

The impact of intervention to the incidence of natural focus diseases during the outbreak of COVID-19 in Jiangsu Province, China

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Research Article

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Abstract

Doxorubicin (DOX) is a well-known chemotherapeutic drug for most malignancies including breast cancer and leukemia whilst the usage of DOX is limited owing to its cardiotoxicity. The present study analyzed the effects of crocin on doxorubicin's cardiotoxic effect in rat myocardium and searched their mechanistic interaction in the pathogenesis of DOX-induced myocardial toxicity. Forty rats were divided into four groups; (a) control (received normal saline as a dose of 1 ml/kg by ip for 15 days), (b) Crocin (received crocin as a dose of 40 mg/kg/24h by ip for 15 days), (c) DOX (received DOX as a dose of 2 mg/kg/48h by ip in six injection, cumulative dose 12 mg/kg), and (d) DOX+Crocin (received DOX as a dose of 2 mg/kg/48h by ip in six injection and crocin as a dose of 40 mg/kg/24h ip for 15 days). According to the present study, DOX administration caused significant increases in lipid indices (triglyceride, low-density lipoproteins and very low-density lipoproteins) as well as cardiac markers (Creatine kinase-muscle/brain and Cardiac Troponin I). Moreover, DOX caused significant increases in oxidative stress parameters (malondialdehyde and total oxidant status) as well as decreases in antioxidant defense systems (glutathione, superoxide dismutase, catalase and total antioxidant status). The present study also demonstrated that co-administration of crocin with DOX significantly ameliorated the lipid profile and biochemical parameters in rats receiving DOX. The results were supported by histopathological and immunohistochemical evaluations. Taken together, our results reveal that crocin might be a cardioprotective agent in DOX treated patients for cancer.

Introduction

Corona Virus disease 2019 (COVID-19) was first detected in Wuhan, Hubei Province of China in December 2019[1, 2]. The movement of people between Jiangsu and Hubei Provinces led to the massive burden in controlling COVID-19 epidemic in Jiangsu Province[3], on January 22, 2020, the first confirmed case of COVID-19 was found in Jiangsu[4], soon followed by an outbreak of 684 cases as of Dec 31. Government actively respond to the outbreak of COVID-19 with some countermeasures, including lockdown, travel restrictions, suspension of work and so on[5, 6].

Several studies have shown that corresponding prevention and control measures were effective in controlling the increase of COVID-19 cases[7, 8, 9], including travel restrictions, restrict population movement, suspension of work and so on. However, these interventions also influenced the surveillance and spread of other infectious diseases[10, 11], including the natural focus diseases[12, 13]. A study in Japan showed that seasonal influenza activity in the country was lower than in previous years due to COVID-19 outbreak in 2020[14]. Another study found that the implementation of the social distance led to an increase in dengue cases in Thailand[15]. Therefore, there is no consistent research result on the impact of COVID-19 interventions on other infectious diseases.

Autoregressive Integrated Moving Average (ARIMA) model is one of infectious disease prediction models[16, 17], which can be used to fit seasonal and non-seasonal time series, called seasonal ARIMA model and non-seasonal ARIMA model. In this study, we established an ARIMA model based on the

reported incidence from 2015 to 2019, and predicted the incidence in 2020, compared the predicted incidence with the reported incidence, and then explored the impact of COVID-19 on routine surveillance of natural focus diseases during COVID-19 outbreak in Jiangsu Province. In this study we aimed at providing scientific evidences for the prevention and control of natural focus diseases during COVID-19.

Method

Study area

Jiangsu, in the eastern province of China, with an area of 40,000 square miles and a population of about 80 million (ranked fifth most populated amongst the provinces in China). As of December 31, 2020, Jiangsu Province had more than 600 confirmed cases of COVID-19, and several studies reported the presence of different types of natural focus diseases in Jiangsu province[18, 19, 20, 21], At present, Jiangsu Province has not published an article about the impact of COVID-19 on natural focus disease. Therefore, it is of great value to find the impact of COVID-19 on routine surveillance of natural focus diseases.

Data collection

We collected the reported cases of natural focus diseases (brucellosis, malaria, hemorrhagic fever with renal syndrome[HFRS], dengue, Severe Fever With Thrombocytopenia Syndrome[SFTS], Rabies, Tsutsugamushi and Japanese encephalitis [JE]) from 2015–2020 and data of the confirmed COVID-19 patients from January 22, 2020 to December 31, 2020 in Jiangsu Province by referring to the Health Records of Jiangsu Provincial Center for Disease Control and Prevention (Jiangsu Provincial CDC). The confirmed patients of COVID-19 were diagnosed based on the criterion of World Health Organization (WHO) interim guidance[22]. This study was approved by the Ethical Committee of Jiangsu provincial CDC. All data analyzed were anonymized.

