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Hand-foot-and-mouth disease and weather factors in Guangzhou, southern China

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SUMMARY

Hand-foot-and-mouth disease (HFMD) is becoming one of the common airborne and contact transmission diseases in Guangzhou, southern China, leading public health authorities to be concerned about its increased incidence. In this study, we aimed to examine the effect of weather patterns on the incidence of HFMD in the subtropical city of Guangzhou for the period 2009–2012, and assist public health prevention and control measures. A negative binomial multivariable regression was used to identify the relationship between meteorological variables and HFMD. During the study period, a total of 166 770 HFMD-confirmed cases were reported, of which 11 died, yielding a fatality rate of 0·66/10 000. Annual incidence rates from 2009 to 2012 were 132·44, 311·40, 402·76, and 468·59/1 000 00 respectively. Each 1 °C rise in temperature corresponded to an increase of 9·38% (95% CI 8·17–10·51) in the weekly number of HFMD cases, while a 1 hPa rise in atmospheric pressure corresponded to a decrease in the number of cases by 6·80% (95% CI −6·99 to −6·65), having an opposite effect. Similarly, a 1% rise in relative humidity corresponded to an increase of 0·67% or 0·51%, a 1 m/h rise in wind velocity corresponded to an increase of 4·01% or 2·65%, and a 1 day addition in the number of windy days corresponded to an increase of 24·73% or 25·87%, in the weekly number of HFMD cases, depending on the variables considered in the model. Our findings revealed that the epidemic status of HFMD in Guangzhou is characterized by high morbidity but low fatality. Weather factors had a significant influence on occurrence and transmission of HFMD.

Key words: Correlation analysis, hand-foot-and-mouth disease (HFMD), meteorological variables.

INTRODUCTION

Hand-foot-and-mouth disease (HFMD) is caused by a number of different enteroviruses. The disease is transmitted through direct contact with respiratory droplets, faeces, and blister fluid of infective patients or through contact with a contaminated environment, e.g. water, food, or surfaces [1]. The clinical presentations of HFMD are characterized by fever and vesicular exanthema mostly in hands, feet and oral mucosa [2]. The disease is usually mild and self-limiting, but sometimes serious neurological and cardiopulmonary complications may occur in HFMD outbreaks, particularly when the causative virus is enterovirus 71 [3, 4].

Recent epidemics have tended to be located in the Asian Pacific regions. In 2008, a large wave of

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HFMD epidemics occurred in mainland China, Taiwan, Malaysia, Singapore, and Hong Kong. In mainland China, epidemics started in Fuyang city, Anhui province, resulting in 353 severe cases and 22 deaths, and then rapidly developed into a nationwide epidemic, covering 28 provinces within 3 months with 345 159 reported cases [5]. To control the HFMD infections and decrease mortality from HFMD in China, in May 2008 the Chinese Ministry of Health (MOH) legislated that HFMD be listed as a notifiable Class C communicable disease [6]. In Guangzhou, the largest trading city in southern China, HFMD is becoming one of the common airborne and contact transmission diseases. Preventive measures such as avoiding direct contact with infective patients, disinfection of virally contaminated items or premises, and good personal hygiene practices have been strongly recommended and sometimes mandatorily implemented by local government. Despite these measures the annual incidence of HFMD remained the highest of all reportable infectious diseases since 2008, leading public health authorities to be concerned about its increased incidence.

Currently, effective chemoprophylaxis or vaccination approaches for dealing with HFMD are still not available [7]. Programmes to prevent this disease concentrate on monitoring and predicting HFMD incidence. In recent decades, weather variables have been widely studied for their potential as early warning tools to control climate-sensitive infectious diseases [8]. Previous studies have reported that the incidence of HFMD exhibited seasonal variation in a number of different areas. For example, a bimodal seasonal pattern has been detected in the UK, which is characterized by peaks in HFMD incidence in the summer and late autumn/early winter [9]. In Belgium, HFMD infections are typically present throughout the year, showing small peaks in summer and autumn [10], while the incidence of HFMD is highest in summer in Taiwan [11]. The seasonality of HFMD suggests that meteorological variables might be influential in the spread of the disease.

