Transmissibility of Hand, Foot, and Mouth Disease in 97 Counties of Jiangsu Province, China, 2015-2020

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Abstract

Background: Hand, foot, and mouth disease (HFMD) has been a serious disease burden in the Asia Pacific region represented by China, and the transmission characteristics of HFMD in regions haven't been clear. This study calculated the transmissibility of HFMD at county levels in Jiangsu Province, China, analyzed the differences of transmissibility and explored the reasons.

Methods: We built susceptible-exposed-infectious-asymptomatic-removed (SEIAR) model for seasonal characteristics of HFMD, estimated effective reproduction number (R_{eff}) by fitting the incidence of HFMD in 97 counties of Jiangsu Province from 2015 to 2020, compared incidence rate and transmissibility in different counties by non -parametric test, rapid cluster analysis and rank-sum ratio.

Results: The average daily incidence rate was between 0 and 4 per 100,000 in Jiangsu province from 2015-2020. The 97 counties could be divided into three levels: low incidence, medium incidence and high incidence, and occurred that the average daily incidence rate dropped sharply in 2016-2017, and increased sharply in 2017-2018 years. The Quartile of Reff in Jiangsu Province from 2015 to 2020 was 1.54 (0.49, 2.50), Rugao district in Central Jiangsu and Jianhu district in Northern Jiangsu had the highest transmissibility by rank-sum ratio. R_{eff} generally decreased in 2017 and increased in 2018 in most counties, and the median level of R_{eff} was lowest in 2017 (P<0.05).

Conclusion: Transmissibility was different in 97 counties of Jiangsu Province, and the reasons for the differences may be related to the climate, demographic characteristics, virus subtypes, vaccination and other infectious diseases.

Author Summary

Hand foot and mouth disease (HFMD) is a common infectious disease in children all over the world. In China, about 2 million children are infected with HFMD every year, which is a high incidence area of HFMD in Asia. Most of these studies focused on a large region such as a country or a province, and the results of these studies didn't further explore the transmissibility and influencing factors in different counties in country or province. In this study, the authors built susceptible-exposed-infectious-asymptomatic-removed (SEIAR) model for seasonal characteristics of HFMD, estimated effective reproduction number (R_{eff}) by fitting the incidence of HFMD in 97 counties of Jiangsu Province from 2015 to 2020. The prevalence and transmissibility of HFMD in Jiangsu have regional and seasonal characteristics. The reasons for the differences may be related to the climate, demographic characteristics, virus subtypes, vaccination and other infectious diseases. This study provides a reference for the control of HFMD in different districts, and provides a new idea for the study of HFMD transmissibility in the future.

Introduction

Hand foot and mouth disease (HFMD) is an infectious disease caused by enteroviru, enterovirus 71(EV71) and coxsackievirus A16 (CA16) are the main pathogens causing HFMD worldwide[1]. The virus is mainly transmitted by fecal-oral route [2]. The disease mainly occurs in children under the age of 10, especially in school-age children aged 5-6[3]. The main manifestations of patients are low-grade fever, macular papules or papular rashes on the hands and soles of feet, and oral pain ulcers, among them which infected Cox A16 may be accompanied by some atypical lesions, such as large herpes and nodules on the trunk, limbs and face, neurological complications may occur when it's serious[4].

HFMD is a serious public health problem. Since the first report of HFMD in Canada in 1950s, HFMD has been popular all over the world, and Asia is a high incidence area of HFMD[5]. In recent years, the disease burden of HFMD in China, Singapore, Vietnam, Malaysia and Japan has been increasing, China had become the largest epidemic area of HFMD in Asia Pacific region in 2008, and it was classified as class C legal infectious disease which the incidence rate was the highest among all the diseases that be reported in China, and caused 2 million children to be infected each year[6]. However, up to now, there is no specific effective treatment for HFMD, and the HFMD vaccine with better efficacy (94.8% – 97.4%) is mainly for EV71 [7]. Therefore, it is particularly important to study the incidence, transmission characteristics and influencing factors of HFMD and find appropriate prevention and control measures.

The transmission dynamics model can be used to study the transmissibility and influencing factors of HFMD, and susceptible-infectious-removed (SIR), time-susceptible-infectious-removed, susceptible-exposed-infectious-removed (SEIR) or SEIAR models have been mostly used to fit and estimate the transmissibility of HFMD and its different serotypes [8-12]. Based on these models, some studies introduce isolation measures or environmental factors to build susceptible-exposed-infectious-hospitalized-removed (SEIQR) and susceptible-exposed-infectious-asymptomatic-recovered-environment (SEIARW) models to evaluate the impact of isolation or environmental factor control on transmissibility [13-15], to put forward targeted prevention and control measures. Most of these studies focused on a large region such as a country or a province, and the results of these studies didn't further explore the transmissibility and influencing factors in different counties in country or province. However, studies have shown that weather can affect the spread of HFMD [16], a study found that the relationship between climate and HFMD varies from region to region [17], and climate couldn't fully explain the spread of HFMD, another research considered that isolation measures affect the epidemic peak of HFMD[18], and semester, Spring Festival holiday and highway passenger volume were the main factors affecting the peak[19]. Therefore, it is necessary to further study the regional transmissibility of HFMD and explore its related influencing factors, to provide more effective information for the actual prevention and control of HFMD in different counties.

In order to further explore the transmissibility and its influencing factors of HFMD in different counties, we used the incidence data of 2015-2020 HFMD in Jiangsu Province. We built a seasonal SEIAR model to fit the incidence rate of HFMD, then calculated the change of HFMD transmissibility of 97 counties in Jiangsu from 2015-2020. Finally, we compared the transmissibility of HFMD in three regions (Central

Jiangsu, Northern Jiangsu and Southern Jiangsu) and 97 counties which were contained in three regions in Jiangsu Province, and analyzed the influencing factors of the transmissibility, to provide a reference for controlling the outbreak of HFMD.

Methods

Data sources

Jiangsu province locates in the eastern coastal area of Chinese mainland, between the east longitude 116º18’-121º57’, and the north latitude 30º45’-35º20’. The whole province is in the transition from subtropical zone to warm temperate zone, with mild climate and moderate rainfall. The data of HFMD cases came from the China Information System for Disease Control and Prevention, including the number of cases, deaths reported daily and date of onset. The case types include clinical diagnosis cases and laboratory diagnosis cases. The demographic information came from the statistical yearbook of Jiangsu Province, including the number of permanent residents at the end of the year, birth rate and mortality rate.

According to the statistical yearbook of Jiangsu Province, Jiangsu Province is divided into three regions. The three regions are bounded by the Huaihe River and irrigation canal, it has subtropical humid monsoon climate in the South and a warm temperate humid and semi-humid monsoon climate in the north. The Yangtze River is the natural boundary of Jiangsu Province. Jiangsu province divides the south of the Yangtze River into Southern Jiangsu, and the north of the Huaihe River into Northern Jiangsu, while the area between the Yangtze River and the Huaihe River belongs to Central Jiangsu. The area of the three regions is similar, but there are obvious differences in social and economic development, the regional economy is best in Southern Jiangsu, then in Central Jiangsu and the last is in Northern Jiangsu [20].

Three regions include 97 counties, and these counties including counties, districts and county-level cities. Among them, the Northern Jiangsu region includes Huai'an (7 counties), Lianyungang (6 counties), Suqian (5 counties), Yancheng (9 counties) and Xuzhou (counties), with a total of 37 counties; Central Jiangsu includes Nantong (8 counties), Taizhou (counties) and Yangzhou (6 counties), with a total of 20 counties; Southern Jiangsu includes Changzhou (6 counties), Nanjing (11 counties), Suzhou (10 counties), Wuxi (7 counties) and Zhenjiang (6 counties), with a total of 40 counties.

Case definition

The diagnosis of HFMD was carried out according to the guide issued by the National Health and Family Planning Commission of the people's Republic of China [21]. The mild form of HFMD with or without fever was the most common form of HFMD, accompanied by neurological complications (aseptic meningitis, encephalitis, encephalomyelitis, acute flaccid paralysis or autonomic nervous system dysfunction) HFMD was confirmed by RT-PCR, real-time PCR or virus isolation using throat swabs or stool samples.

The transmission models of HFMD

According to the epidemiological feature of HFMD and our previous studies[8,9,11]，the SEIAR model could be used for the simulation in the model, the population was divided into susceptible individuals (S), exposed individuals (*E*), infectious individuals (*I*), asymptomatic individuals (*A*) and recovery individuals (*R*). The model diagram is shown in Figure S1.

The differential equations of the model were used to describe the dynamic changes of each state. The corresponding model equations were as follows:

1）The model assumed that HFMD cannot propagate vertically, so the new individuals born in all kinds of people are susceptible. Then we set birth rate (*br*), the natural mortality rate (*dr*), and the mortality rate of the infectious individuals (*f*). The mortality rate of all kinds of people in the disease spectrum is low, and the mortality rate of population attributable to HFMD is even lower, we set the mortality rate of the whole population as the sum of the mortality of the whole population and the mortality of HFMD.