ARIMA model fitting and prediction

Due to the seasonal characteristics of natural focus diseases in Jiangsu Province (except for dengue), $ARIMA(p, d, q) \times (P, D, Q)_s$ was adopted for natural focus diseases($ARIMA(p, d, q)$ model was adopted for dengue). Use the autocorrelation and partial autocorrelation features to identify the model, test the significance of the established model parameters, and analyze the residuals between the value of model fitted and reported, make ACF diagrams and PACF diagrams for the residual sequence, and use the Box-Ljung residual white noise test method to determine whether the residual sequence is a white noise sequence, if $P > 0.05$, then residual is a white noise sequence, indicated that the established model is suitable and can be used for prediction.

Statistical analysis

The data were entered in Microsoft Excel 2019 (Microsoft Crop., USA). Nonparametric tests were used to analyze the difference between the reported incidence and the predicted incidence in 2020, difference

between reported incidence in 2020 and previous four years, difference between the duration from illness onset date to diagnosed date(DID) in 2020 and the previous four years. The determination coefficient (R^2) was used to evaluate the goodness of fit of the model simulation, regression analysis was used to calculate R^2 . Statistical analyses and establishment of ARIMA model were conducted with SPSS 13.0 software (IBM Corp., Armonk, NY, USA), and GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA).

Results

The incidence trend and curve fitting results of natural focus disease

Natural focus diseases in Jiangsu Province have a long-term seasonality trend. The incidence of natural focus disease was high between September and December each year, with an increasing trend from September and a decreasing trend after reaching its peak in November (Fig. 1-A).

The ARIMA (1,0,0)(0,1,0)₁₂ model was adopted under comprehensive considerations including model parameter test, white noise test (Table 1) and 95% confidence interval(CI). $R^2=0.795$, $P<0.05$, indicating that the model fitted the incidence from 2015 to 2019 well, and could be used to predict incidence of natural focus of disease in Jiangsu Province in 2020. From the prediction results in Figure 1-A, it could be seen that the reported incidence in 2020 was lower than the predicted incidence, and the difference was statistically significant ($U=31$, $P<0.05$)

Table 1

ARIMA model parameters and white noise test of natural focus diseases, malaria, SEFS and dengue.

Disease	Model and parameter test						White noise test	
	Model	parameter	Estimates	Std Error	<i>t</i>	<i>P</i>	Box-Ljung	<i>P</i>
Natural focal disease	ARIMA (1,0,0) (0,1,0) ₁₂	AR	0.438	0.132	3.326	<0.05	0.185	0.667
		Non-Seasonal lag 1						
		Seasonal difference	1					
Malaria	ARIMA (1,0,1) (1,1,0) ₁₂	AR	0.97	0.05	19.01	<0.05	0.089	0.765
		Non-Seasonal lag 1						
		MA	0.79	0.12	6.37	<0.05		
		Non-Seasonal lag 1						
		AR	-0.44	0.14	-3.18	<0.05		
		Seasonal lag 1						
		Seasonal difference	1					
SFTS	ARIMA (0,1,1) (1,0,0) ₁₂	AR	0.78	0.21	3.67	<0.05	0.304	0.581
		Non-Seasonal lag 1						
		AR	0.98	0.22	4.47	<0.05		
		Non-Seasonal lag 1						
		Non-Seasonal difference	1					
Dengue	ARIMA (1,1,1)	MA	0.44	0.12	3.70	<0.05	1.171	0.279
		Non-Seasonal lag 1						

ARIMA Autoregressive Integrated Moving Average, AR Autoregressive, MA Moving Average, HFRS Hemorrhagic fever with renal syndrome, SFTS Severe Fever With Thrombocytopenia Syndrome, JE Japanese encephalitis

AR	0.64	0.11	6.02	<0.05
Seasonal lag 1				
Non-Seasonal difference	1			

ARIMA Autoregressive Integrated Moving Average, AR Autoregressive, MA Moving Average, HFRS Hemorrhagic fever with renal syndrome, SFTS Severe Fever With Thrombocytopenia Syndrome, JE Japanese encephalitis

The monthly distribution of natural focus disease

The monthly incidence in 2020 was compared with the year from 2015 to 2019 (Figure 2). The results showed that the incidence of brucellosis in July, August September and November 2020 (Figure 2-A) , SFTS in April to November 2020 were higher than the same period in the previous four years (Figure 2-D) ($P < 0.05$). The incidence of malaria in April to December 2020 (Figure 2-B), HFRS in March, April and December 2020 (Figure 2-C), dengue in July to November 2020 were lower than the same period in the previous four years (Figure 2-E) ($P < 0.05$). No statistically significant differences were found in other natural focus diseases.

The incidence trend and curve fitting results of Malaria, SFTS and dengue

The incidence of malaria and SFTS in Jiangsu Province have a long-term trend and seasonality. The incidence of dengue was relatively low in 2015-2017, and has increased since 2018. The peak incidence in 2018 and 2019 were concentrated in June to October.

