99.24%	Likely resistant species	Sensitive species
0.03%Deltamethrin	93%	24.07%	Likely resistant species	Resistant species
0.04% Permethrin	64%	53.57%	Resistant species	Resistant species
0.5% Propoxur	100%	95.71%	Sensitive species	Likely resistant species
0.5% Malathion	99%	99.31%	Sensitive species	Sensitive species
0.08%Beta-cypermethrin	38%	30.89%	Resistant species	Resistant species
0.07%Lambda-cyhalothrin	75%	66.67%	Resistant species	Resistant species
2% Chlorpyrifos	100%	100%	Sensitive species	Sensitive species
0.4%Beta-cypermethrin	43%	68.87%	Resistant species	Resistant species

Table 4 Insecticide resistance of *Ae. albopictus* larvae

Pesticide	Population	Regression equation	LC50 （mg/L）	95%CI	Resistance multiple
Disulphion	Sensitive strain	y=21.469+8.712x	0.003434	0.003306,0.003554	
	Huli	y=9.652+4.099x	0.004417	0.004123,0.004705	1.29
	Xiang’an	y=9.174+4.126x	0.005978	0.005569,0.006477	1.74
Propoxur	Sensitive strain	y=7.226x -0.146	1.048	0.948,1.128	
	Huli	y=4.617x -2.378	3.273988	3.084269,3.491614	3.12
	Xiang’an	y=3.331x-1.644	3.114534	2.844933,3.423473	2.97
Pyripropoxyfen	Sensitive strain		0.00001006	0.00000624,0.00001449	
	Huli	y=1.907+0.531x	0.000257	0.000154,0.000403	25.55
	Xiang’an	y=2.837+0.740x	0.000148	0.000094,0.000224	14.71