2）Transmission of HFMD occurs via person–person, and the transmissibility between infectious individual and asymptomatic one may be different. So, the k was defined as the relative transmissibility rate of asymptomatic to symptomatic individuals. At the same time, we assumed the S will be potentially infectious as long as they are in contact with infectious individuals or asymptomatic individuals, and the coefficient of the infection rate was set as β.

3）Infectious individuals (I) and asymptomatic individuals (*A*) came from the susceptible individuals, so we considered that there was a certain proportion of exposed individuals pE ($0 \leqslant p \leqslant 1$) transformed into I after incubation, another part of exposed individuals (1- p) E were transformed into A after incubation as well. At a certain time (t), the development speed from the E to I pathway is the same as the E to A pathway and we set the speed as ω ($0 \leq \omega \leq 1$). So the proportional coefficient of E to I was set as $p\omega$, and E to A was set as $(1 - p)\ \omega$.

4）In our model, I and A may move to R, and the speed of recovering was in direct proportion to the number of individuals. The proportional coefficients were γ and γ' respectively.

5）When I and A moved to R, the recovered individuals may have immunity, So we assumed that the recovered individuals have permanent immunity that they would no longer be infected, so R was set as the end of the model.

$$\frac{dS}{dt}=nbr-\beta S(I+kA)-drS$$

$$\frac{dE}{dt}=\beta S(I+kA)-\omega E-drE$$

$$\frac{dI}{dt}=p\omega E-drI-\gamma I-fI$$

$$\frac{dA}{dt}=(1-p)\omega E-\gamma' A-drA$$

$$\frac{dR}{dt}=\gamma I+\gamma' A-drR$$

$$n=S+E+R+I+A$$

Parameter estimation

The parameters *β, ω, ω ', γ, γ', k, p* and *f* represented the infection rate coefficient, incubation period coefficient, latent period coefficient, removal rate coefficient of dominant infection, removal rate coefficient of recessive infection, infectivity coefficient of recessive infection compared with dominant infection, the proportion of dominant infection and fatality rate of dominant infection respectively.

1) The birth rate (*br*) and death rate (*dr*) were collected from 97 counties' statistical yearbooks in Jiangsu Province.

2) Studies showed that the proportion of dominant infection ranges were 19%-47% [2,22,23], selecting the median value 44.23%, therefore p = 0.4423.

3) The ranges of the incubation period (1/ω) were 3-7 days[2,24,25], selecting the median value 5 days, therefore ω = 0.2. The latent period was set to 5 days, therefore ω'= 0.2.

4) The duration of symptomatic infection was 2 weeks [10,25], therefore, the rate of disease removal γ = 0.0714. The duration of asymptomatic infection ranged from 2 to 4 weeks [22,23], Median of 3 weeks was chosen as the disease removal rate of asymptomatic patients, therefore, γ'= 0.0476.

5) The mortality of symptomatic infection ranged from 0.0001 to 0.0005 [26,27], selecting the median value 0.0003. Parameter β is estimated by curve fitting.

6) There is no clear data or references to support the parameter κ, which is still uncertain. Therefore, in this study, we assumed κ = 1 for calculation, and sensitivity analysis was carried out to calculate its impact on the model.

The significance of each variable and parameter of the model is shown in Table 1.

Transmissibility evaluation index

In this study, the population was not completely susceptible and artificially adopted some prevention and control measures, so we chose the effective reproduction number (R_{eff}) to calculate transmissibility. The calculation formula was as follows:

$$R_{eff} = \beta S(\frac{1-p}{\gamma} + \frac{\kappa p}{\gamma'})$$

Simulation methods and statistical analysis

Berkeley Madonna 8.3.18 software (developed by Robert Macey and George Oster of the University of California at Berkeley. Copyright©1993-2001 Robert I. Macey & George F. Oster) was used for the curve fitting. The fourth-order Runge-Kutta method, with a tolerance set at 0.001, was used to perform the curve fitting.

The coefficient of determination (R^2) was used to assess the goodness-of-fit. SPSS 13.0 software (IBM Corp. Armonk, NY, USA) was used to calculate the R^2. Non-parametric tests, fast clustering analysis and rank-sum ratio and linear regression analysis were used to further analyze the differences in different regions. Rank sum ratio process: the R_{eff} values from 2015 to 2020 were divided into the mean value in the first half of the year and the mean value in the second half of the year. Rank principle, the smaller the R_{eff} was, the larger the rank was. The rank-sum ratio *RSR* was calculated by ranking. Probit was calculated through *RSR* distribution, and the regression equation of *RSR* and probit was constructed. The comprehensive comparison results of R_{eff} in various regions are determined through the regression equation.

Result

County-level incidence map of HFMD in Jiangsu Province from 2015 to 2020

The average daily incidence of HFMD in various counties of Jiangsu Province was in the range from 0 per 100,000 to 4 per 100,000. In 2018, the median average daily incidence rate M (0.5 per 100,000) was the highest. In 2020, the median average daily incidence rate M (0.003 per 100,000) was the lowest. Comparing the average daily incidence rate in Jiangsu Province from 2015 to 2020 with that in 2009-2013[28], except the average daily incidence rate in 2020 was smaller than in previous years, the average daily incidence rate in other years had a larger range and the highest daily average incidence rate was 6.67 times the highest in 2009-2013.

According to the incidence map (Figure 1), we found that in 2020, the average daily incidence rate of three regions (Southern Jiangsu, Northern Jiangsu and Central Jiangsu) all was in the range from 0 per 100,000 to 0.5 per 100,000, however, from 2015 to 2019, the average daily incidence rate in Southern Jiangsu was generally more serious than that in Northern Jiangsu and Central Jiangsu. From 2015 to 2020, the average daily incidence rate of all counties in Central Jiangsu was in the range from 0 per

100,000 to 0.5 per 100,000, except for 2018, it has been well controlled in other years. In northern Jiangsu, with the exception of Huai'an, where the incidence rate was lower, the incidence rate in other counties showed an alternating trend of increase and decrease. According to Figure 2-4, we found that the HFMD outbreaks in Jiangsu Province showed obvious seasonality. The outbreaks in Southern Jiangsu were basically two seasons a year, and the peak height and duration of the two outbreaks were relatively consistent. The counties of Central Jiangsu were also basically two seasons a year. The peak height and duration of the outbreak in two seasons a year were relatively consistent, but the peak height of the outbreak in 2018 was significantly higher than that in other years. The outbreaks in Northern Jiangsu were more complex. the counties in three major cities (Huai'an, Lianyungang, and Suqian) showed a trend of seasonal outbreaks. While the counties in Yancheng city showed 2-3 outbreaks a year and the counties in the Xuzhou city showed a steady two-season outbreak.

According to the change of the average daily incidence rate in the region from 2015 to 2020, we could divide 97 counties into three typical situations by fast cluster analysis. The first kind was that the average daily incidence was at a high level, basically maintained at 1 per 100,000. Gangzha District in Nantong City, Gongyeyuan District in Suzhou City and Sucheng District in Suqian City were represented which the highest average daily incidence rate in 2015-2020 was 3.7 per 100,000, 1.8 per 100,000, 1.5 per 100,000, respectively. Except for the gradual decline of the Kaifa Disticts since 2017, other counties showed the average daily incidence rate was one year down, one year up which descending significantly in 2017, and increasing significantly in 2018, and incidence rate in 2018 is almost higher than that in 2016. Medium epidemic counties of HFMD was the second kind. The average incidence rate of HFMD in the middle epidemic counties is basically in the range from 0.5 per 100,000 to 1 per 100,000 in 2015-2019. Huishan District in Wuxi City, Suyu District in Suzhou City and Tinghu District in Zhenjiang City were represented which the average daily incidence rate was 0.57 per 100,000 to 1 per 100,000, 0.54 per 100,000 to 1 per 100,000. 0.50 per 100,000 to 0.89 per 100,000, respectively. Except for Yancheng (Tinghu and Yandu District), the incidence rate increased slowly in 2017 and declined in 2017-2020 years, other counties showed the average daily incidence rate was one year down, one year up and in 2016 and 2018 was the most prominent, about 2 times that of the year before and after. Low incidence counties of HFMD was the third kind. The average incidence rate in 2015-2019 of HFMD in the low epidemic counties was basically in range of 0.01 per 100,000 to 0.5 per 100,000. Among them, the three lowest incidence rate counties were the counties of Binhai (0.01 per 100,000 to 0.10 per 100,000), Pizhou (0.06 per 100,000 to 0.11 per 100,000) and Xinqi (0.09 per 100,000 to 0.15 per 100,000) in Yancheng City. Almost all counties showed the average daily incidence rate was one year down, one year up and that in 2016 and 2018 was the most prominent which basically maintained at 0.10 per 100,000. Seldom counties showed that downward trend after 2017 which represented by some counties in Yancheng City. Very few counties (Gulou and Jiawang counties in Xuzhou City) showed an upward trend after 2017. (Figure 1)

Fitting results of SEIAR model of HFMD in Jiangsu Province from 2015 to 2020

The fitting results of the daily incidence rate over time in the 97 counties of Jiangsu Province from 2015 to 2020 are shown in Figure 2-4. The correlation analysis between the fitting value and the actual reported value showed that the mean of coefficient of correlation R^2 was 0.50 ± 0.15, so the model was fitted well (Table S1). The fitting result of Southern Jiangsu (Figure 2) was that except for Tianning (R^2=0.240, P<0.05) and Zhonglou (R^2=0.233, P<0.05) counties in Changzhou City, the R^2 of other counties were in range of 0.377-0.816 (P<0.05), and the median was 0.55±0.09. The fitting result of Northern Jiangsu (Figure 3) was that expect for Yancheng City (Sheyang, Gulou and Xiangshui District), Xuzhou City (Quanshan, Suining, Tongshan and Yunlong District) whose R^2<0.300, the R^2 of other counties was in range of 0.300-0.726 (P<0.05), and the median was 0.50±0.10. The fitting result of Medium Jiangsu (Figure 2) was that the R^2 of 20 counties were in range of 0.446-0.806 (P<0.05), and the median was 0.60±0.13.

