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Development and comparison of forecast models of hand-foot-mouth disease with meteorological factors

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Hand-foot-mouth disease (HFMD) is an acute intestinal virus infectious disease which is one of major public health problems in mainland China. Previous studies indicated that HFMD was significantly influenced by climatic factors, but the associated factors were different in different areas and few study on HFMD forecast models was conducted. Here, we analyzed epidemiological characteristics of HFMD in Yiwu City, Zhejiang Province and constructed three forecast models. Overall, a total of 32554 HFMD cases were reported and 12 cases deceased in Yiwu City, Zhejiang Province. The incidence of HFMD peaked every other year and the curve of HFMD incidence had an approximately W-shape. The majority of HFMD cases were children and 95.76% cases aged ≤ 5 years old from 2008 to 2016. Furthermore, we constructed and compared three forecast models using autoregressive integrated moving average (ARIMA) model, negative binomial regression model (NBM), and quasi-Poisson generalized additive model (GAM). All the three models had high agreements between predicted values and observed values, while GAM fitted best. The exposure-response curve of monthly mean temperature and HFMD was approximately V-shaped. Our study explored epidemiological characteristics of HFMD in Yiwu City and provided accurate methods for early warning which would be great importance for the control and prevention of HFMD.

Hand-foot-mouth disease (HFMD) is an acute intestinal infectious disease which is caused by Enterovirus 71 (EV71), Coxsackie virus A16 (CA16), and other intestinal viruses^{1,2}. It is mainly transmitted by direct contact or indirect contact with saliva, nasal mucus or other nasopharyngeal secretions of HFMD patients³. The main clinical symptoms include fever, vesicular exanthema on hands, feet, mouths, or buttocks⁴. Most patients recover within 7–10 days without any clinical attention due to its typically mild and self-limiting nature. However, HFMD cases caused by EV71 are more severe and they have severe complications including myocarditis, pulmonary edema, aseptic meningoenzephalitis, or even death⁵. Most HFMD patients are infants or children aged ≤ 5 years old⁶.

HFMD was firstly identified in New Zealand in 1957 and then it was confirmed, especially in Asia-Pacific regions^{7–10}. In recent years, HFMD outbreaks were frequently reported in Japan, Malaysia, Singapore, Vietnam and Cambodia^{11–16}. In mainland China, about 13.80 million HFMD cases including 130 thousand serious cases and 3300 deaths were reported from 2008 to 2015.

Previous studies reported that HFMD incidence was significantly influences with meteorological factors such as temperature, relative humidity, and so on^{6,17–19}.

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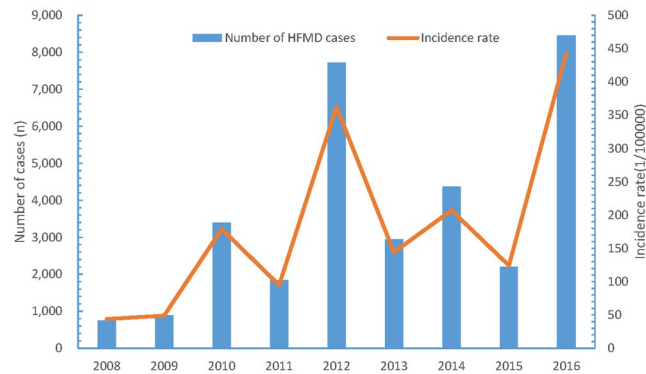


Figure 1. Annual numbers and incidences of HFMD in Yiwu City from 2008 to 2016.

However, few studies were focus on forecast models of HFMD incidence which is of vital importance for HFMD prevention. Zhejiang is a southeastern coastal province of China and a total of 875945 HFMD cases were identified from 2008 to 2015²⁰. Here, we not only analyzed the association between HFMD occurrence and meteorological factors in a city of Zhejiang Province, but also constructed and compared three prediction models for HFMD.

Materials and Methods

Data collection. HFMD cases were diagnosed according to “HFMD Control and Prevention Guide” issued by the National health commission of the People’s Republic of China. HFMD cases should be reported to China Information System for Disease Control and Prevention (CISDCP, <http://www.cdpc.chinacdc.cn>) within 24 h after diagnosis. Information about HFMD cases from 2008 to 2016 in Yiwu City, Zhejiang Province, such as gender, age, occupation, and date of illness onset were obtained from CISDCP. Ethical approval for the study was obtained from the Chinese Center for Disease Control and Prevention Ethics Committee (No. 201214). Informed consent was obtained from all subjects or, if subjects were under 18, from a parent and/or legal guardian. All methods were carried out in accordance with relevant guidelines and regulations and all experimental protocols were approved by Chinese Center for Disease Control and Prevention when HFMD cases were diagnosed in hospitals.