Figures

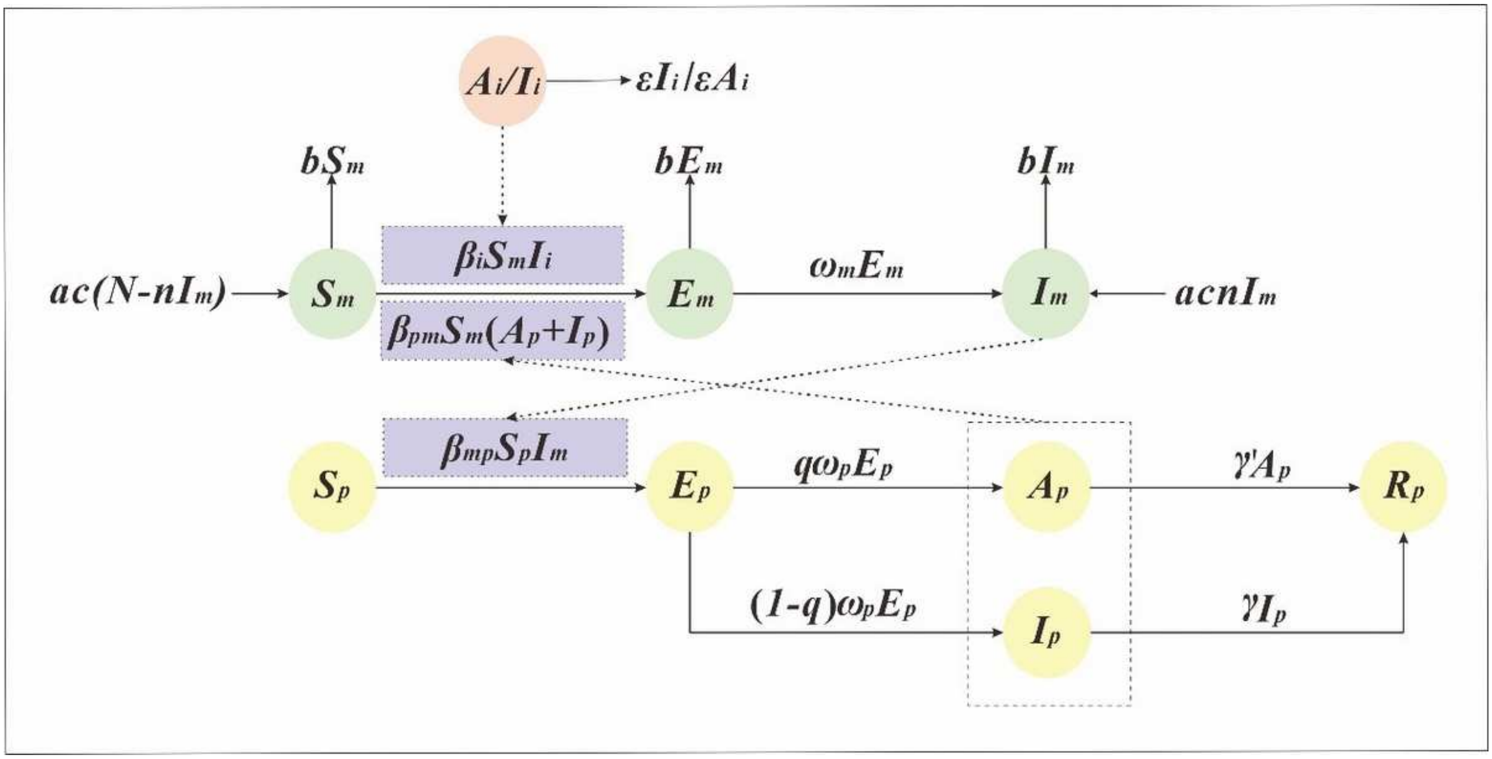

Figure 1

The flowchart of the development of the dengue fever transmission model

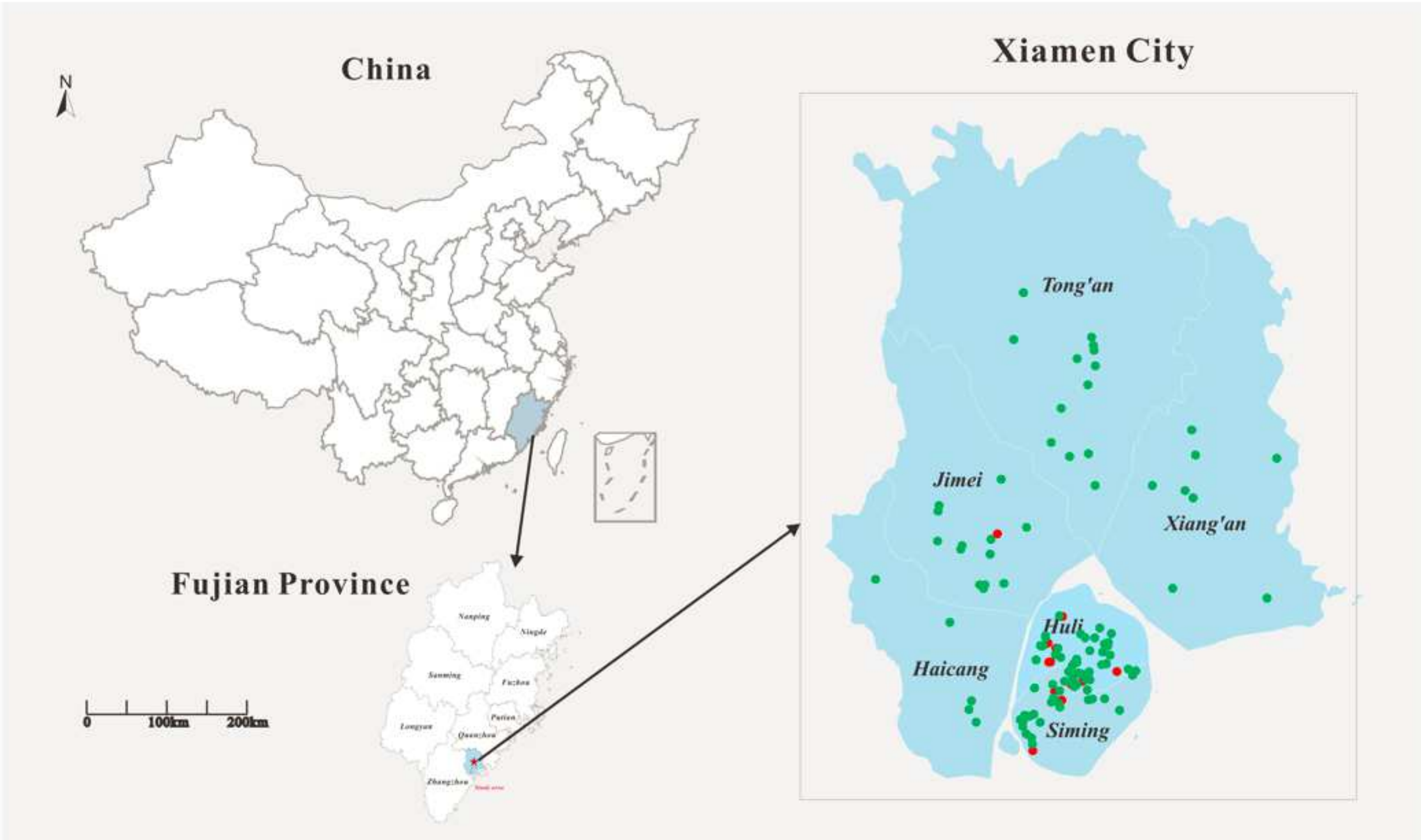