The relationship between meteorological variables and HFMD has been documented in a few studies and the findings are inconsistent [12–15]. For example, a Singapore study showed that weekly maximum temperature elevated HFMD incidence and a Hong Kong study also supported this positive association [13, 14], whereas another study from Japan found that the number of days per week where the average temperature was >25 °C was negatively associated with HFMD incidence [15]. In addition, a recent study in Japan found a non-significant association between rainfall and HFMD, in contrast to findings in Singapore [12, 13]. Moreover, high wind speed was shown to be a risk factor for HFMD in the Hong Kong study [14], but no other study supported these findings. Moreover, the relationship between HFMD and other meteorological variables (e.g. air pressure) and weather events (e.g. hot days, windy days) has not yet been estimated. Therefore, there is an urgent need to investigate such relationships which can help in establishing the development of an early warning system for HFMD.

In this study, we aimed to estimate the effects of diverse climate variables, such as temperature, relative humidity, rainfall, air pressure, and duration of hot days and windy days, on the incidence of HFMD in the subtropical city of Guangzhou for 2009–2012, in order to assist public health prevention and control measures.

Ethical approval

This study was approved by the ethics committee of Guangzhou Center for Disease Control and Prevention (GZCDC).

MATERIALS AND METHODS

Study area

Guangzhou is 7434·4 km^2 in size, situated in north latitude 22° 26′ N to 23° 56′ N and east longitude 112° 57′ E to 114° 3′ E, with over 7·94 million registered inhabitants and 4·76 million floating population (2010 census data). It traverses the Tropic of Cancer, and the climate is characterized as humid subtropical and influenced by the Asian monsoon. Summers are wet with high temperatures and a high humidity index. Winters are mild, dry and sunny. The annual mean temperature ranges from 18 °C to 25 °C. The annual rainfall is typically between 1500 mm and 2000 mm (Fig. 1).

Surveillance data of HFMD

Since May 2008, the Chinese Ministry of Health has categorized HFMD as a Class C infectious disease. This means, as for other national reportable diseases, physicians who diagnose suspected or confirmed HFMD cases must report these cases to GZCDC via the National Notifiable Disease Report System

Fig. 1 [*colour online*]. Geographical location of the study area (Guangzhou).

(NNDRS). For a patient's illness to meet the case definition for HFMD the following clinical signs (fever, papules and herpetic lesions on the hands or feet, rashes on the buttocks or knees, inflammatory flushing around the rashes and little fluid in the blisters, sparse herpetic lesions on oral mucosa) must be present and samples should be taken for laboratory confirmation (fourfold rise in antibody titre, antigen detected in blood, PCR-detected samples from throat, fluids from blisters and stools).

Unlike other sentinel surveillance data, the data collected from NNDRS is nationwide, which is more representative for an actual HFMD epidemic. A recent data quality inspection report has demonstrated that the data are of good quality, with reporting completeness of 99·84% and accuracy of the information reported of 92·76% [16]. In this study, we used the data of daily reported HFMD cases in Guangzhou from 1 January 2009 to 31 December 2012.

Meteorological data

Simultaneous meteorological data, including daily average temperature (°C), relative humidity (as a percentage), atmospheric pressure (in hPa), wind velocity (m/s) and rainfall (mm) were obtained from the documentation of the Guangzhou Meteorological Bureau. A hot day was defined as having a daily average temperature $\geqslant 30$ °C, which is higher than the summer mean temperature plus 2 standard deviations. A windy day was defined as having a daily average wind velocity $\geqslant 7$ m/s, which represents gentle breeze, moderate breeze, fresh breeze and stronger according to the Classification of Wind Speeds. The weather data were measured at a fixed-site station located in a central district of Guangzhou. Meteorological instruments included barometers, pressure readings, thermometers, anemometers, actinometers, psychrometers, evaporimeters, and weather vanes. The measurements of temperature, relative humidity, atmospheric pressure and wind velocity were usually taken every 3 h before the daily average was calculated. However, for rainfall, the daily total was used.