As for malaria, the ARIMA (1,0,1)(1,1,0)₁₂ model was adopted under comprehensive considerations including model parameter test, white noise test (Table 1) and 95% *CI*. $R^2=0.365$, $P < 0.05$, indicating that the model fitted the incidence from 2015 to 2019 well, and could be used to predict incidence of malaria in Jiangsu Province in 2020. From the prediction results in Figure 1-B, it could be seen that the reported incidence in 2020 was lower than predicted incidence, and the difference was statistically significant ($U=14$, $P < 0.05$).

As for SFTS, the ARIMA (0,1,1) (1,0,0)₁₂ model was adopted under comprehensive considerations including model parameter test, white noise test (Table 1) and 95% *CI*. $R^2=0.454$, $P < 0.05$, indicating that the model fitted the incidence from 2015 to 2019 well, and could be used to predict incidence of SFTS in Jiangsu Province in 2020. From the prediction results in Figure 1-C, it could be seen that the reported incidence in 2020 was higher than predicted incidence, but the difference was not statistically significant ($U=68$, $P < 0.05$).

As for dengue, the ARIMA (1,1,1) model was adopted under comprehensive considerations including model parameter test, white noise test (Table 1) and 95% *CI*. $R^2=0.774$, $P < 0.05$, indicating that the model

fitted the incidence from 2015 to 2019 well, and could be used to predict incidence of dengue in Jiangsu Province in 2020. From the prediction results in Figure 1-D, it could be seen that the reported incidence in 2020 was lower than predicted incidence, and the difference was statistically significant ($U=1$, $P=0.05$)

The gender distribution of natural focus diseases

As for malaria, in males, the incidence in 2020 was lower than the previous 4 years (Figure 3-B1), while in females, the incidence in 2020 was lower than 2016 (Figure 3-B2), and the difference were statistically significant ($P=0.05$). As for SFTS, in females, the incidence in 2020 was higher than 2015 (Figure 3-D2), and the difference was statistically significant ($P=0.05$). As for dengue, in males, the incidence in 2020 was lower than 2017, 2018 and 2019 (Figure 3-E1), and the difference were statistically significant ($P=0.05$). The incidences of other natural focus diseases in males and females in 2020 were not statistically different from the previous four years ($P=0.05$).

The age distribution of brucellosis, malaria and HF of natural focus diseases

As for malaria, in the age group 20-60 years, the incidence in 2020 was lower than the previous four years (Figure 4-B2 and Figure 4-B3), and the difference were statistically significant ($P=0.05$).

As for SFTS, in the age group 40-60 years, the incidence in 2020 was higher than 2015 and 2018 (Figure 4-D3), in the age group ≥ 60 years, the incidence in 2020 was higher than 2015 (Figure 4-D4), and the difference were statistically significant ($P=0.05$).

As for dengue, in the age group 20-40 years, the incidence in 2020 was lower than 2018 and 2019 (Figure 4-E2), in the age group 40-60 years, the incidence in 2020 was lower than 2016, 2017 and 2018 (Figure 4-E3), and the difference were statistically significant ($P=0.05$).

The incidences of other natural focus diseases in each age group in 2020 were not statistically different from the previous four years ($P=0.05$).

Urban and rural distribution of natural focus diseases

As for brucellosis (Figure 5-A1), in urban, the number of cases in 2020 was higher than 2015, 2016 and 2019, and the difference was statistically significant ($P=0.05$).

As for malaria (Figure 5-B1 and Figure 5-B2), in both urban and rural, the number of cases in 2020 were lower than the previous four years, and the difference was statistically significant ($P=0.05$).

The number of cases of other natural focus diseases in urban and rural in 2020 were not statistically different from the previous four years ($P=0.05$).

Distribution of the DID for natural focus diseases

The DID in 2020 was compared with the previous four years. The results showed that the DID of brucellosis and SFTS in 2020 was shorter than 2015-2018; the DID of Tsutsugamushi in 2020 was shorter than the previous four years, and the difference were statistically significant ($P \leq 0.05$). The DID of other natural focus diseases in 2020 were not statistically different from previous four years ($P > 0.05$) (Table 2).

Table 2

Distribution of duration from illness onset date to diagnosed date for natural focus diseases, Jiangsu Province, China, 2015–2020

Year	Median (IQR)(days)							
	Brucellosis	Malaria	HFRS	SFTS	Dengue	Rabies	Tsutsugamushi	JE
2015	16(7–35)*	2(1–4)	6(4–9)	12(8–16)*	5(3–7)	3(2–4)	5(2–9)*	24(7–42)
2016	17(4–31)*	3(2–5)	6(4–10)	14(9–19)*	6(4–14)	3(2–5)	5(2–9)*	38(11–56)
2017	15(7–30)*	3(2–6)	6(4–10)	11(7–20)*	7(5–9)	3(2–5)	6(3–9)*	29(18–79)
2018	10(4–27)*	3(2–5)	7(3–11)	9(7–14)*	7(4–10)	3(2–4)	6(2–9)*	76(7–85)
2019	8(1–16)	3(2–5)	7(3–10)	8(6–12)	6(4–8)	3(1–6)	5(2–8)*	-
2020	7(1–20)	3(2–5)	6(2–11)	8(4–12)	6(4–10)	5(3–6)	5(2–8)	9(8–10)
IQR inter-quartile range, HFRS Hemorrhagic fever with renal syndrome, SFTS Severe Fever With Thrombocytopenia Syndrome, JE Japanese encephalitis								
*P values have statistical significance.								