Figure 2

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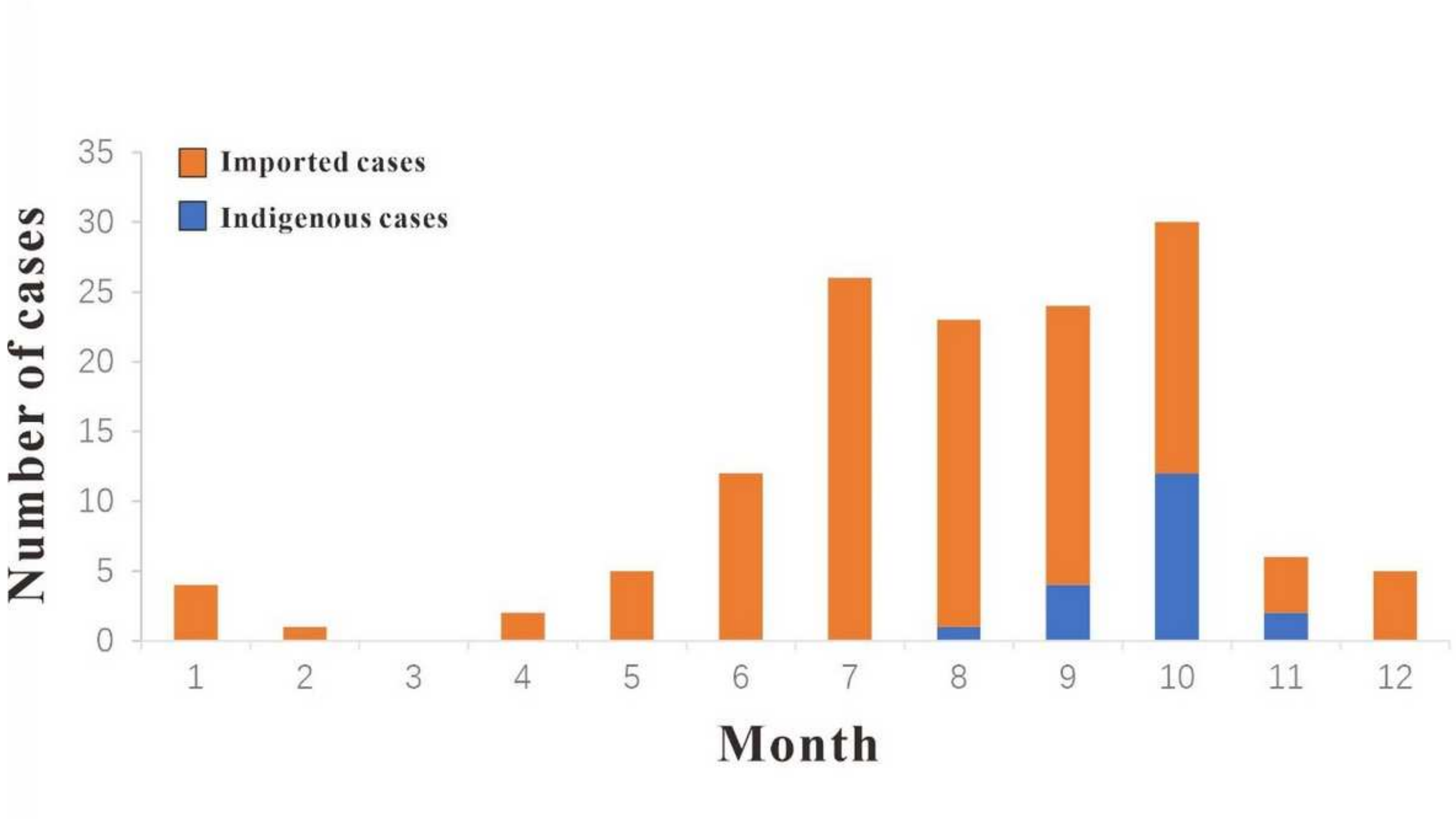

Figure 3

Reported cases of DF in Xiamen City, P.R. China, in 2019.