Data analysis

The HFMD annual incidence rate was calculated as the total number of HFMD new cases reported during 1 January to 31 December of a year, divided by the total population of the same year. A negative binomial multivariable regression was used to explore the relationship between meteorological variables and HFMD. Negative binomial distribution is a Poisson distribution with an extra-dispersion term, the extra dispersion term acts as a random effect that subjects the Poisson means to additional variation that has a gamma distribution. Given the data were over-dispersed, we chose a negative binomial distribution

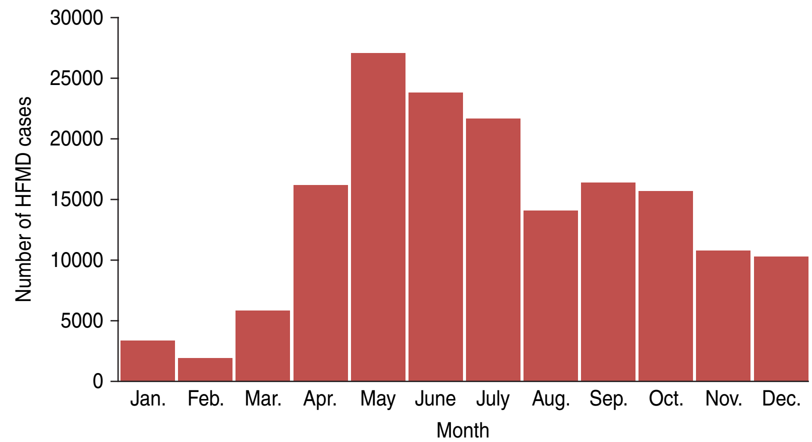

Fig. 2 [*colour online*]. Monthly distribution of hand-foot-and-mouth disease (HFMD)-confirmed cases in Guangzhou, southern China, 2009–2012.

model rather than a Poisson model. The cases were HFMD occurrences. Data were presented as the prevalence of HFMD/100 000 inhabitants grouped by week of onset. The meteorological variables were calculated by weekly average or aggregated. A preliminary analysis was conducted through Pearson's correlation coefficient (r) matrix within meteorological variables. This indicated that the model constructed using contemporaneously both temperature and atmospheric pressure suffered from collinearity problems, because the two variables showed strong negative correlation (r=–0·81, P<0·01). Thus, we constructed two separate negative binomial regression models: the first included average temperature but no atmospheric pressure, while the second included atmospheric pressure but no average temperature. Both models included additionally relative humidity, wind velocity, rainfall, number of windy days per week, number of hot days per week, and year and month as independent variables. To quantify the effects of meteorological variables, we computed the influences $(e^{\beta} - 1) * 100$, which virtually correspond to the percent increase. We tested the interactions between temperature and wind speed, which indicated that the interaction term was not significant in the model. The final model included only those variables that reached a P value of <0·05. However, in order to control the monthly fluctuant, the 'month' variable was forced into the final model even though it was not significant. We used the logarithm of predicted rate to examine the linearity between predictor and continuous variable. In addition, the residual was checked using Pearson goodness of fit. These analyses were performed using SAS v. 8.01 (SAS Institute Inc., USA). P values <0·05 were considered statistically significant.

RESULTS

From 1 January 2009 to 31 December 2012, a total of 166 770 HFMD-confirmed cases were reported in Guangzhou, southern China, of which 62·74% (104 632) were males and 37·26% (62 138) were females. Eleven cases in the 1–14 years age group died, yielding a fatality rate of 0·66/10 000. The greatest number of cases was in the 0–5 years age group, which accounted for 93·67% (156 214) of total cases reported. Annual incidence rates from 2009 to 2012 were 132·44/1 00 000 311·40/1 00 000 402·76/1 00 000 and 468·59/1 00 000 respectively. Monthly changes in the number of cases showed HFMD cases were detected throughout the year. A sharp peak in the number of cases occurred in May–July, 43·43% of all cases were reported during this period. A small peak occurred in September–October, the number of cases reported during this period accounted for 19·16% of total cases (Fig. 2).

During the study period, minimum and maximum temperature was 1·80 °C and 38·60 °C, respectively, and average temperature was 22·23 °C. The relative humidity ranged from 25·00% to 99·00%, with an average of 73·94%. The atmospheric pressure ranged from 987·40 hPa to 1026·60 hPa, with an average of 1006·77 hPa. The wind velocity ranged from 0·40 m/s to 9·10 m/s, with an average of 1·90 m/s. The daily rainfall ranged from 0 mm to 214·70 mm, with a cumulative amount of 7309·60 mm for the 4-year period (Fig. 3).