Discussion

A kind of pneumonia of unknown cause occurred in Wuhan, Hubei, China in December 2019[23], and was named COVID-19 on February 11[24] by the WHO. Following the confirmation of the first case of COVID-19 in Jiangsu Province, the provincial government has been striving and focusing on epidemic prevention and control. Appropriate countermeasures including restriction of population mobility, lockdown and so on have been taken, thus the number of daily confirmed new cases peaked and then declined rapidly over time in Jiangsu Province[25]. It indicated that the public preventive measures in limiting transmission of COVID-19 were highly effective. Moreover, these measures also had an impact on other diseases[26, 27, 28].

In this study, we established ARIMA model to fit the incidence of natural focus diseases, comprehensive consideration of various factors to select the optimal model, and then used the optimal model to

predicted incidence in 2020. Our research results found that the reported incidence of natural focus diseases (including brucellosis, malaria, HFRS, dengue, SFTS, Rabies, Tsutsugamushi and JE) in 2020 was lower than the predicted incidence, the differences was statistically significant. Although we could not directly evaluate the effect of each measure, restriction of population mobility would by far be among the most influential methods for the reduction in natural focus diseases transmission. We also found that the DID of brucellosis, SFTS and Tsutsugamushi in 2020 was shorter than before, indicating that during the outbreak of COVID-19, the surveillance efficiency of some natural focus diseases in Jiangsu Province had changed. There was also a research called that COVID-19 had caused a serious burden on the public health system of many countries, but the prevention and control measures of other diseases should not be neglected[29].

The results showed that the reported incidence of brucellosis in July, August, September and November 2020 were higher than the same period in the previous four years. A study showed that sheep/goat were the main contacted animals[30], therefore, the reason might be that in the second half of 2020, with the resumption of work and production, pastoralists had more opportunities to contact with livestock, thus the probability of infection increased. The reported incidence of SFTS in April to November 2020 were higher than the same period in the previous four years, while the reported incidence of malaria in April to December 2020, dengue in July to November 2020 were lower than the same period in the previous four years, In addition, the incidence of malaria and SFTS in 2020 had a huge change compared with the incidence in the previous years. The incidence of dengue had an upward trend in 2015–2019, but it dropped in 2020. Therefore, we modeled malaria, SFTS and dengue separately. By building an ARIMA model, the results showed that the reported incidence of malaria and dengue in 2020 were lower than predicted incidence, and the difference were statistically significant. As for malaria, our finding was inconsistent with the studies in other areas or countries[31]. The reason might be that malaria was predominantly endemic in these countries and was mainly caused by the bite of anopheles mosquitoes, but in Jiangsu Province, most malaria cases were imported cases from abroad[32]. The “Infectious Disease Surveillance System” of Chinese CDC shows that the cases of dengue in Jiangsu Province were all the imported cases from abroad. During the outbreak of COVID-19 in China, the main non-pharmacological interventions, such as lockdown, travel restrictions, keeping social distance, suspension of work and production and wearing masks were applied. Interventions which can affect natural focus diseases consisting of lockdown, travel restriction and suspension of work and production. For example, travel restrictions could directly reduce the reported cases of dengue and malaria, since the most cases of malaria and dengue in Jiangsu were imported cases. Furthermore, suspension of work and production might lead to the reduction in reported cases of brucellosis. We also found that the reported incidence of SFTS in 2020 was higher than the predicted incidence, but the difference was not statistically significant, the reason might be that the incidence of SFTS had been on the rise in 2015–2019, so the incidence itself might rise in 2020. The real reason and mechanism need to be further studied.

The results of age distribution showed that the reported incidence of malaria in age group 20–60 years was lower than the previous four years. This might be due to the fact that the most of the population entering the province from abroad were the working population, so the incidence of malaria in this age

group was significantly affected by COVID-19 prevention and control measures. The result also showed that the reported incidence of dengue in age group 40–60 years was lower than 2016–2018. This might be due to the fact that the cases of dengue were mainly in the age group of 20–60 years, therefore, these age group were more affected by the decreased of imported cases.

Another interesting finding was that the gender distribution in our analysis showed a lower incidence of dengue in males in 2020 than 2017–2019. According to the surveillance, the incidence of dengue fever in males was much higher than females, therefore, the incidence of males was more likely to be affected by the decreased of imported cases. The incidence of malaria in males in 2020 was lower than the previous four years, too. The majority of imported malaria cases in Jiangsu were males[32], so the incidence of malaria in males in 2020 might be greatly affected by the decrease of imported cases. In addition, we found that the reported incidences of malaria in both urban and rural were lower than the previous four years. The results indicates that the incidence of malaria has been affected regardless of the overall incidence, gender distribution, age distribution, urban or rural areas.