Transmissibility of HFMD in Jiangsu Province from 2015 to 2020

The Quartile of R_{eff} in Jiangsu Province from 2015 to 2020 was 1.54 (0.49, 2.50), 95% reference range: less than 5.88, and the highest R_{eff} could reach 20000 times of the lowest. R_{eff} showed a periodic change in the unit of year, and there is at least one R_{eff} peak in the adjacent years, and its peak was greater than 1.0.

The Quartile of R_{eff} in Southern Jiangsu from 2015 to 2020 was 1.54 (0.40, 2.50), 95% reference range: less than 5.80, and the highest R_{eff} could reach 25000 times of the lowest. According to the periodic change of R_{eff} in different counties, 40 counties could be divided into 6 types as the following: 1) Most counties' R_{eff} increased abruptly in 2018 with the highest peak height, represented by Suyang (No.2), Jianye (No.9), Pukou (No.12) and so on; 2) Some counties' R_{eff} was basically at a high level, and remained above 2.0 with a cyclical change, represented by Jiangyin (No.10), changshu (No.18), Huqiu (No.21) and so on; 3) Some counties' R_{eff} in 2015-2017 showed a regular cyclical change, and the R_{eff} values in each year were basically similar, but the R_{eff} values in 2018-2019 had a downward trend, represented by Nanjing City Jiangning(No.10) and Liuhe (No11), Suzhou City Xiangcheng (No.26); 4) R_{eff} was about 1.0 after 2015, and even lower 1.0, represented by Jintang (No.1), Runzhou (No.39); 5) R_{eff} changed periodically at about 1.0 level from 2015 to 2018, but rose abruptly in 2019, represented by Xuanwu (No.16) in Nanjing City.(Figure 5).

The Quartile of R_{eff} in Northern Jiangsu from 2015 to 2020 was 1.70 (0.67, 3.00), 95% reference range: less than 5.80, and the highest R_{eff} could reach 8000 times of the lowest. According to the periodic change of R_{eff} in different counties, 37 counties could be divided into 4 types as the following: 1) R_{eff} was basically at a high level, and remained above 1.0 with a cyclical change, we could found most of these counties in Yancheng City (Dafeng, Dongtai, Jianhu, Xiangshui and Yandu District), Xuzhou City (Jiawang, Peixian, Suining and Tongshan District) and so on; 2) Some counties' R_{eff} was about 1.0 after 2015, represented by Xuzhou City Fengxian (No.68) Gulou (No.69), Yunlong (No.77) and so on. 3) Some counties' R_{eff} increased abruptly in 2018 with the highest peak height, represented by Huaian(No.41), Sihong (No.56), Xinqi (No.76) and so on; 4) R_{eff} was cyclical and had an upward trend, represented by Lianyun City Guangyun (No.51), Haizhou(No.52), Kaifaqu (No.53) and so on; (Figure.6)

The Quartile of R_{eff} in Medium Jiangsu from 2015 to 2020 was 1.63 (0.64, 3.33), 95% reference range: less than 13.91, and the highest R_{eff} could reach 100000 times of the lowest. According to the periodic change of R_{eff} in different counties, 20 counties could be divided into 4 types as the following: 1) Most counties' R_{eff} was basically at a high level, and remained above 1.0 with a cyclical change, represented by Rugao (No.84), Tongzhou (No.85), Jiangdu (No.96) and so on; 2) R_{eff} was about 1.0 after 2015, represented by Chongchuan (No.78), Gangzha (No.79), Haian (No.80) and so on; 3) R_{eff} increased abruptly in 2018-2019 with the highest peak height, most of them could been found in Taizhou City (Hailing, Jiangyan and Xinghua District); 4) R_{eff} was higher than 1.0 in 2015-2016, decreased to below 1.0 in 2017-2018, and increased to above 1.0 in 2019, represented by Taizhou City (Jingjiang District). (Figure.7)

Analysis on the different transmissibility in three regions of Jiangsu Province

Comparing transmissibility in three regions

We analyzed the difference of R_{eff} in the three major regions by Kruskal-Wallis H test, the results showed that the median of R_{eff} in Southern Jiangsu, Northern Jiangsu, and Central Jiangsu were statistically significant (χ^2=8.697, P=0.013), and the median of R_{eff} in Southern Jiangsu is the smallest among the three regions (P<0.05).

Comparison of the transmissibility of cities in the three major regions

We analyzed the difference of R_{eff} of the cities within the three major regions by Kruskal-Wallis H test, the results showed that the median of R_{eff} of the five major cities in the southern Jiangsu region, Changzhou, Nanjing, Suzhou, Wuxi, and Zhenjiang were statistically different (χ^2=13.512, P=0.009), and the median R_{eff} of Changzhou was lower than the other four cities (P<0.05); In the northern Jiangsu region, the median of R_{eff} of the five major cities of Huai'an, Lianyun, Suqian, Yancheng, and Xuzhou were different (χ^2=45.494, P=0.000), and the level of the median of R_{eff} of Yancheng was the highest, higher than the other four cities (P<0.05), and the median of R_{eff} of Suqian was the smallest, lower than the other four cities (P<0.05). There was no statistically significant difference in the median size of R_{eff} in the five major cities of Nantong, Taizhou and Yangzhong in the central Jiangsu region (χ^2=2.604, P=0.272).

Comparison of the transmissibility of 97 counties

We compared the transmissibility of 97 counties by the Rank -sum ratio (RSR). According to the RSR distribution table (Table 2), we constructed RSR and Probit regression equation which could be obtained as: (F=1813.37, P=0.000), through this equation, the of each district could be calculated and using it to classify the transmissibility into 6 levels which showed in Table 3. From 1 to 6, the transmissibility was getting weaker and weaker. The result showed that counties with the strongest transmissibility were Rugao in central Jiangsu and Jianhu in northern Jiangsu, while the weakest were Liyang and Jintan in southern Jiangsu, and Sihong in northern Jiangsu. Most counties were in 3-4 level indicating that those counties' transmissibility was relatively similar, especially in the same region or city.

Comparison of R_{eff} in different years in Jiangsu Province from 2015 to 2020

We compared the R_{eff} in different years by Kruskal-Wallis H test, the result showed that the median of R_{eff} for each year from 2015 to 2019 was different (χ^2=21.283, P=0.000), and the median of R_{eff} in 2017 was smaller than that in other years (P<0.05).

Discussion

In this study, the seasonally adjusted SRIAR model was used to study the transmissibility of HFMD among 97 counties in Jiangsu Province, to provide suggestions for local CDC, community in Jiangsu Province and other areas with similar transmissibility of HFMD.

Analysis of the different incidence rate in various counties

The incidence rate of Southern Jiangsu was higher than Northern Jiangsu and with a peak of two seasons in a year which was consistent with earlier studies of HFMD in Jiangsu Province[28] , but in this study, we found that some counties of Northern Jiangsu had one seasonal peak. We considered the reasons for the different incidence rate and seasonal in various counties may be as following: 1) The climate zone of the regions is inconsistent. Liu W et al. found that the incidence rate of HFMD in Jiangsu was proportional to the average temperature and rainfall, but negatively correlated with the days of rainfall(≥0.1mm), low temperature, high temperature and sunshine duration[28]. A systematic review showed that the incidence of HFMD increased significantly when the temperature and relative humidity increased by 1℃ and 1%, respectively [28], moderately warm environment promotes the spread of the HFMD virus. We thought that Southern Jiangsu is warmer than the Northern Jiangsu what may cause the incidence rate is higher, and the winter in the northern region was too cold to prevent the spread of hand foot mouth disease. 2) The demographic characteristics of regions are different. The south of Jiangsu Province is a densely populated area. Studies have found that most of the cases in this area are infants and children under 5 years old, so the incidence rate was different. 3) The epidemic virus serotypes are different. Zhuang ZC et al. thought CA-V16 may lead to the peak of HFMD in autumn or winter and the high incidence of adults[29], CA6 often causes herpangina (HA), which is characterized by salivary blister pain. However, in many countries, HFMD does not contain HA data in hand-to-mouth disease reported to NNDSS, which often leads to a loss of reporting and a reduction in its incidence rate[5]. In recent years, studies have shown that the subtypes of HFMD virus in regions of Jiangsu Province are different[30], so we thought the serotype of virus in regions of Jiangsu is different, resulting in its incidence rate and seasonal difference. 4) Immune protection. It may because of most patients in Northern Jiangsu got protective antibodies after infection in spring, which prevented the epidemic of HFMD in autumn and winter.