Table 1. *Pearson's correlation coefficient (r) matrix of meteorological variables in Guangzhou, southern China, 2009–2012*

	Air pressure	Wind velocity	Average temperature	Relative humidity	Rainfall
Air pressure	1·00				
Wind velocity	0·03 ($P=0·29$)	1·00			
Average temperature	−0·81 ($P<0·001$)	−0·29 ($P<0·001$)	1·00		
Relative humidity	−0·43 ($P<0·001$)	−0·05 ($P=0·05$)	0·15 ($P<0·001$)	1·00	
Rainfall	0·04 ($P=0·12$)	−0·04 ($P=0·18$)	0·01 ($P=0·66$)	−0·02 ($P=0·34$)	1·00

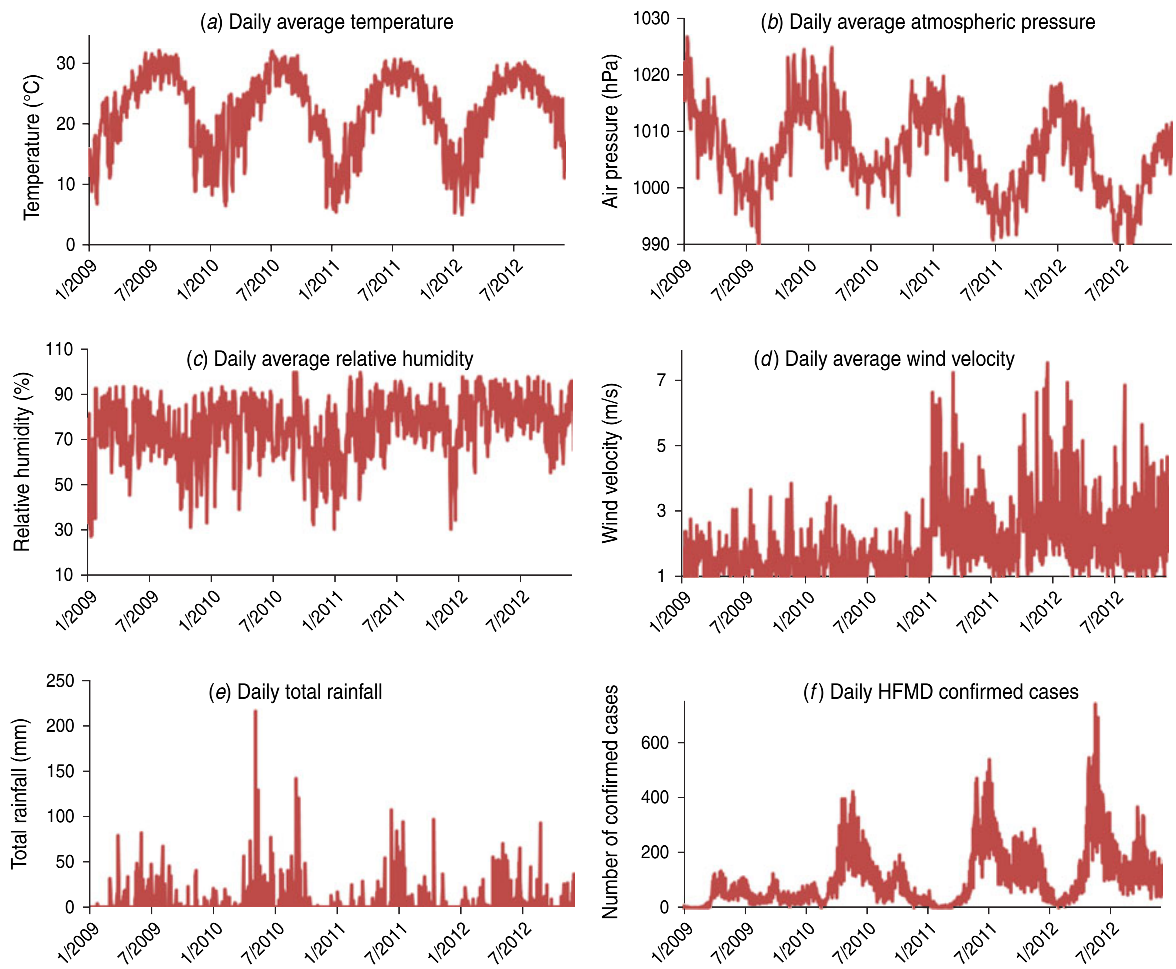

Fig. 3 [*colour online*]. Daily distribution of (*a*) average temperature; (*b*) average atmospheric pressure; (*c*) average relative humidity; (*d*) average wind velocity; (*e*) total rainfall; (*f*) hand-foot-and-mouth disease (HFMD)-confirmed cases in Guangzhou, southern China, 2008–2012.

The correlations between independent variables revealed a strong correlation ($r=-0·81$, $P<0·01$) between average temperature and atmospheric pressure (Table 1). Therefore, to avoid collinearity problems, we decided to explore the relationship of temperature and atmospheric pressure in HFMD cases by using two different models, including either temperature or atmospheric pressure together with all other predictors. In the two models, temperature ($P<0·01$) and atmospheric pressure ($P<0·01$) were highly significant; wind velocity, number of windy days per week, relative humidity, and year were also significant in both models (all $P<0·05$). After adjusting by 'year' and 'month', Each 1 °C rise in temperature

Table 2. *Negative binomial regression model of meteorological factors associated with risk of hand-foot-and-mouth disease (HFMD) incidence in Guangzhou, southern China, 2009–2012*

	β	S.E.	P	Percent increase= $(e^{\beta}-1)*100$	95% CI for percent increase (%) Lower boundary	Upper boundary