Limitation

This study has limitations. Firstly, we limited to pinpoint the real reasons for the decrease of natural focus diseases, it may be related to: a) After the outbreak of COVID-19, the number of people who take the initiative to see a doctor may decrease, resulting in a reduction in reported incidence; b) The incidence of natural focus diseases itself had fallen. Secondly, some other factors, such as climatic factors, economic factors and so on, which might affect the spread of the disease[33, 34], were not considered in this study. However, in our research, we established a model to fit the incidence of the disease from 2015 to 2019, used the optimal model to predict the incidence of 2020, and then compared the actual incidence before reaching a conclusion. Therefore, these factors mentioned above might have little influence on our conclusion.

Conclusion

The interventions for COVID-19 may have preventive effects on some natural focus diseases in Jiangsu Province. The reported incidence of natural focus diseases decreased during the outbreak of COVID-19 in 2020, especially malaria and dengue. COVID-19 prevention and control measures, such as lockdown, travel restrictions, suspension of work and production, had the greatest impact on males and people in the age group of 20–60 years. The incidence of malaria was affected regardless of the overall incidence, gender distribution, age distribution, urban and rural areas.

Abbreviations

CDC: Center for Disease Control and Prevention; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus 2; HFRS: hemorrhagic fever with renal syndrome; SFTS: Severe Fever With

Thrombocytopenia Syndrome; JE: Japanese encephalitis; ARIMA: Autoregressive Integrated Moving Average

Declarations

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Ethics approval and consent to participate

This effort of disease control was part of CDC's routine responsibility in Jiangsu Province, China. Therefore, institutional review and informed consent were not required for this study. All data analyzed were anonymized.

Consent for publication

Not applicable.

Availability of data and material

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TMC, CJB, LL and ZZZ designed research; JLH, LL, ZZZ, CL, JFH, ZYL, WKL, LL, PHL, TLY and XQC analyzed data, TMC, LL, ZZZ, NZ, MNH, RJ, MY, YZZ, YW, JWX, JFH, ZYL, SNL, SYL and JLH conducted the research and analyzed the results; TMC, JLH, XQC, LL and ZZZ wrote the manuscript. All authors read and approved the final manuscript.