Analysis of the different incidence rate in various years at the same regions

We analyzed the different incidence rates in various years as following aspects: 1) From the perspective of climate change. Although the incidence and spread of HFMD are related to climate factors[28], according to some meteorological researches, the temperature and rainfall in 2017 and 2018 are not abnormal compared with other years[31,32]. Therefore, the average incidence rate of 2017 and 2018 decreased significantly, and the increase may not be related to climatic factors. 2) Protective effect of the vaccine. Since 2016, the HFMD vaccine for EV71 has been put into use[33,34], The incidence rate of HFMD in 2017 may be due to the decrease in incidence rate due to vaccination and vaccination. 3) Changes of epidemic virus subtypes. The increase in incidence rate in 2018 may be due to the vaccine being mainly targeted at EV71, but the current vaccine does not have any protective effect on CA16 and other subtypes[34]. According to the data from 2008 to 2010, EV71 and CA16 were the leading epidemics of HFMD in this province, accounting for nearly 1:11[35]. Relevant studies have shown that CA6 has gradually become the main pathogen of HFMD in the world. The prevalence of Finland[36], Spain[37], the United States[38] in Europe and Japan in Asia [39]increased to 70% or more from 2008 to 2011, and Guangdong [40] and Changchun[40] in China increased to more than 60% in 2013. In this study, we also found that there are two peaks a year in most years, while many prevalent peaks occurred in 2018 in incidence rate fitting results. Therefore, the repeated outbreaks after 2017 may be caused by CA16 infection or new virus subtypes after vaccination. 4) The impact of other infectious diseases. In this study, we found that the average daily incidence rate of HFMD was lower than that of the previous 10 times in the first half of 2020. This indicated that the protective measures against COVID-19, such as school closures, business discontinued, frequent hand washing and wearing masks, and maintaining social distance, have affected the prevalence of HFMD to some extent. Other research also showed that the incidence rate of HFMD was affected by road passenger volume and population mobility during the term and Spring Festival. The combined effect was more significant than that of meteorological factors on the epidemic of hand foot mouth disease[19].

Analysis of the difference of transmissibility of three regions in Jiangsu Province

The average R_{eff} of HFMD in Jiangsu Province from 2015 to 2020 was 1.54, which was similar to the research results of foreign and most domestic provinces and regions, but the R_{eff} was lower than that of Shenzhen, Guangdong Province[25]. We found that the R_{eff} in Southern Jiangsu was less than that in Northern Jiangsu which we contrary to the incidence rate of the regions. We considered the reason may be as the following: 1) Because of the area and population of Southern Jiangsu are bigger than that of in Northern and Central Jiangsu, causing the number of susceptible persons was larger in Southern Jiangsu, so that the transmissibility of Southern Jiangsu was lower, while the incidence rate was higher. 2) The large population base of Southern Jiangsu will also increase the risk of HFMD indirectly caused by other infectious diseases. Studies have shown that the incidence rate of onychomycosis is related to HFMD with Cox A16 serotype[41,42], especially adult population. Based on the above analysis, we suggested that South Jiangsu should pay more attention to a wide range of publicity in the season of

HFMD onset, and for the central and Northern Jiangsu areas with strong transmissibility of HFMD, strengthening the implementation of protective measures is more helpful to reduce its prevalence.

Analysis of the comprehensive comparison results of transmissibility in 97 counties

Jianhu District in Northern Jiangsu and Rugao District in Central Jiangsu had the strongest comprehensive evaluation of transmissibility, but the trend of transmissibility was different. Jianhu District maintained high transmissibility from 2015 to 2016, and has a downward trend from 2017 to 2019. From the previous research we could find that in Yancheng City, where Jianhu is located, HFMD is highly prevalent among infants., while the higher the level of maternal antibody to EV71, the stronger the protection for infants[43]. Therefore, the implementation of vaccine immunization in Jianhu District has a certain protective effect, but it is also necessary to further strengthen the propaganda and education and detect whether there is a new virus subtype epidemic. The transmissibility in Rugao District had uptrend from 2017-2020, Research showed that the HFMD in Rugao District had been more serious in recent years, and the incidence rate and incidence ratio were the first places in class C infectious diseases[44] where also had critically ill patients in 2015-2020. There are inappropriate nursing and poor health environment in the rural areas of this district, and the vaccination situation is also low. We need to focus on improving the health environment, strengthen the publicity and health education, improve the awareness of epidemic prevention, and improve the epidemic situation monitoring, especially the analysis and monitoring of virus subtypes of severe patients.

Analysis of the different transmissibility of various years

The trend of HFMD transmissibility over time showed that R_{eff} was the lowest in 2017 which may be related to the implementation of EV71 vaccine in 2016. Because we found the incidence rate in 2017 was also lowest, so the immunity of the vaccine to EV71 and the publicity of vaccination reduced the number of susceptible people and infected people, which reduced the actual transmissibility of HFMD. But what's interesting is that in many counties, most of the transmissibility suddenly increased in 2018, and the peak height could be higher than that in 2015 and 2016. We think this may be due to the different subtypes of HFMD virus that dominated the epidemic in different years, or the change of transmissibility caused by a variety of viruses. The serotypes of HFMD virus are very extensive. Studies have shown that human enterovirus (HEV)-A includes coxsackievirus a (CA) 2-8, 10, 12, 14, 16 and EV71 [41,45]. Although EV71 and Cox A16 were the main causes of HFMD outbreaks, other HEV-A pathogens were found in sporadic HFMD cases[45,46], In addition, some studies have shown that the basic reproduction number of different types of enterovirus is different, and the basic reproduction number of coxsackievirus is the highest[47], Recent studies also showed that EV 71 and CA16 were the main pathogens of HFMD in Suzhou in 2017, and CA6 was the main pathogen of HFMD in 2018[48], and the co-infection of EV71 / Cox A16 and CA6 / CA10 was also found in Suzhou[30]. In a study on HFMD in Changsha, China, EV71 interacts with Cox A16, and the interactions between EV71 and other enteroviruses and between Cox A16 and other enteroviruses are all directional[49]. Therefore, we suggested that based on the classification of different transmissibility described by results to select counties to monitor the subtypes of HFMD, and the HFMD vaccine for different subtypes should be developed to cope with the change of epidemic pathogens.

Limitations

Due to the limitation of data, this study has some limitations. In this model, factors that may affect the transmissibility, such as age and gender, are not included, which may have some impact on the results, and the actual data of possible influencing factors such as climate characteristics, virus types, population data were not collected for correlation analysis with transmissibility of HMFD in various counties.

Conclusion

1. The epidemic situation of HFMD in Jiangsu Province from 2015 to 2019 is more severe than 2009-2013. The impact of COVID-19 lead to the reduction of the epidemic of HFMD in Jiangsu Province in 2020.
2. The prevalence and transmissibility of HFMD in Jiangsu have regional and seasonal characteristics. The higher the incidence rate in the three regions, the lower the transmissibility. The peak period of the epidemic will be changed from one season to two seasons.
3. The differences of epidemic and transmissibility of HFMD in Jiangsu Province are related to the climate, population, virus subtypes, vaccination and other infectious diseases, among which the difference of virus subtypes may be the most important factor.
4. Rugao District in Central Jiangsu and Jianhu District in Northern Jiangsu have the strongest transmissibility of HFMD among 97 counties of Jiangsu Province. The vaccination rate should be increased in Jianhu District, and health publicity, health conditions and virus subtype monitoring should be strengthened in Rugao District.
5. The transmissibility of counties is similar in some cities or regions, it is suggested that the representative areas should be selected for virus subtype surveillance according to the characteristics of transmissibility in Jiangsu Province.

Declarations

Author contributions: Wei Z, TC, JR, Jian-li Hu and Hongwei Li made substantial contributions to conception and design, Wei Z, Hesong Z, YN and Xiaoqing Cheng collected the data; Wei Z, JR, BD、BZ、YS and Wei Z conceived the experiments, Wei Z, JR, Hesong Z, Lijing H, Lexin Zhang, Simiao Zuo, Junru Li, XingCheng Huang conducted the experiments and analyzed the results; Wei Z, JR wrote the manuscript. TC, Jian-li Hu, and Hongwei Li revised it critically for important intellectual content. All authors approved the final manuscript and agreed to be accountable for all aspects of the work;

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Data and materials availability: All data is available in the main text or the supplementary materials

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Tables

Table 1 Parameter definitions and values of SEIAR model

Parameter	Description	Unit	Value range	Value	Method
br	Birth rate	1	0-1	-	Actual data
dr	Death rate	1	0-1	-	Actual data
β	Transmission relative rate	$\text{individual}^{-1}\cdot\text{Day}^{-1}$	0-1	-	Curve
κ	Transmissibility coefficient of A relative to I	1	0-1	1	-
p	Proportion of asymptomatic	1	0-1	0.4423	Actual data
ω	Incubation relative rate	Day-1	0-1	0.2	2, 24, 25
ω'	Latent period relative rate	Day-1	0-1	0.2	2, 24, 25
γ	Recovery rate of the infectious	Day-1	0-1	0.07143	22, 23
γ'	Recovery rate of the asymptomatic	Day-1	0-1	0.04762	22, 23
f	Fatality rate of HFMD cases	1	0-1	0.0003	Actual data