(A)						
(Intercept)	−565·9840	6·7813	0·0036	–	–	–
Average temperature	0·1000	0·0007	0·0008	10·5171	10·4066	10·6277
Wind velocity	0·0300	0·0001	0·0116	3·0455	2·7368	3·2518
Windy days	0·2010	0·0158	0·0006	22·2625	21·7744	23·9862
Hot days	−0·1130	0·0250	0·1311	−10·6849	−22·0420	0·0610
Rainfall	0·0000	0·0123	0·0907	−0·0045	−0·0091	0·0002
Relative humidity	0·0090	0·0004	0·0005	0·9041	0·7145	1·0050
Year	0·2830	0·0034	0·0011	32·7105	31·9166	33·6427
Month	0·0020	0·0010	0·0581	0·2002	−0·0024	0·4008
(B)						
(Intercept)	−425·5790	7·1372	0·0015	–	–	–
Atmospheric pressure	−0·0630	0·0005	0·0004	−6·1057	−6·1995	−6·0117
Wind velocity	0·0100	0·0001	0·0124	1·0050	0·8032	1·6129
Windy days	0·2000	0·0157	0·0014	22·1403	20·3218	24·8946
Hot days	−0·0550	0·0240	0·0757	−5·3515	−9·9099	0·0700
Rainfall	0·0000	0·0000	0·1601	−0·0049	−0·0051	0·0046
Relative humidity	0·0070	0·0004	0·0004	0·7025	0·4008	0·9041
Year	0·2470	0·0035	0·0009	28·0179	27·1249	28·9172
Month	0·0024	0·0090	0·0630	0·2403	−0·0022	0·4711
(C)						
(Intercept)	−411·3370	11·0069	0·0032	–	–	–
Average temperature	0·0897	0·0009	0·0014	9·3846	8·1663	10·5096
Wind velocity	0·0393	0·0001	0·0096	4·0082	3·0455	5·0336
Windy days	0·2210	0·0047	0·0008	24·7323	23·6024	25·9481
Relative humidity	0·0067	0·0009	0·0011	0·6672	0·4410	0·8738
Year	0·2655	0·0076	0·0013	30·4083	27·6089	33·3091
Month	0·0017	0·0048	0·1109	0·1701	−0·0080	0·3107
(D)						
(Intercept)	−299·5700	5·5537	0·0027	–	–	–
Atmospheric pressure	−0·0704	0·0008	0·0009	−6·8007	−6·9934	−6·6496
Wind velocity	0·0262	0·0003	0·0012	2·6546	1·5621	3·5653
Windy days	0·2301	0·0036	0·0035	25·8726	25·4453	26·2634
Relative humidity	0·0051	0·0011	0·0069	0·5113	0·3105	0·6924
Year	0·2338	0·0041	<0·0001	26·3392	23·5777	29·3174
Month	0·0022	0·0042	0·2511	0·2202	−0·0090	0·4108