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Figures

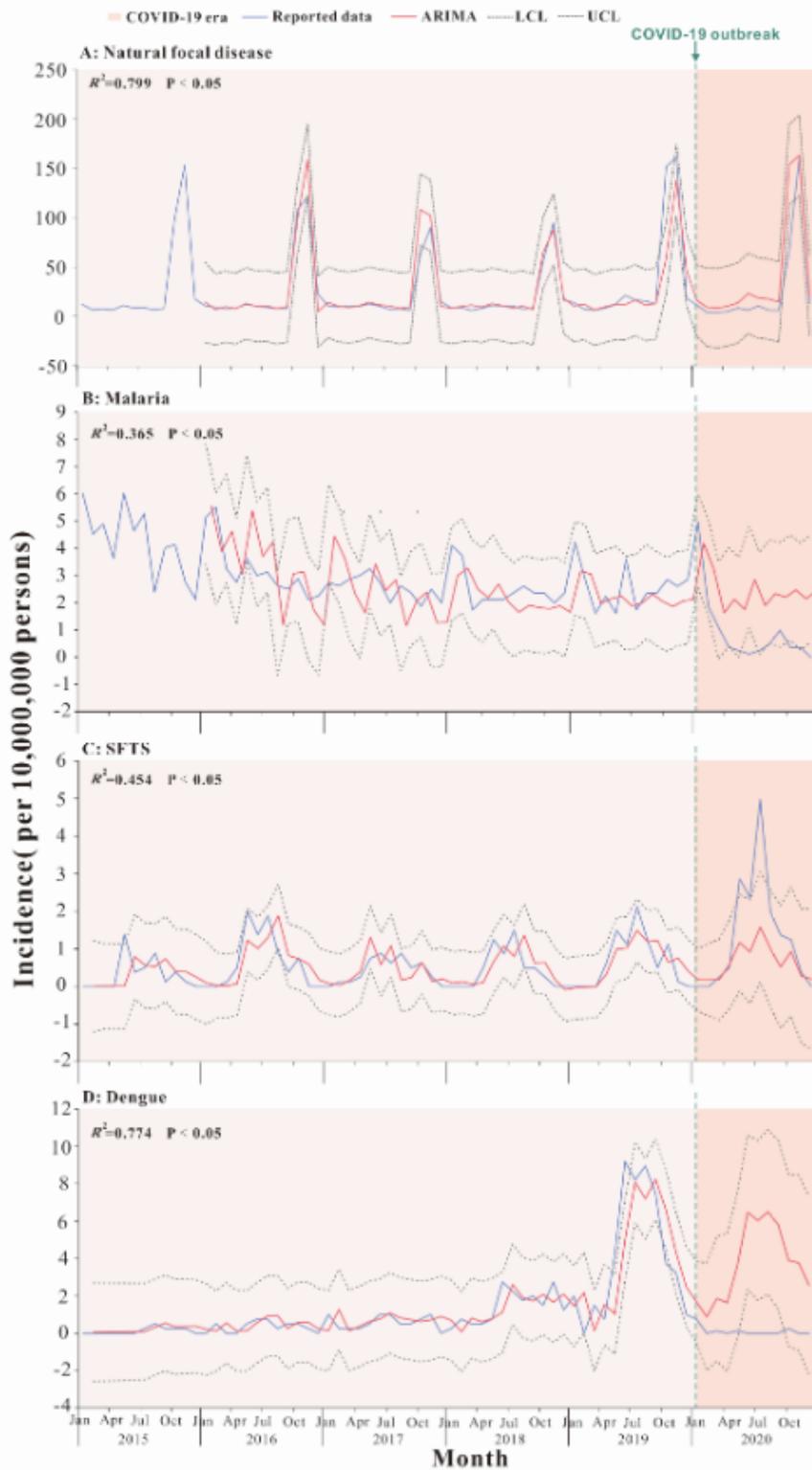


Figure 1

The incidence trend and curve fitting results of natural focus disease, malaria, SFTS and dengue. Jiangsu Province, China, 2015–2020. (A) Natural focus diseases; (B) Malaria; (C) SFTS; (D) Dengue.

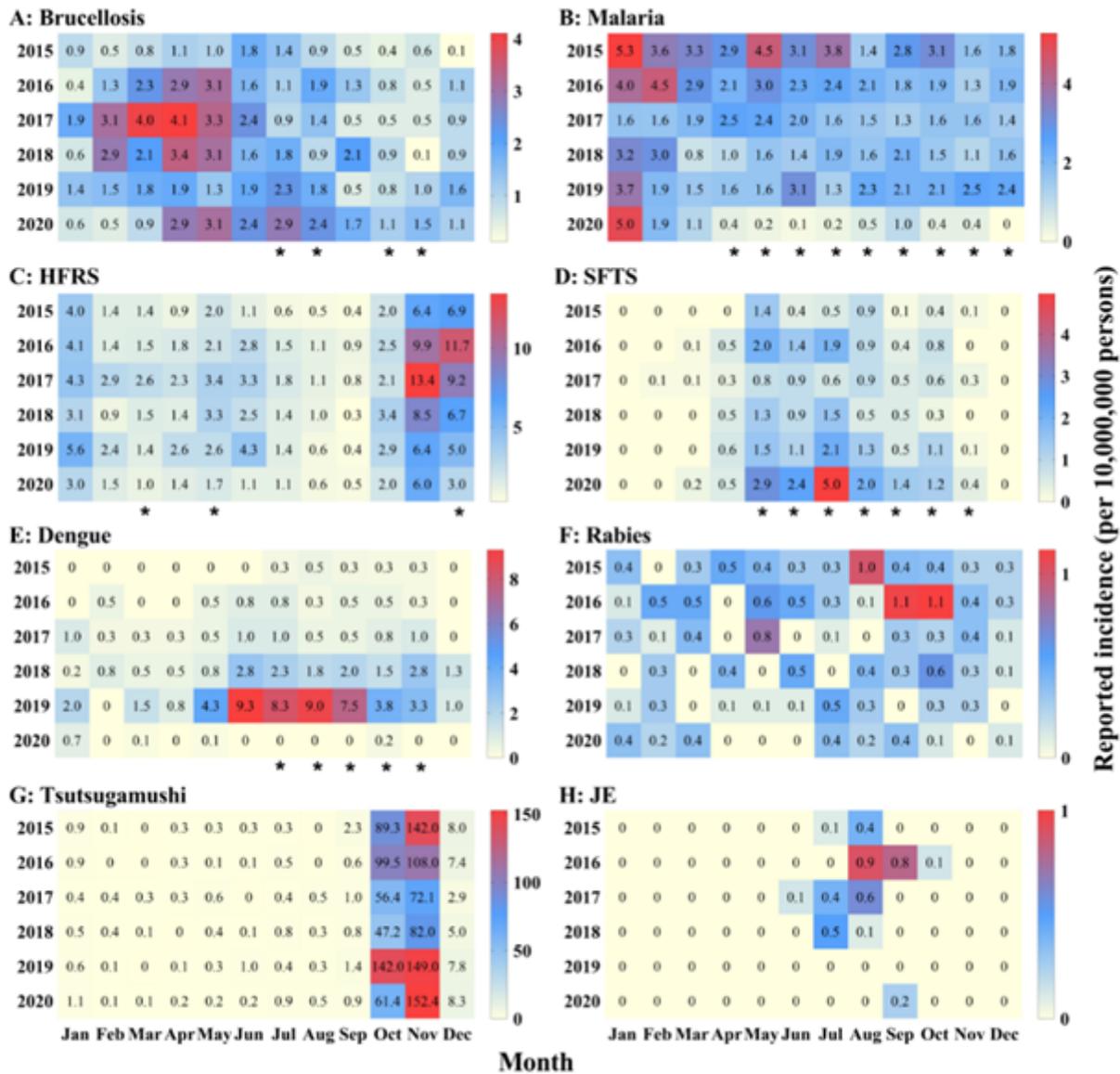


Figure 2

Month distribution of natural focus diseases, Jiangsu Province, China, 2015–2020. (A) Brucellosis; (B) Malaria; (C) HFRS; (D) SFTS; (E) Dengue; (F) Rabies; (G) Tsutsugamushi; (H) JE.