Table 2. The distribution of *RSR*

RSR	*f*	$\sum f$	*R*	*R`*	(*R`*/n)**100%*	Probit
0.1	1	1	1	1	1.031	2.685
0.11	1	2	2	2	2.062	2.959
0.16	1	3	3	3	3.093	3.133
0.18	1	4	4	4	4.124	3.263
0.23	1	5	5	5	5.155	3.370
0.26	1	6	6	6	6.186	3.461
0.27	1	7	7	7	7.216	3.540
0.28	1	8	8	8	8.247	3.611
0.29	1	9	9	9	9.278	3.676
0.3	1	10	10	10	10.309	3.736
0.31	2	12	11, 12	11.5	11.856	3.818
0.33	1	13	13	13	13.402	3.892
0.35	1	14	14	14	14.433	3.939
0.37	1	15	15	15	15.464	3.983
0.38	3	18	16, 17, 18	17	17.526	4.066
0.39	3	21	19, 20, 21	20	20.619	4.180
0.4	2	23	22, 23	22.5	23.196	4.268
0.42	2	25	24, 25	24.5	25.258	4.334
0.43	2	27	26, 27	26.5	27.320	4.397
0.45	2	29	28, 29	27.5	28.351	4.428
0.46	1	30	30	30	30.928	4.502
0.47	4	34	31, 32, 33, 34	32.5	33.505	4.574
0.48	3	37	35, 36, 37	36	37.113	4.671
0.49	2	39	38, 39	38.5	39.691	4.739
0.5	2	41	40, 41	40.5	41.753	4.792
0.51	5	46	42, 43, 44, 45, 46	44	45.361	4.883
0.52	3	49	47, 48, 49	48	49.485	4.987
0.53	5	54	50, 51, 52, 53, 54	52	53.608	5.091

0.54	4	58	55, 56, 57, 58	56.5	58.247	5.208
0.55	8	66	59, 60, 61, 62, 63, 64, 65, 66	62.5	64.433	5.370
0.57	1	67	67	67	69.072	5.498
0.58	2	69	68, 69	68.5	70.619	5.542
0.59	2	71	70, 71	70.5	72.680	5.603
0.6	1	72	72	72	74.227	5.650
0.61	4	76	73, 74, 75, 76	74.5	76.804	5.732
0.62	1	77	77	77	79.381	5.820
0.64	1	78	78	78	80.412	5.856
0.65	7	85	79, 80, 81, 82, 83, 84, 85	82	84.536	6.017
0.66	3	88	86, 87, 88	87	89.691	6.264
0.67	1	89	89	89	91.753	6.389
0.68	2	91	90, 91	90.5	93.300	6.498
0.73	1	92	92	92	94.845	6.630
0.75	1	93	93	93	95.876	6.737
0.76	1	94	94	94	96.907	6.867
0.77	1	95	95	95	97.938	7.041
0.79	1	96	96	96	98.970	7.315
0.84	1	97	97	97	99.999	9.265

Table 3. Ranking of Reff in 97 counties of Jiangsu Province from 2015 to 2020

Grade	P_x	Probit	^ RSR	District
1	$<P_{2.275}$	<3	<0.192	**Northern Jiangsu:** Jianhu **Central Jiangsu:** Rugao
2	$P_{2.275}$~	3~	0.192~	**Southern Jiangsu:** Pukou, Gulou **Northern Jiangsu:** Yandu, Tongshan, Tinghu, Sheyang, Xinyi, Xiangshui, Dafeng **Central Jiangsu:** Tongzhou, Baoying, Gaoyou, Jiangdu
3	$P_{15.866}$~	4~	0.343~	**Southern Jiangsu:** Danyang,Yixing, Jiangning, Huqiu, Jurong, Liuhe, Xishan, Dantu, Kaifaqu, Gongyeyuan, Jingkou, Wuzhong, Gusu, Wujin, Zhangjiagong, Huishan, Taicang, Binhu, Jianye, Xin, **Northern Jiangsu:** Binhai, Jianhu, Ganyu, Qingjiangou, Dontai, Peixian, Funing, Suining, Dongahi **Central Jiangsu:** Yizheng, Gaogang, Xinghua, Rudong, Jiangyan
4	P_{50}~	5~	0.494~	**Southern Jiangsu:** Qixia, Changshu, Yuhuatai, Tianning, Zhonglou, Kunshan, Jiangyin, Qinhuai, Xiangcheng, Liangxi **Northern Jiangsu:** Siyang, Xuyi, Lianyugang, Fengxian, Jiawang, Yunlong, Haizhou, Guannan, Huaiyin, pizhou,Suyu **Central Jiangsu:** Hailing, Chongchuan, Taixing, Haimen, Jingjiang, Guangling, Haian
5	$P_{84.134}$~	6~	0.645~	**Southern Jiangsu:** Yangzhong, Sushui, Xuanwu, Wujiang, Gaocun, Xinbei, Gulou, Runzhou **Northern Jiangsu:** Huaian, Muyang, Quanshan, Sucheng, Lianshui, Guanyun **Central Jiangsu:** Qidong, Hanjiang
6	$P_{97.725}$~	7~	>0.796	**Southern Jiangsu:** Suyang, Jintang **Northern Jiangsu:** Sihong