CI, Confidence interval.
Negative binomial regression model for weekly HFMD incidence without atmospheric pressure (A) and without average temperature (B). Final model without atmospheric pressure (C) and without average temperature (D).

corresponded to an increase of 9·38% (95% CI 8·17–10·51) in the weekly number of HFMD cases, while a 1 hPa rise in atmospheric pressure corresponded to a decrease in the number of cases by 6·80% (95% CI −6·99 to −6·65), showing an opposite effect. Similarly, a 1% rise in relative humidity corresponded to an increase of 0·67% or 0·51%, a 1 m/h rise in wind velocity corresponded to an increase of 4·01% or 2·65%, and a 1 day addition in the number of windy days corresponded to an increase of 24·73% or 25·87%, in the weekly number of HFMD cases, depending on the variables considered in the model (Table 2). Pearson goodness of fit for both models indicated $P>0·05$.

DISCUSSION

Over the last decade, HFMD has posed a great threat to the health of the population and become a public health priority in China [17]. During our 4-year study period, a total of 166 770 confirmed cases were detected, which indicated that HFMD was highly prevalent in Guangzhou. However, despite the substantial number of cases, the overall fatality rate of HFMD for 2009–2012 was 0·66/10 000 which is significantly lower than previously reported from Cambodia [18], Vietnam [19] and some other cities of China [20]. This indicates that currently, the epidemic status of HFMD in Guangzhou, southern China, is characterized by high morbidity but low fatality

Similar to findings from Taiwan [21], Singapore [22], and other areas [23, 24], the HFMD-confirmed cases reported in Guangzhou were significantly more male than female, with the largest number of reported cases in the 0–5 years age group. However, contrary to the situation in Mongolia and northern China [25], where only a single peak of HFMD was observed in July, the present study demonstrates that two incidence peaks were detected in Guangzhou every year, the higher one occurring in May–July, and the smaller one in September–October. These two peaks were reached about 1 month earlier than in other Asian countries, e.g. Japan [12] and Viet Nam [26].

The increasing evidence for rapid global climate change has highlighted the need for investigations examining the relationship between weather variability and infectious diseases. However, the impact of weather fluctuations on HFMD is still not well understood [12]. Our study, which was conducted in Guangzhou, demonstrated that weather factors have a significant influence on HFMD activity. We found that high temperature and high humidity presented a higher risk of HFMD infection. These findings are consistent with a previous study in Tokyo, Japan, which suggested that higher temperature and humidity may have influenced the increase of HFMD incidence observed there between 1999 and 2002 [15], and with the findings of a more recent study in Hong Kong indicating that HFMD consultation rates were positively associated with temperature and humidity [14]. However, a recent study in Singapore showed that in addition to a maximum daily temperature >32 °C, rainfall of up to 75 mm was also associated with an increased incidence of HFMD [13]. Although we also examined the effects of rainfall on HFMD incidence, no evidence of an association with the number of HFMD cases was detected. This discrepancy might be due to the effects of relative humidity, which were controlled for in the present study, but not in the study conducted in Singapore. In addition, a laboratory-based study suggested that enteroviruses are resilient to the environmental conditions of the gastrointestinal tract, and that their stability in external environmental conditions is dependent on temperature, humidity, and UV radiation [1]. For these reasons, an increased number of enteroviral infections might be expected to occur during the summer and early autumn seasons in temperate areas; meanwhile, enteroviral infections might maintain a constant level throughout the year in tropical and subtropical areas [27], and as indicated by the present study, HFMD in Guangzhou was detected throughout year.