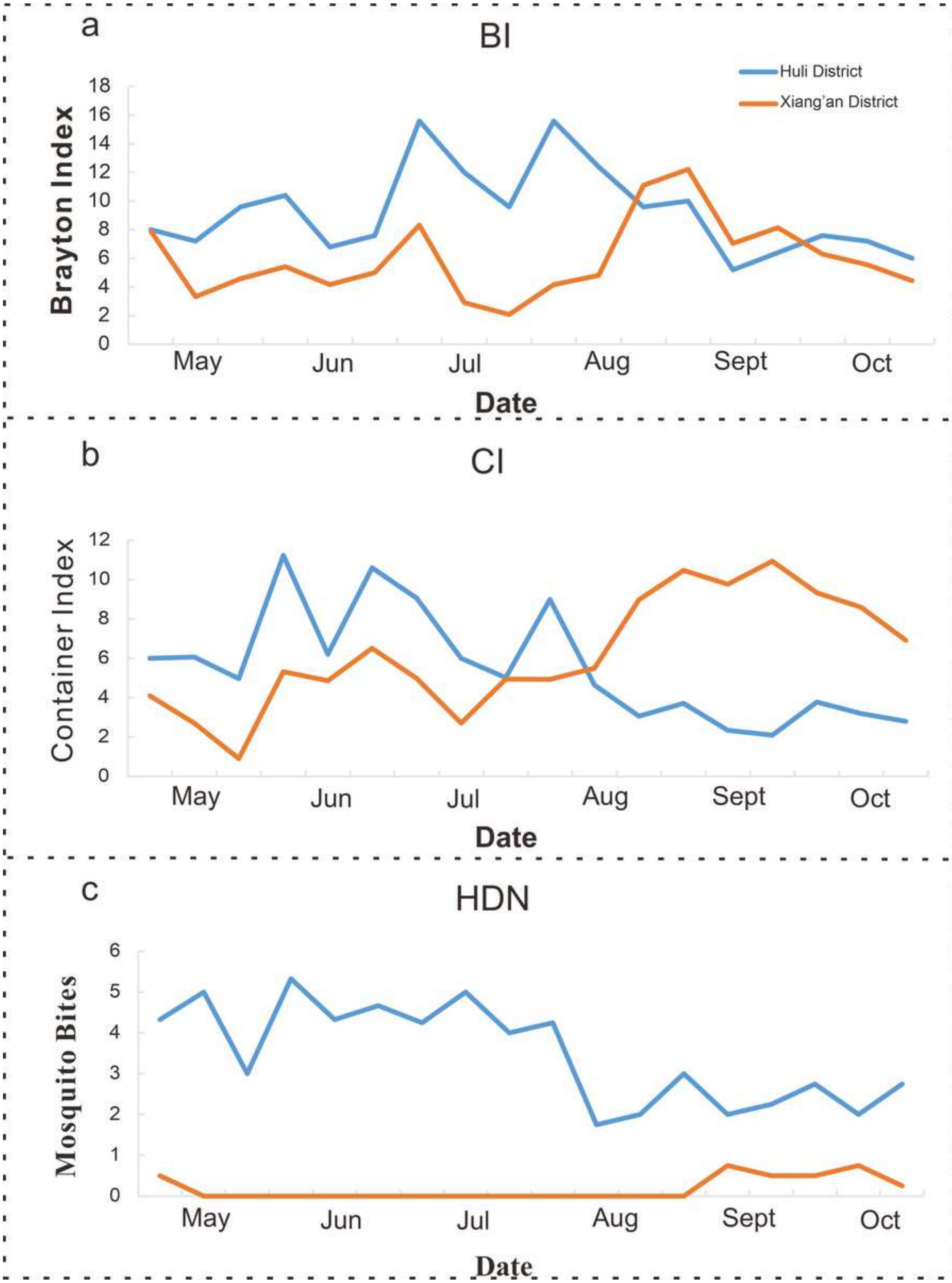

Figure 4

Monitoring results of mosquito-borne ecology. (a) Breteau index; (b)Container index; (c) Human-baited double net trapping.