Figures

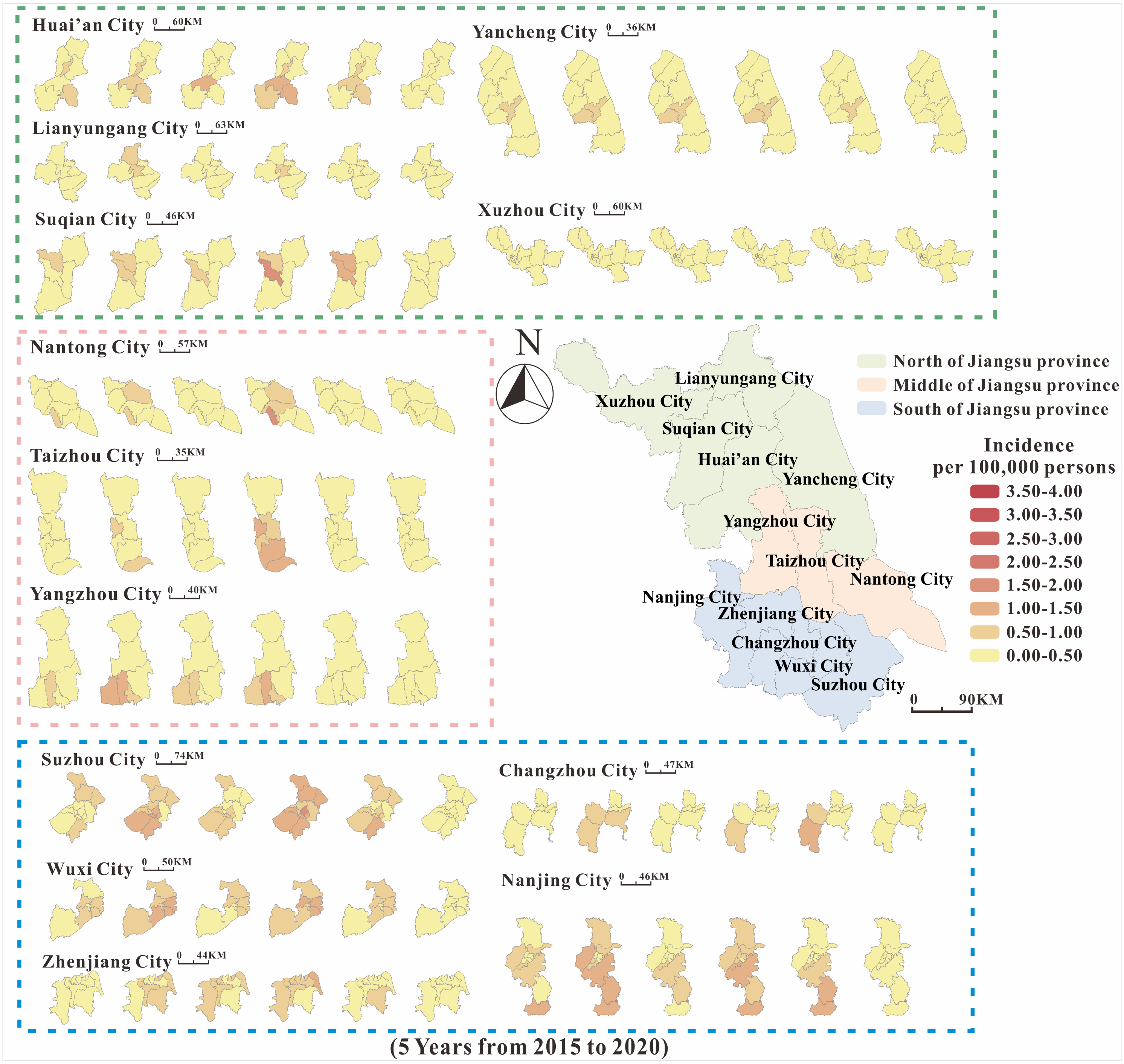

Figure 1

Map of average daily morbidity in Jiangsu Province form 2015-2020

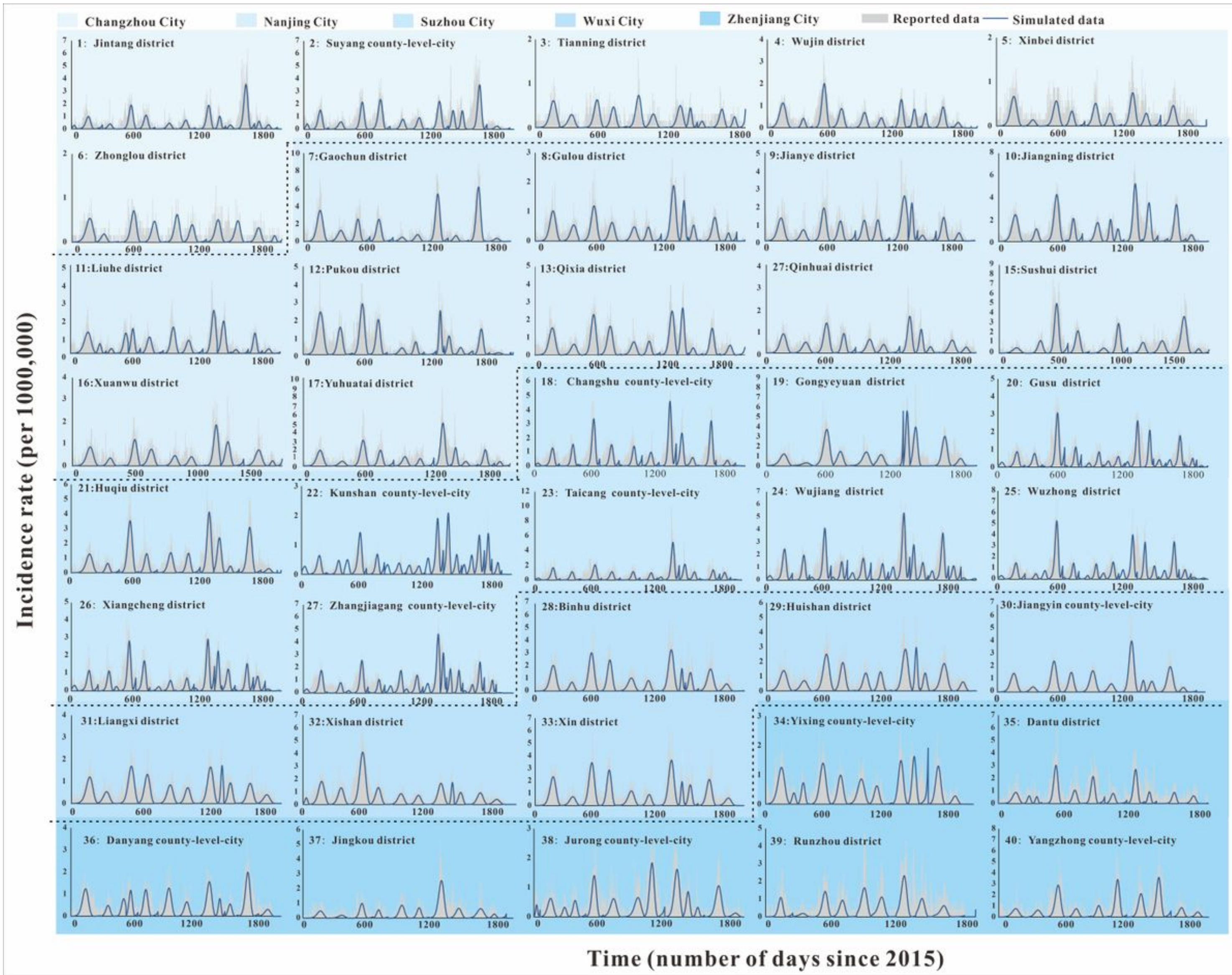

Figure 2

The simulated incidence rate of different regions in Southern Jiangsu. No. 1-40 refers to Southern Jiangsu, including Changzhou city No. 1-6 (Jintang district, Suyang county-level-city, Tianning district, Wujin district, Xinbei district, Zhonglou district, respectively), Nanjing city No. 7-17 (Gaochun district, Gulou district, Jianye district, Jiangning district, Liuhe district, Pukou district, Qixia district, Qinhuai district, Sushui district, Xuanwu district, Yuhuatai district, respectively), Suzhou city No.18-27 (Changshu county-level-city, Gongyeyuan district, Gusu district, Huqiu district, Kunshan county-level-city, Taichng county-level-city, Wujiang district, Wuzhong district, Xiangcheng district, Zhangjiagang county-level-city, respectively), Wuxi city No. 28-34 (Binhu district, Huishan district, Jiangyin county-level-city, Liangxi district, Xishan district, Xin district, Yixing county-level-city, respectively) and Zhenjiang city No. 35-40 (Dantu district, Danyang county-level-city, Jingkou district, Jurong county-level-city, Runzhou district, Yangzhong county-level-city, respectively)

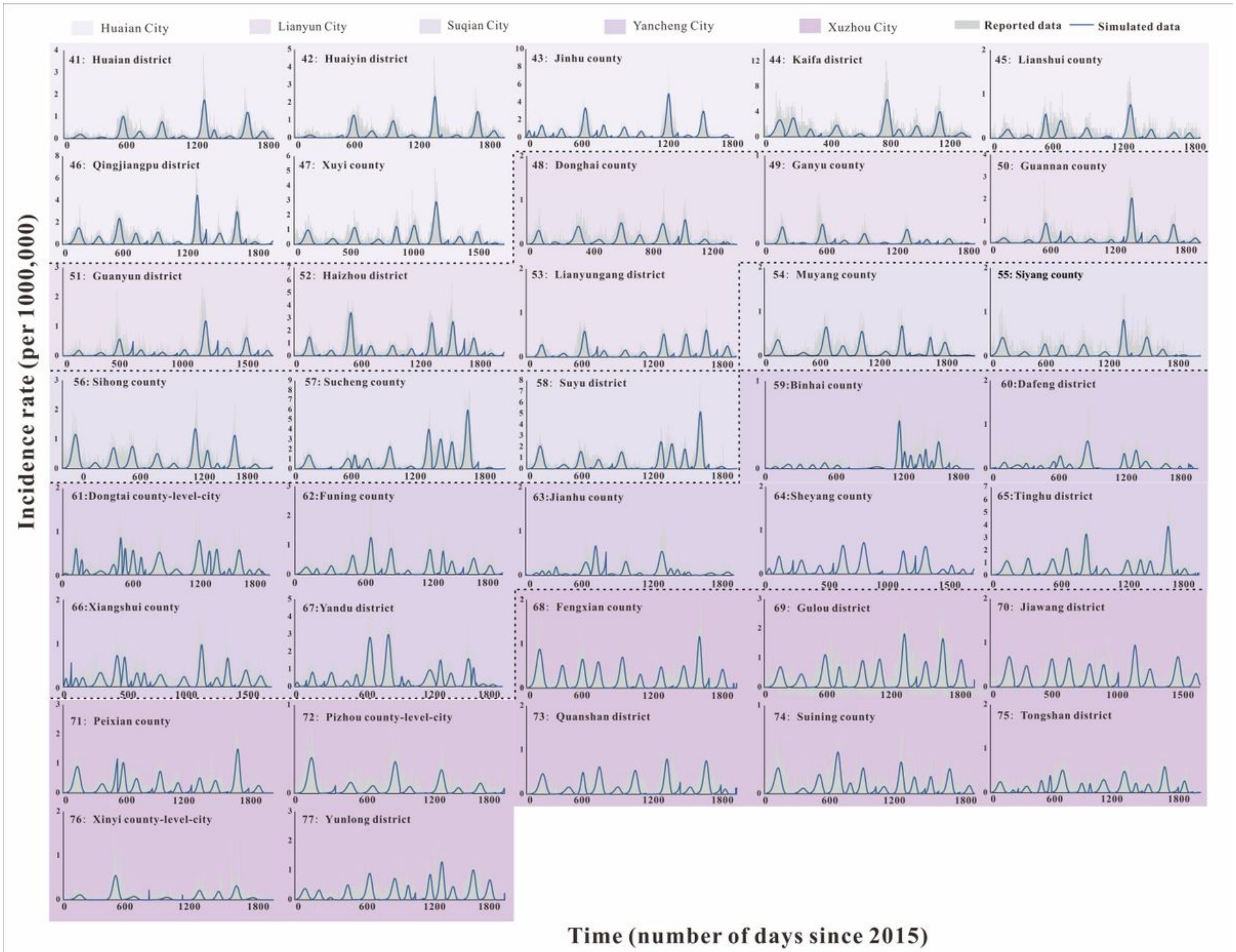

Figure 3

The simulated incidence rate of different regions in northern Jiangsu. No. 41-77 refers to Northern Jiangsu, including Huaian city No. 41-47 (Huaian district, Huaiyin district, Jinhu county, Kafaqu district, Lianshui county, Qingjiangpu district, Xuyi county, respectively), Lianyun city No. 48-53 (Donghai county, Ganyu county, Guannan county, Guanyun district, Haizhou district, Lianyungang district, respectively), Suqian city No. 54-58 (Muyang county, Siyang county, Sihong county, Sucheng district, Suyu district, respectively), Yancheng city No. 59-67 (Binhai county, Dafeng district, Dongtai county-level-city, Funing county, Jianhu county, Sheyang county, Tinghu district, Xiangshui county, Yandu district, respectively), Xuzhou city No. 68-77 (Fengxian county, Gulou district, Jiawang district, Peixian county, Pizhou county-level-city, Quanshan district, Suining county, Tongshan district, Xinyi county-level-city, Yunlong district, respectively).