We found that atmospheric pressure was negatively associated with HFMD occurrence. Each 1 hPa rise in atmospheric pressure corresponded to a decrease in the number of cases by 6·80%. A similar finding was also observed in the north of China [28], which indicated that air pressure behaved in the opposite way to incidence distribution of HFMD. However, no studies have yet been published revealing the underlying mechanism. A possible explanation might be that lower atmospheric pressure may weaken the human immune system's strength or organisms [29]. For example, Danet *et al.* [30] reported that a 10 mbar decrease in atmospheric pressure was associated with a 12% increase in coronary disease incidence rates; Styra *et al.* [31] found that the correlation between a decrease in atmospheric pressure and an increase in cardiovascular disease was 25–44%.

Our study indicates that wind speed had a significant effect on the incidence of HFMD infection; each 1 m/s rise in wind velocity may lead to an increase of 4·01% or 2·65% in the weekly number of HFMD cases. This finding is in agreement with findings from Hong Kong which showed wind speed could elevate HFMD consultation rates [14]. Furthermore, we also found that a windy day was positively associated with HFMD occurrence. There is some evidence to suggest that pathogens can be spread from one region to another along air streams by wind [32]. That means microorganisms (including viruses) from an infectious source may disperse over longer distances due to increased wind velocity and ultimately be inhaled, ingested, or come into contact with more individuals who have had no contact with the infectious source [33–36]. For example, in Greece, the wind speed was found to be positively associated with the occurrence of hospitalized varicella cases [37]. In the USA, high wind speed was considered as a predictor for increasing the number of cases in a norovirus outbreak [38]. However, as far as airborne transmission diseases are concerned, most published studies reached the opposite conclusion. It has been proved that higher wind speed markedly reduces the amount of airborne infectious particles in the air, which eventually leads to a significant reduction in exposure to infectious particles [39]. Therefore, more studies, which take these variables into account, need to be undertaken.

Some methodological limitations must be acknowledged for this study: first, surveillance data for HFMD do not capture all cases in the community. This under-reporting of infections can occur anywhere in the report chain, from the initial decision of the patient to not seek healthcare to failure to record the case in the disease registry, due to the mildness or lack of symptoms; second, the incubation period of 3–7 days for every case cannot be determined exactly and this is the reason we chose to use weekly aggregated data of HFMD cases reported and weekly average/aggregated meteorological data; however, the direction of these approximations, are likely to be random, suggesting that our risk estimates are reliable; third, our study did not incorporate the pathogen of HFMD such as EV71, CA16 and other enteroviruses. Enterovirus surveillance in USA for the period 1970–2005 showed that EV71 and CA16 had an endemic circulation pattern and that around 70% of cases were reported during warmer seasons between June and October [40]. In some regions the predominant viruses causing HFMD are EV71 and CoxA16 in spring and summer, and other enteroviruses in autumn and winter [25]. Future research should therefore concentrate on the relationship between enterovirus subtypes and meteorological variables; finally, although this investigation was an ecological study and we emphasized the direct impact of climate, some intervening variables probably existed, and we also cannot exclude that we could not identify and consider some potential confounding variables.

Global climate change has profound impacts on infectious disease. Elucidation of the effects of weather variability on the epidemiology of infectious diseases is becoming important for disease control by public health officials and practitioners. The results of this study may aid in the prediction of epidemics and in preparation for the effects of climate changes on the epidemiology of HFMD through implementation of preventive public health interventions, such as promoting good hygiene practices, temporary closure of educational institutions, and campaigns that include press releases and media events to encourage preventive activities. It is expected that such activities might be practically useful for preventing or limiting the spread of HFMD infections. Of course, some findings in the present study require replication, especially in different areas with different weather patterns.

In conclusion, we have reported on the current epidemic status of HFMD in Guangzhou, southern China, which is characterized by high morbidity but low fatality. We also found that climate parameters could help in predicting HFMD activity. A rise of average temperature, relative humidity, wind speed and windy days may increase the risk of HFMD infection, whereas an increase in atmospheric pressure may reduce the risk of HFMD infection. Our findings provide preliminary but fundamental information that may be useful for better understanding epidemic trends of HFMD and developing an early warning system.

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DECLARATION OF INTEREST

None.

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