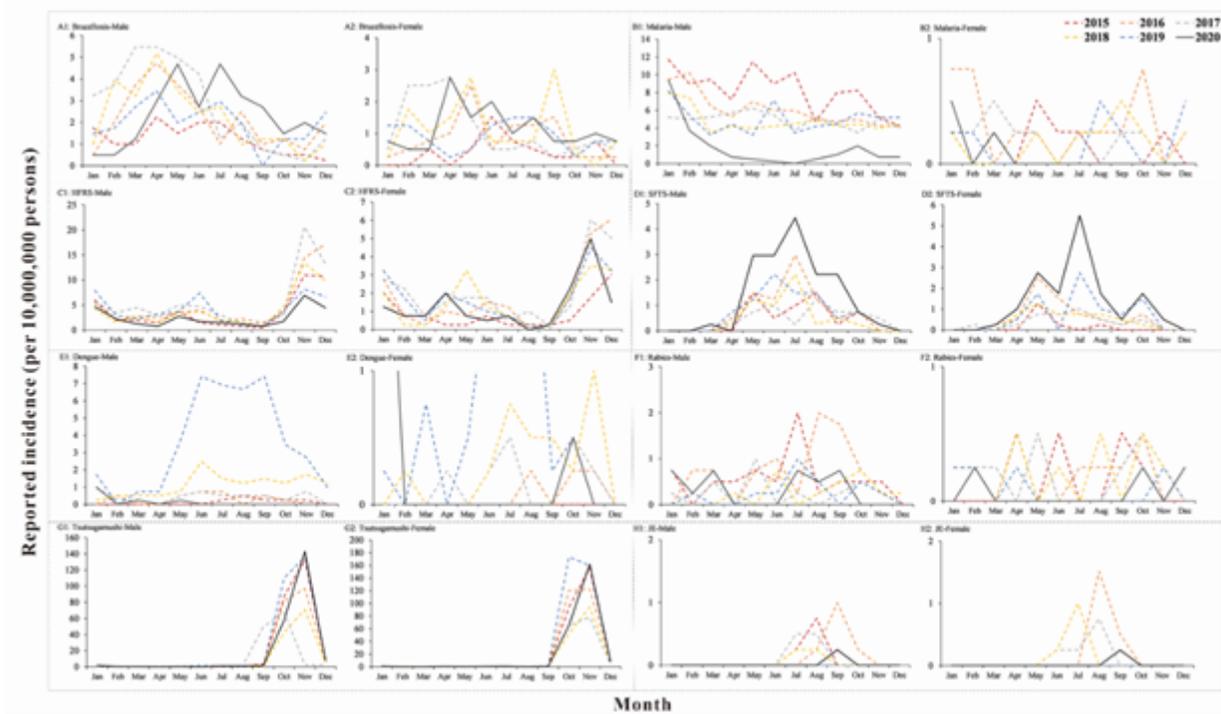


Figure 3

Gender distribution of natural focus diseases, Jiangsu Province, China, 2015–2020. (A) Brucellosis; (B) Malaria; (C) HFRS; (D) SFTS; (E) Dengue; (F) Rabies; (G) Tsutsugamushi; (H) JE.