Meteorological data including sunshine duration, monthly precipitation, monthly maximum temperature (T_{max}), monthly minimum temperature (T_{min}), monthly mean temperature (T_{mean}), monthly wind speed (W_{speed}), monthly minimum relative humidity (RH_{min}), and monthly mean relative humidity (RH_{mean}) in Yiwu City were downloaded from the China Meteorological Administration Network (<http://data.cma.cn/>).

Statistical analysis. Statistical analysis was performed with the use of R 3.5.0 and Statistical Product and Service Solutions (SPSS 20.0; Chicago, IL). Descriptive statistics were used to analyze the demographic characteristics and seasonal distribution of HFMD in Yiwu City, Zhejiang Province, China. We used Chi square test to compare gender distribution and seasonal distribution of HFMD cases in different years.

The dataset from 2008 to 2015 was used to develop forecast models and the dataset from the dataset of 2016 were used to test the fit of forecast models. Prior to development of forecast models, correlation analysis was conducted to identify collinearity of independent variables.

ARIMA model was constructed as previously described²¹. Briefly, partial autocorrelation function (PACF) and autocorrelation function (ACF) were analyzed to decide the parameters (p , d , q). The optimal model was selected according to Akaike information criterion (AIC).

The number of monthly HFMD cases in the study is over-dispersed (variance/mean = 502.98), so negative binomial model was selected to analyze the relationship of HFMD and meteorological data. Furthermore, quasi-Poisson generalized additive model (GAM) was also selected to develop forecast model as meteorological factors may have a non-linear relationship with HFMD occurrence. These models were also developed and the optimal models were selected as previously described²¹.

In order to compare the agreement between observed data and forecast data of three models, F test was conducted and intraclass correlation coefficient (ICC) was calculated.

Results

Overall, a total of 32554 HFMD cases were reported and 12 cases deceased in Yiwu City, Zhejiang Province. The number of report HFMD cases from 2008 to 2016 were 747, 886, 3391, 1845, 7724, 2938, 4369, 2196, and 8458, respectively (Fig. 1). Of note, the incidence of HFMD peaked every other year and the curve of HFMD incidence had an approximately W-shape.

About 63.32% HFMD cases were male (20613/32554) and gender distribution of HFMD cases in different years was not similar ($\chi^2 = 41.939$, $P = 0.000$). The numbers of < 1 year old group, 1~ years old group, 2~ years old group, 3~ years old group, 4~ years old group, 5~ years old group and > 5 years old group were 4002, 10140, 7668, 5632, 2609, 2170, and 333, respectively. Most HFMD cases were children and 95.76% cases aged ≤ 5 years old from 2008 to 2016. The majority of HFMD cases were scattered children and kindergarten’s children which accounted for 64.13% and 33.36%, respectively.

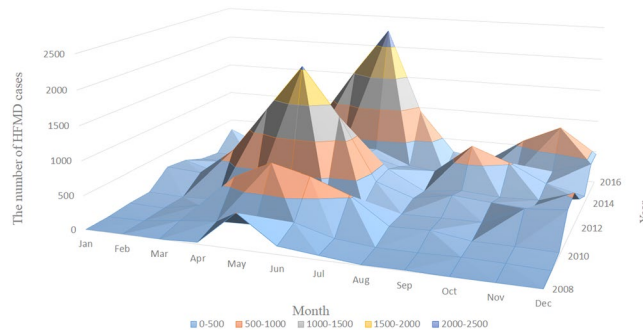


Figure 2. Seasonal distribution of HFMD in Yiwu City from 2008 to 2016.

Variable	P ₀	P ₂₅	P ₅₀	P ₇₅	P ₁₀₀
Number of monthly HFMD cases	0	61.50	181.50	402.75	2263.00
Sunshine duration (h)	29.40	103.90	133.45	172.00	311.40
Monthly minimum temperature (°C)	-0.10	7.53	15.45	22.75	27.80
Monthly maximum temperature (°C)	4.90	15.68	23.80	29.65	37.20
Monthly mean temperature (°C)	2.00	11.05	18.80	25.78	32.00
Monthly precipitation (mm)	6.30	64.38	122.10	192.75	504.50
Monthly wind speed (m/s)	1.00	1.70	1.80	1.90	2.30
Monthly minimum relative humidity (%)	12.00	19.00	23.50	31.00	49.00
Monthly mean relative humidity (%)	52.00	64.00	69.00	76.00	91.00

Table 1. Monthly HFMD occurrence and meteorological factors in Yiwu City from 2008 to 2016.

