



## Short-term effects of meteorological factors and air pollution on childhood hand-foot-mouth disease in Guilin, China



Guoqi Yu<sup>a</sup>, Yonghong Li<sup>b</sup>, Jiansheng Cai<sup>a</sup>, Dongmei Yu<sup>a</sup>, Jiexia Tang<sup>a</sup>, Wenwen Zhai<sup>c</sup>, Yi Wei<sup>a</sup>, Shiyi Chen<sup>a</sup>, Quanhui Chen<sup>a</sup>, Jian Qin<sup>a,d,\*</sup>

<sup>a</sup> Department of Environmental and Occupational Health, Guangxi Medical University, Shuangyong Road, 22, Nanning, Guangxi Zhuang Autonomous Region, China

<sup>b</sup> Guangxi Center for Disease Control and Prevention, Acute Infectious Disease Prevention and Control Institute, Nanning, Guangxi Zhuang Autonomous Region, China

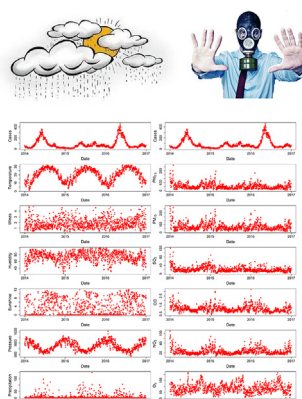
<sup>c</sup> Department of Health Related Social and Behavioral Science, West China School of Public Health, Sichuan University, Chengdu, Sichuan, China

<sup>d</sup> Guangxi Colleges and Universities Key Laboratory of Prevention and Control of Highly Prevalent Diseases, Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, China

### HIGHLIGHTS

- A total of 88,742 HFMD cases, daily weather and air pollution data during 2014–2016 were included in the analysis;
- Extreme temperature, precipitation and wind speed can affect the HFMD incidence;
- Extremely low values of PM<sub>2.5</sub> and high values of O<sub>3</sub> showed certain protective effects.
- Male children and children aged 0–3 year are vulnerable groups to extreme environment.

### GRAPHICAL ABSTRACT



Note: part of the element were modified from Internet.

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### ABSTRACT

**Background:** Previous studies have always focused on the impact of various meteorological factors on Hand-foot-mouth disease (HFMD). However, only few studies have investigated the simultaneous effects of climate and air pollution on HFMD incidence.

**Methods:** Daily HFMD counts among children aged 0–14 years in Guilin city were collected from 2014 to 2016. Distributed lag nonlinear models (DLNM) were used to assess the effects of extreme meteorological factors and air pollution indicators, as well as the effects of different lag days on HFMD incidence. Furthermore, this study explored the variability across gender and age groups.

**Results:** Extreme temperatures, high precipitation and low-O<sub>3</sub> concentration increased the risk of HFMD. Hot effect was stronger and longer lasting than cold effect. Risks of rainy effect and low-O<sub>3</sub> effect continued to increase as lag days extended, with the maximum RR values: 1.60 (1.38, 1.86) (90th vs median) and 1.48 (1.16, 1.89) (1th vs median) at 0–14 lag days, respectively. By contrast, extremely high wind speed, low precipitation, low PM<sub>2.5</sub> and high O<sub>3</sub> exerted a certain protective effect on HFMD incidence. The corresponding minimum RR values were: 0.85 (0.74, 0.98) (90th vs median) at 0–14 lag days, 0.98 (0.97, 0.99) (10th vs median) at 0–14 lag days, 0.73 (0.61, 0.88) (1th vs median) at 0–14 lag days and 0.81 (0.73, 0.90) (99th vs median) at 0–7 lag days, respectively.

\* Corresponding author at: Department of Environmental and Occupational Health, School of Public Health, Guangxi Medical University, Shuangyong Road 22, Nanning, 530000, Guangxi Zhuang Autonomous Region, China.

E-mail address: [qinjian@gxmu.edu.cn](mailto:qinjian@gxmu.edu.cn) (J. Qin).

Male children and children aged 0–1 years (followed by 1–3 years) were the most susceptible subgroups to extreme climatic effects and air pollution.

**Conclusions:** Our results indicated that daily meteorological factors and air pollution exert non-linear and delayed effects on pediatric HFMD, and such effects vary depending on gender and age. These findings may serve as a reference for the development of an early warning system and for the adoption of specific interventions for vulnerable groups.

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## 1. Introduction

Hand-foot-mouth disease (HFMD) is an acute infectious disease caused by enteroviruses, such as human enterovirus 71 (EV-71) and Coxsackievirus A group 16 (Ang et al., 2009). HFMD is prevalent among preschoolers, and severe cases are mostly caused by EV-71 infection. This disease is self-limiting and mainly spreads through fecal-oral transmission or through close contact. Although its typical clinical symptoms are mild (such as rashes on hands, feet, and hip, as well as oral mucosal herpes), it occasionally causes severe complications, such as meningitis and encephalitis, which may lead to death. No effective vaccines and specific antiviral therapies for HFMD have been developed (Mao et al., 2016).