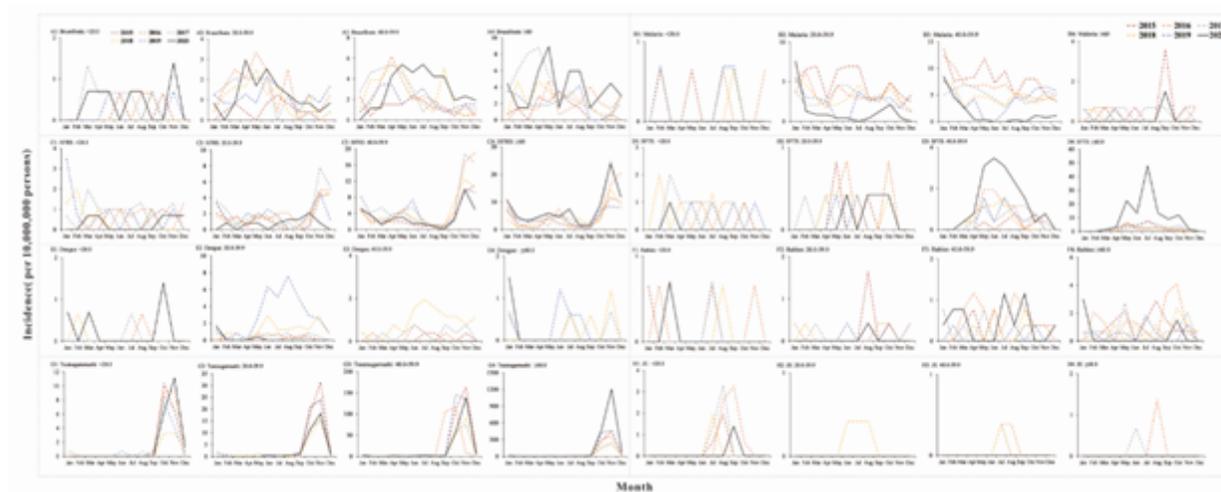


Figure 4

Age distribution of natural focus diseases, Jiangsu Province, China, 2015 – 2020. (A) Brucellosis; (B) Malaria; (C) HFRS; (D) SFTS; (E) Dengue; (F) Rabies; (G) Tsutsugamushi; (H) JE.

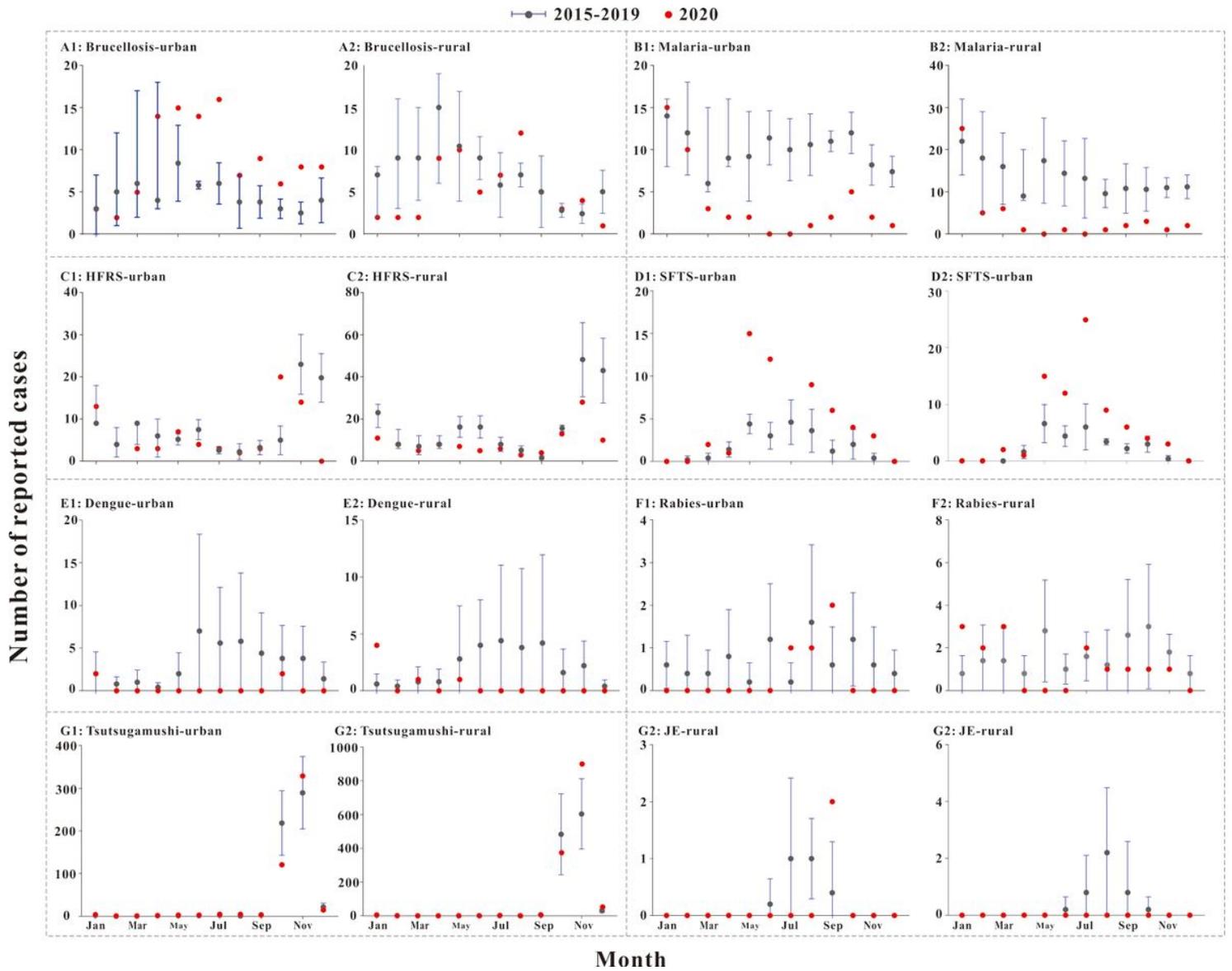


Figure 5

Urban and rural distribution of natural focus diseases, Jiangsu province, China, 2015 – 2020. (A) Brucellosis; (B) Malaria; (C) HFRS; (D) SFTS; (E) Dengue; (F) Rabies; (G) Tsutsugamushi; (H) JE.

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