HFMD cases occurred in every month from January to December, but most cases were reported between April and July (19742/32554) from 2008 to 2016. The month distribution of HFMD cases in different years was not similar ($\chi^2 = 9159.738$, $P = 0.000$). The number of HFMD cases reported in 2008, 2009, 2010, 2012, 2013, 2015 and 2016 peaked in May and June, and that in 2011 peaked in November and December (Fig. 2).

The median of monthly HFMD of 108 months from January 2008 to December 2016 was 181.50 cases and the highest number was 2263 cases. The median values of sunshine duration, T_{min}, T_{max}, T_{mean}, monthly precipitation, W_{speed}, RH_{min}, and RH_{mean} were 133.45 h, 15.45 °C, 23.80 °C, 18.80 °C, 122.10 mm, 1.80 m/s, 23.50%, and 69.00%, respectively (Table 1). According to results of correlation analysis, T_{max}, T_{min}, and T_{mean} were highest correlated, and RH_{min} and RH_{mean} were collinearity. So we selected one of T_{max}, T_{min}, and T_{mean}, and one of RH_{min} and RH_{mean} when we constructed forecast models.

Prior to construction of ARIMA model, results of ADF test indicated time series of monthly HFMD cases was stationary ($DF = -3.5224$, $P = 0.04343$) and results of Lung-Box test indicated that the time series was not of random ($\chi^2 = 57.613$, $P = 0.000$). According to the results of ACF, PACF, and AIC, ARIMA (0, 0, 2) × (0, 1, 1)₁₂ was selected as the optimal model (Fig. 3). Monthly minimum temperature was significantly associated with the number of monthly HFMD cases. Using the optimal ARIMA model, the predicted numbers of monthly HFMD cases of 2016 in Yiwu City were 229, 265, 325, 729, 1136, 1466, 1593, 109, 245, 130, 511, and 713, respectively. The predicted values were in good agreement with observed data (Fig. 4). ICC of the optimal ARIMA model was 0.878 indicating that this model was excellent (Table 2).

Based on the AIC values, the optimal NBM was the following:

$$\log(\mu_t) = \beta_0 + as.factor(month) + \beta_1(Caset1) + \beta_2(Wspeed) + \beta_3(Wspeedt1) + \beta_4(Tmean) + \beta_5(Tmeant1)$$

μ_t , β_0 , month, Caset1, Wspeed, Wspeedt1, Tmean, Tmeant1 represented the number of predicted HFMD cases during month t, the intercept, the month ordinal, the number of HFMD cases during the previous month, the wind speed, the mean wind speed during the previous month, the mean temperature, and the mean temperature during the previous month, respectively. The values of β_2 , β_3 , β_4 , and β_5 were 0.4743, 0.2854, 1.1924, and 3.2772, respectively. In another word, HFMD incidence decreased 52.77% or 71.46% if Wspeed or Wspeedt1 increased a unit, HFMD incidence increased 19.24% or 27.72% if Tmean or Tmeant1 increased a unit.

Using the optimal NBM model, the predicted numbers of monthly HFMD cases of 2016 in Yiwu City were 145, 97, 155, 664, 2429, 4459, 2712, 193, 248, 667, 735, and 341, respectively. The predicted values were in good agreement with observed data (Fig. 4). ICC of the optimal ARIMA model was 0.834 indicating that the model was excellent (Table 2).

Based on the values of deviance explained (%), R square, and GCV principles, the optimal GAM was the following:

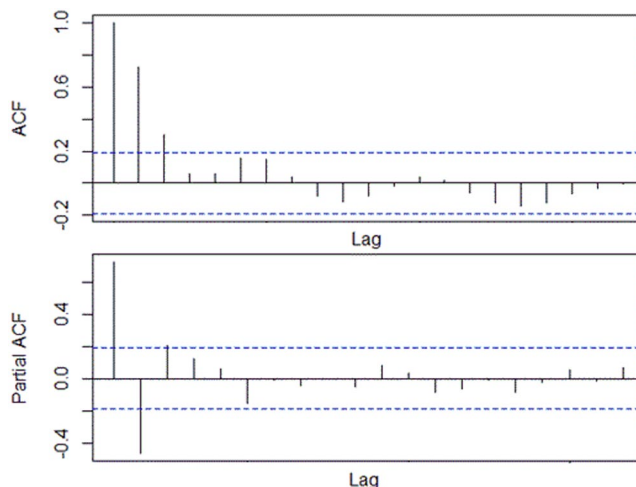


Figure 3. ACF and PACF of ARIMA.