HFMD was first reported in New Zealand in 1957, and it has become an urgent issue in global public health (Zhuang et al., 2015). Frequent HFMD outbreaks were experienced in the Asia-Pacific region in the past decades. In the spring of 2008, a large, unprecedented HFMD outbreak was experienced in Fuyang City (China), wherein 6049 cases and 22 deaths were recorded (Yan et al., 2010). Large-scale HFMD outbreaks also occurred in South Korea and Hong Kong in 2009 and 2011, respectively (Lee et al., 2013; Song et al., 2015). Followed by vast HFMD cases and local outbreaks being observed in Vietnam and Thailand (Nguyen et al., 2014; Puenpa et al., 2014), as well as in Malaysia and India (Nmn et al., 2016; Palani et al., 2016). In addition, mainland China has been suffering from a huge burden caused by HFMD due to its large population base. The incidence of HFMD in 2014 was 203.16/100,000 and the mortality was 18.03/100,000, exceeding those in most East Asian countries (Zhuang et al., 2015). Hence, identification of the risk factors for HFMD and establishment of a targeted early warning system are crucial to the control of HFMD outbreak and reduction of the burden caused by this disease common among children.

HFMD incidence shows a remarkable seasonality (Wang et al., 2011). Studies have suggested that the incidence of HFMD is closely related to meteorological factors (Sumi et al., 2017; Wang et al., 2016a, 2016b; Wei et al., 2015). However, results obtained from different regions and findings on the effects of different meteorological factors are not entirely consistent. A Japanese study has shown that HFMD cases increase by 11.2% for every 1 °C increase in average temperature and by 4.7% for every 1% increase in relative humidity (Onozuka and Hashizume, 2011). Studies conducted in Gansu (China) have reported that a 1 °C increase in average temperature increases the weekly HFMD incidence counts by 5.9% in Tianshui, 2.8% in Lanzhou, and 1.8% in Jiuquan. Moreover, a 1% increase in relative humidity increases the weekly HFMD incidence count by 2.47% in Lanzhou and 1.11% in Tianshui (Gou et al., 2018). Cheng, et al. speculated that extreme rainfall increases the incidence of HFMD, whereas the opposite pattern was reported by another study conducted in Singapore (Cheng et al., 2014; Hii et al., 2011). Moreover, studies have found that relative humidity, sunshine, and wind speed influence the risk of HFMD (Huang et al., 2013; Wang et al., 2016a, 2016b; Yang et al., 2017). However, this result is inconsistent with the findings obtained in Huainan and Hong Kong (Ma et al., 2010; Zhao et al., 2017). Therefore, studies must be conducted in more cities to elucidate these controversial results.

Researches concerning the adverse health effect of air pollution were mostly concentrated on the relationship between air pollution and

chronic non-communicable diseases. However, recent studies indicated that air pollution may mediate and promote the incidence of infectious diseases. Chen et al. found that measles is associated with exposure to ambient PM<sub>2.5</sub>, which can be modified by meteorological factors (Chen et al., 2017a). Air pollution was also found to be significantly associated with the prevalence of influenza-like illness and avian influenza, whose effects varied among different age groups (Chen et al., 2010; Feng et al., 2016; Huang et al., 2016a, 2016b). In addition, Ye et al. found that haze can play an important role in the spread of intestinal infectious diseases such as rotavirus caused diarrhea (Ye et al., 2016). The adhesion of virus to gaseous particulate matter and the inflammatory reaction caused by the dissolution of O<sub>3</sub>, SO<sub>2</sub>, NO<sub>2</sub>, etc. in the respiratory tract may promote the incidence of infectious diseases to some extent (Gralton et al., 2011; Sun et al., 2016). Nonetheless, researches on the relationship between air pollution and other enteric diseases such as hand, foot and mouth disease are very limited. To our knowledge, only two studies had investigated the effect of PM<sub>10</sub> on HFMD incidence, and the results were inconsistent (Huang et al., 2016a, 2016b; Huang et al., 2018). Thus, exploring the impact of meteorological factors and air pollution on HFMD incidence can help clarify the potential factors and deepen our understanding of HFMD incidence.

Guilin City was taken as our research area based on the following reasons. First, HFMD incidence in Guilin City is relatively high, basically more than three times the national average. Second, Guilin City is characterized by ethnic minorities and numerous mountains and rivers, and the geographical environment and lifestyle in this city are quite different from those in plain and coastal areas. DLNM was utilized to quantify the association of climate and air pollution with HFMD incidence. This study aimed to identify the risk factors of HFMD and the populations susceptible to this disease, thereby providing a reference for establishing an early warning system and for formulating target intervention policies to prevent and control infectious diseases.

## 2. Data and methods

### 2.1. Study settings and data sources

Guilin City is a famous tourist destination in southern China, and ethnic minorities live in this city. Guilin has an area of 27,667 km<sup>2</sup> and a population of 5.1 million (in 2016). This city is located in a subtropical monsoon climate zone with mild climate and abundant rainfall and sunshine. The annual average temperature is 20 °C, and the average relative humidity is 73%. Northeast wind is the dominant wind direction throughout the year. Fig. 1 shows the geographical location of Guilin City.

Daily data on HFMD incidence from 2014 to 2016 were obtained from the Infectious Disease Reporting System of the Guangxi Center for Disease Prevention and Control. Clinical diagnosis of HFMD is based on the National Guideline on Diagnosis and Treatment of Hand Foot Mouth Disease issued by the Chinese Ministry of Health. Symptoms of typical cases include acute onset, fever, rashes on hands, feet, and buttocks; HFMD is also frequently characterized by scattered herpes in the oral mucosa and pharyngeal isthmus, which may be accompanied by cough, runny nose, loss of appetite, and diarrhea. HFMD is listed as a category C infectious disease in China. Health departments require that infected patients, patients with suspected infection, or carriers of the

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