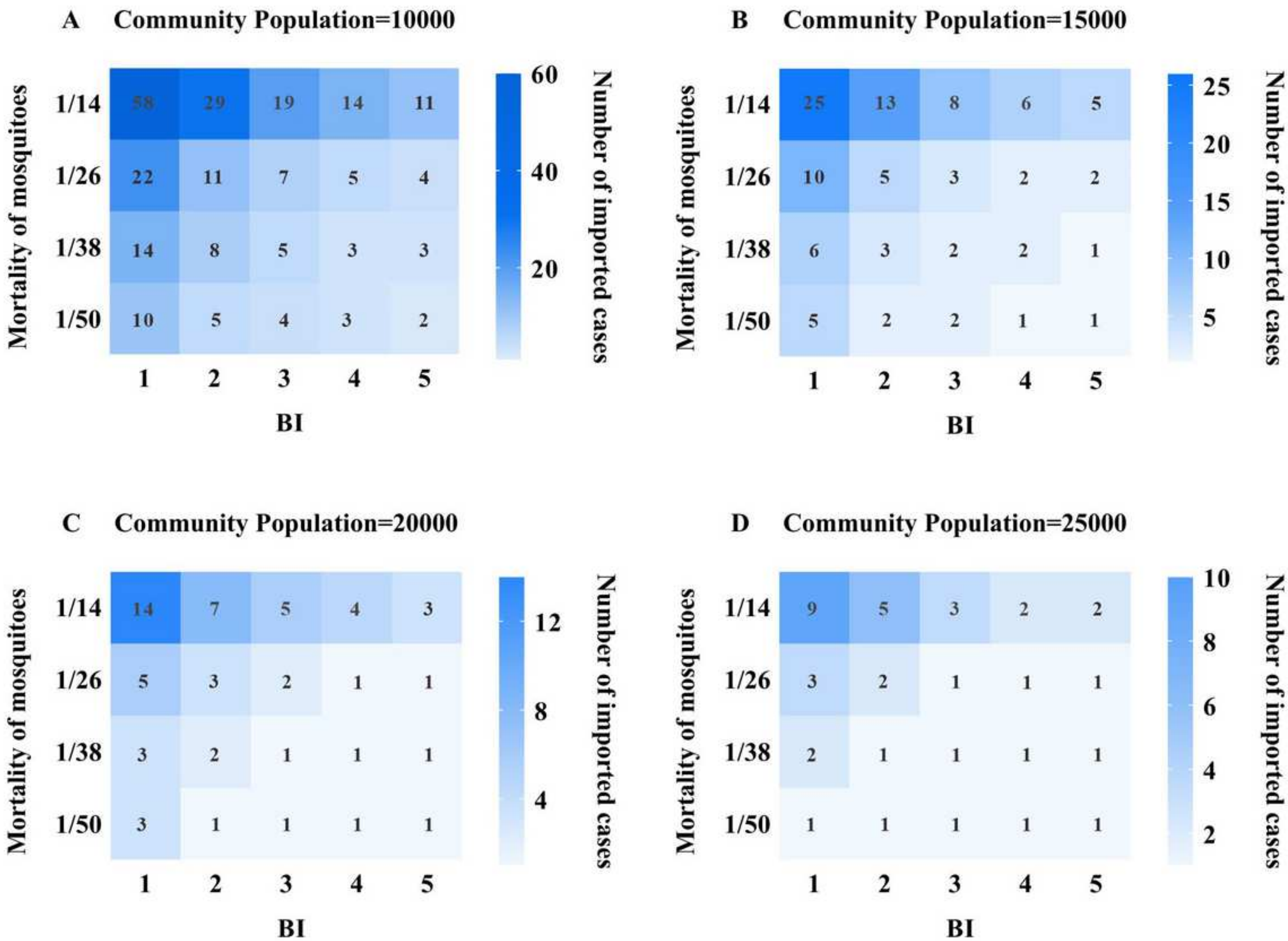

Figure 5

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