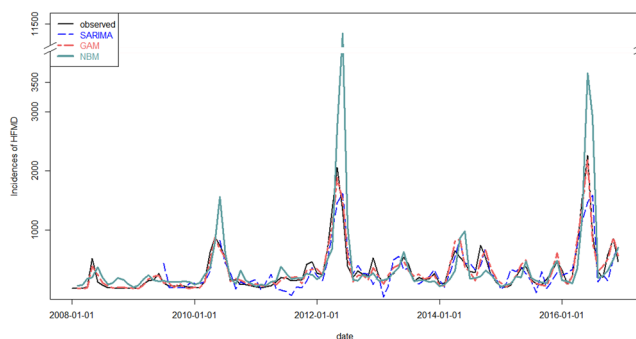


Figure 4. Fit and prediction of three models.

Model	ICC	95% CI of ICC	F-test value	P-value
NBM	0.834	(0.424, 0.952)	6.030	0.003
ARIMA	0.878	(0.577, 0.965)	8.211	0.001
GAM	0.993	(0.976, 0.998)	147.719	<0.001

Table 2. ICC and F test of the three forecast models.

$$\log(\mu_t) = f_0 + as.factor(month) + ns(Caset1, df = 4 * 9) + ns(Tmean, df = 3) + ns(RHmean, df = 4)$$

μ_t , f_0 , month, Caset1, and Tmean represented similar variables in NBM. “RHmean” was the monthly mean relative humidity. As shown in Fig. 4, HFMD cases in the previous month and RHmean were positively associated with HFMD incidence. However, the exposure-response curve of monthly mean temperature and HFMD cases occurrence was approximately V-shaped and Tmean showed positive effects on HFMD incidence when it was higher than 17 °C (Fig. 5). Based on the optimal GAM model, the predicted numbers of monthly HFMD cases of 2016 in Yiwu City were 199, 58, 215, 824, 1399, 2180, 821, 289, 387, 499, 865, and 523, respectively. The predicted values were in good agreement with observed data (Fig. 4). ICC of the optimal ARIMA model was 0.993 indicating that the model was perfect (Table 2).

Discussion

Since HFMD was included in the management of Class C notifiable infectious diseases in mainland China in May 2008, HFMD cases were reported in most provinces of China. A cluster analysis indicated that the incidence rate of HFMD in Zhejiang Province, Hainan Province, Guangxi Province, Shanghai City and Beijing City was higher than that in other provinces²². In Zhejiang Province, at least tens of thousands of HFMD cases were reported every year and 212536 HFMD cases were identified in 2014²⁰. Yiwu City is located in the center of Zhejiang

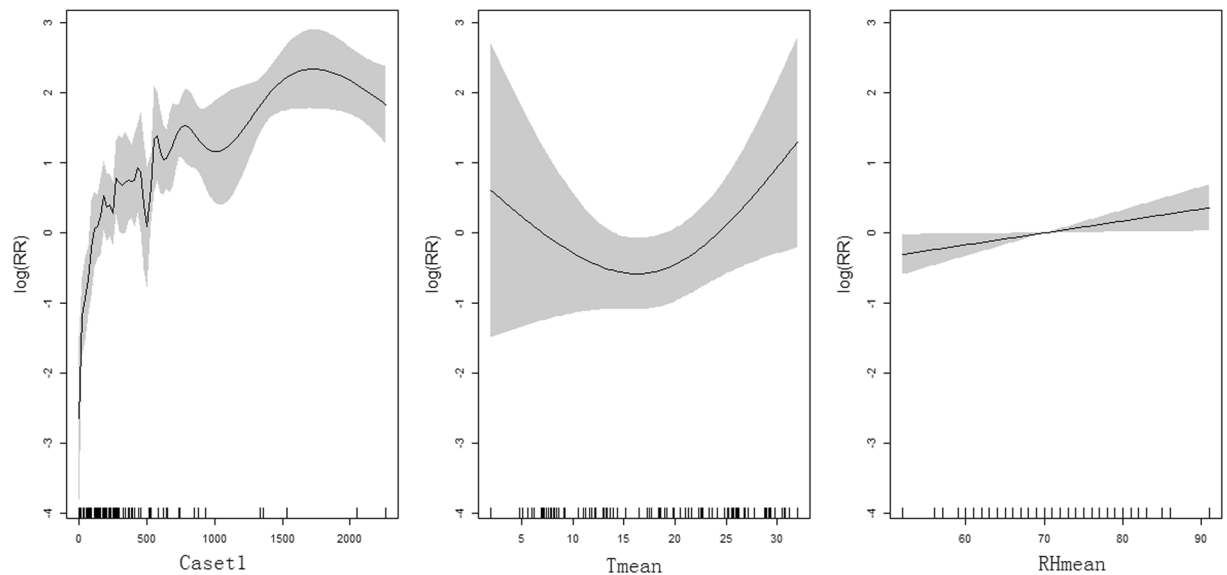


Figure 5. The relationship between HFMD and associated factors.