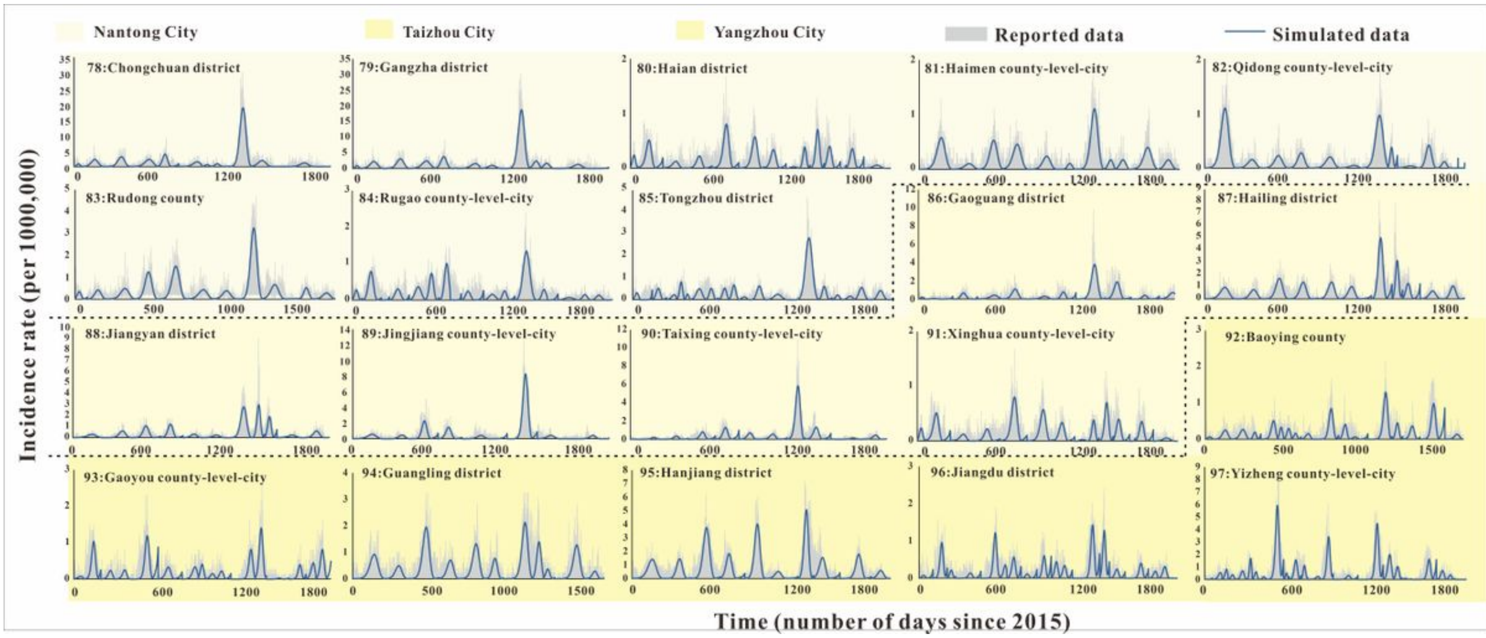

Figure 4

The simulated incidence rate of different regions in Central Jiangsu. No. 78-97 refers to Central Jiangsu, including Nantong city No. 78-85 (Chongchun district, Gangzha district, Haian county-level-city, Haimen district, Qidong county-level-city, Rudong county, Rugao county-level-city, Tongzhou district, respectively), Taizhou city No. 86-91 (Gaogang district, Hailing district, Jiangyan district, Jingjiang county-level-city, Taixing county-level-city, Xinghua, county-level-city respectively), Yangzhou city No. 92-97 (Baoying county, Gaoyou county-level-city, Guangling district, Hanjiang district, Jiangdu district, Yizheng county-level-city, respectively).

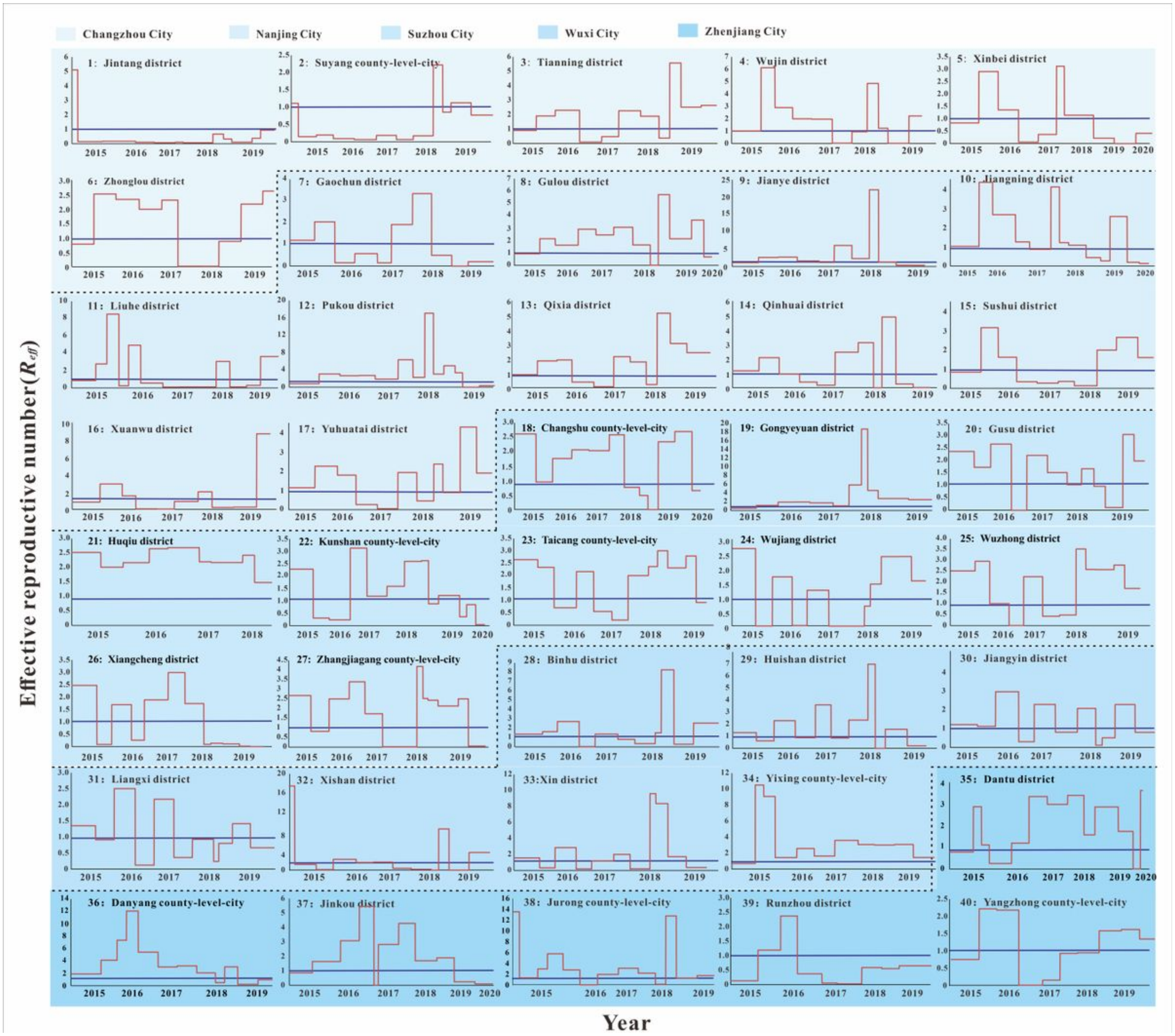

Figure 5

The effective reported number of different regions in Southern Jiangsu. No. 1-40 refers to Southern Jiangsu, including Changzhou city No. 1-6 (Jintang district, Suyang county-level-city, Tianning district, Wujin district, Xinbei district, Zhonglou district, respectively), Nanjing city No. 7-17 (Gaochun district, Gulou district, Jianye district, Jiangning district, Liuhe district, Pukou district, Qixia district, Qinhuai district, Sushui district, Xuanwu district, Yuhuatai district, respectively), Suzhou city No.18-27 (Changshu county-level-city, Gongyeyuan district, Gusu district, Huqiu district, Kunshan county-level-city, Taichng county-level-city, Wujiang district, Wuzhong district, Xiangcheng district, Zhangjiagang county-level-city, respectively), Wuxi city No. 28-34 (Binhu district, Huishan district, Jiangyin county-level-city, Liangxi district, Xishan district, Xin district, Yixing county-level-city, respectively) and Zhenjiang city No. 35-40