Province and clusters of HFMD cases have been identified in this city²³. In this study, we found that the incidence rate of HFMD was upward despite the fluctuations. The results informed that comprehensive measures should be conducted to prevent the increase of HFMD incidence rate.

Similar to other studies, our study indicated that 95.76% HFMD cases aged ≤ 5 years and most cases were male^{24,25}. Decrease immune function, more exposure chance, and genetic susceptibility may contribute this result. Nevertheless, male children aged ≤ 5 years were the emphasis for control and prevention of HFMD. Most HFMD cases were reported during April and July, but the peak period of different years was slightly different. Notably, the peak period in 2011 was November and December. The reason may be that weather factors of November and December, 2011 were suitable for the growth and transmission of HFMD pathogens. The result suggested that control measures should also be conducted in other months according to the fluctuation of HFMD incidence rate.

Previous studies reported that some meteorological factors were associated with HFMD incidence, but the associated factors were different in different areas. A study in Hefei City, China reported that HFMD occurrence was significantly influenced by extreme precipitation and the effect was the greatest at 6 days lag²⁶. Yu G *et al.* reported that high precipitation, extreme temperatures and low-O₃ concentration increased HFMD incidence, whereas extremely high wind speed, low PM_{2.5}, low precipitation, and high O₃ decreased HFMD incidence in Guilin City, China²⁷. Wang P *et al.* found that the year-round temperature and relative humidity, sun duration in winter, and rainfall in summer significantly influenced HFMD incidence²⁸. A study in Hong Kong reported that relative humidity, temperature, rainfall, solar radiation and wind speed were associated with HFMD incidence²⁹. Moreover, Tian L *et al.* found that mean temperature, relative humidity, wind velocity and sunshine hours were all positively associated with HFMD in Beijing City, but Liu W *et al.* found relative humidity had no relationship with HFMD in Jiangsu Province^{24,30}. In our study, NBM and GAM results indicated that monthly mean relative humidity, monthly mean temperature, and wind speed were significantly associated with HFMD. The different risk factors in different areas suggested that different interventions should be conducted in different areas and control measures should be more accurate.

Beside analysis of meteorological factors associated with HFMD incidence, we selected three forecast models using ARIMA, NBM, and GAM to predict HFMD incidence in Yiwu City. During the construction of ARIMA modes, periodic changes, long term trends, and random disturbances were all taken into account. Up to date, ARIMA models have been widely used in infectious diseases prediction including malaria, hemorrhagic fever with renal syndrome (HFRS), and influenza, and so on^{31,32}. Our study found that ARIMA was also suitable for the forecast of HFMD incidence.

Due to over dispersion of monthly HFMD cases, NBM was selected to construct prediction model instead of Poisson model in our study. The optimal NBM also had good agreement between prediction values and observed values, but ICC of this model was the least. We found that the prediction was good in months when the number of HFMD cases was small, but the prediction was not good in months when the number of HFMD cases was large. The prediction value was significantly larger than observed value during HFMD peak periods.

GAM can analyze nonnormally distributed data³³. It can adjust not only nonlinear, nonparametric, and trends, but also confounding effects of seasonality, and weather variables. In our study, we used a quasi-Poisson GAM to analyze relationship between meteorological factors and HFMD and develop HFMD model. ICC of GAM indicated that this model was perfect for prediction of HFMD occurrence. In addition, we found that monthly mean temperature had positive effect on HFMD when it was higher than 17 °C. It suggested that 17 °C of monthly mean temperature could be considered as an alarm value for early warning of HFMD.

In summary, our study not only analyzed epidemiological characteristics of HFMD in Yiwu City but also explored associated meteorological factors and developed three forecast models. All the three models had high agreements between predicted values and observed values, while ICC of GAM was the best. We also identified that temperature, relative humidity, and wind speed were significantly associated with HFMD. The exposure-response curve of monthly mean temperature and HFMD cases occurrence was approximately V-shaped and it showed positive effects on HFMD incidence when it was higher than 17 °C. Our study explored epidemiological characteristics of HFMD in Yiwu City and provided accurate methods for early warning which would be great importance for the control and prevention of HFMD.

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Author contributions

J.S. designed and supervised the study. T.F., T.C. and Z.D. analyzed and interpreted the findings. S.L., Z.M., X.S. and R.H. participated in the collection and analysis of surveillance data. J.S. wrote the drafts of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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