(Dantu district, Danyang county-level-city, Jingkou district, Jurong county-level-city, Runzhou district, Yangzhong county-level-city, respectively)

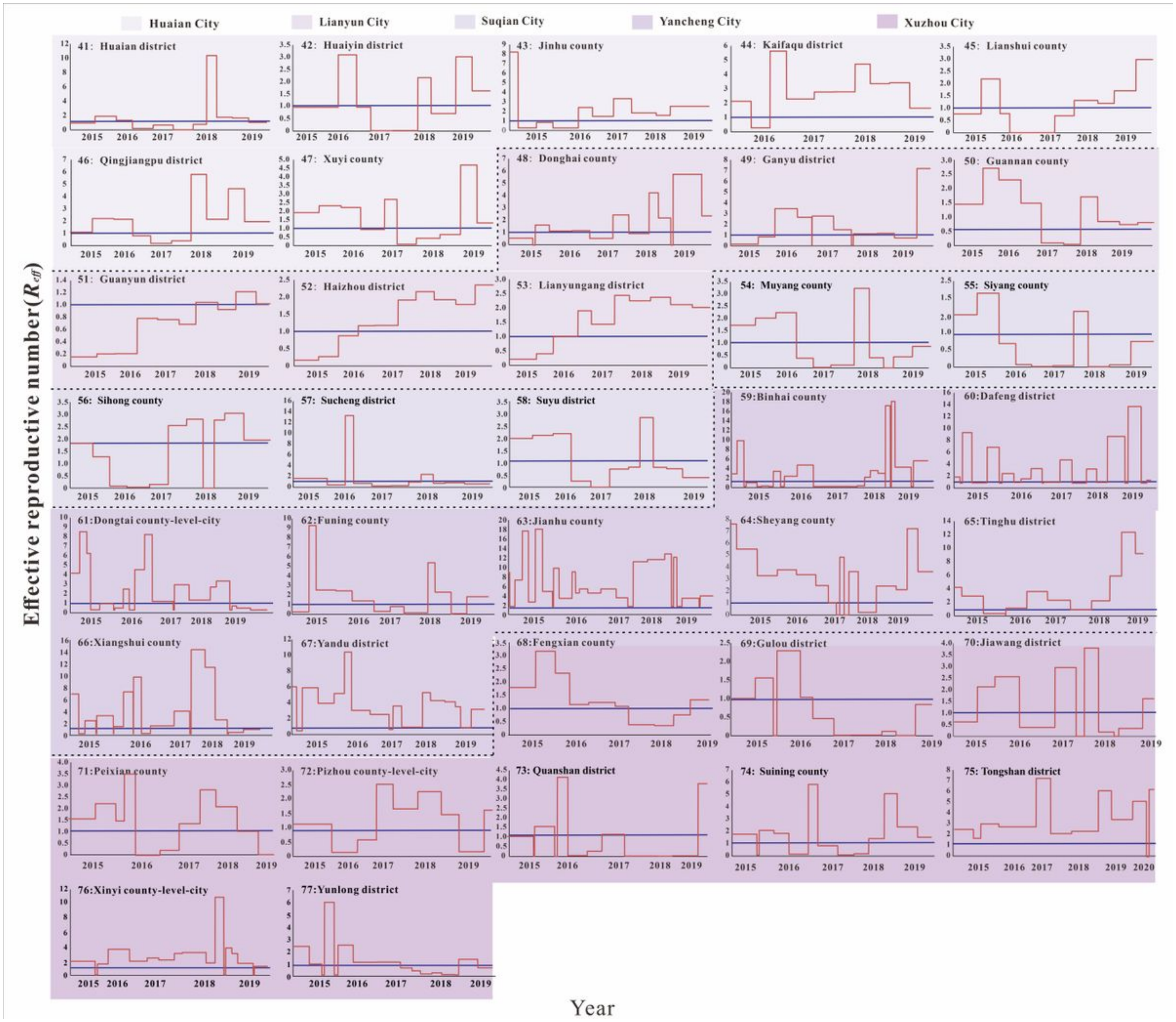

Figure 6

The effective reported number of different regions in northern Jiangsu. No. 41-77 refers to Northern Jiangsu, including Huaian city No. 41-47 (Huaian district, Huaiyin district, Jinhu county, Kafaqu district, Lianshui county, Qingjiangpu district, Xuyi county, respectively), Lianyun city No. 48-53 (Donghai county, Ganyu county, Guannan county, Guanyun district, Haizhou district, Lianyungang district, respectively), Suqian city No. 54-58 (Muyang county, Siyang county, Sihong county, Sucheng district, Suyu district, respectively), Yancheng city No. 59-67 (Binhai county, Dafeng district, Dongtai county-level-city, Funing county, Jianhu county, Sheyang county, Tinghu district, Xiangshui county, Yandu district, respectively), Xuzhou city No. 68-77 (Fengxian county, Gulou district, Jiawang district, Peixian county, Pizhou county-level-city, Quanshan district, Suining county, Tongshan district, Xinyi county-level-city, Yunlong district, respectively).

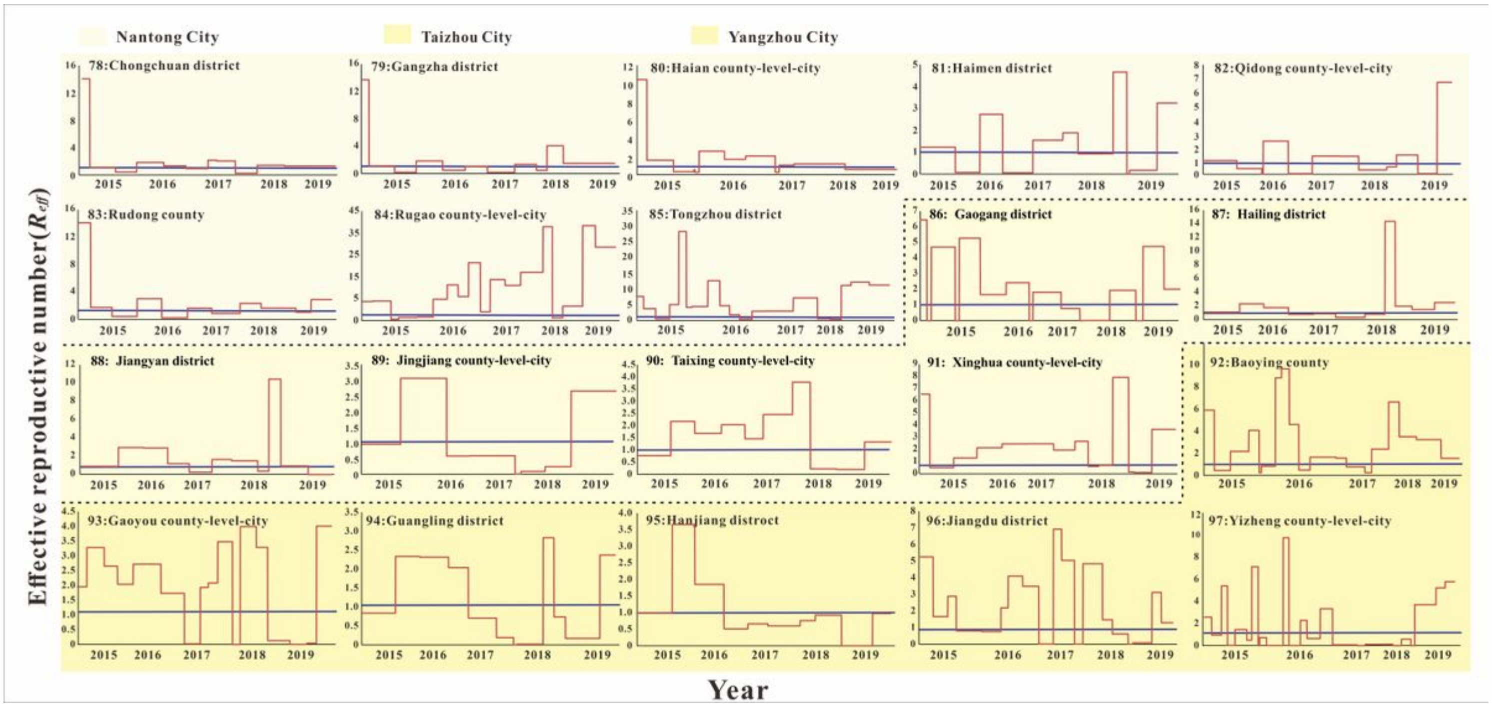

Figure 7

The effective reported number of different regions Central Jiangsu. No. 78-97 refers to Central Jiangsu, including Nantong city No. 78-85 (Chongchun district, Gangzha district, Haian county-level-city, Haimen district, Qidong county-level-city, Rudong county, Rugao county-level-city, Tongzhou district, respectively), Taizhou city No. 86-91 (Gaogang district, Hailing district, Jiangyan district, Jingjiang county-level-city, Taixing county-level-city, Xinghua, county-level-city respectively), Yangzhou city No. 92-97 (Baoying county, Gaoyou county-level-city, Guangling district, Hanjiang district, Jiangdu district, Yizheng county-level-city, respectively).

Supplementary Files

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- supplementTableS1.docx
- FigureS1.FlowchartoftheSEIARmodelforHFMD.jpg