Environment International 100 (2017) 102–109

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

The exposure-response relationship between temperature and childhood hand, foot and mouth disease: A multicity study from mainland China

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ARTICLE INFO

Article history:
Received 16 September 2016
Received in revised form 16 November 2016
Accepted 18 November 2016
Available online 6 January 2017

Keywords:
Childhood infectious disease
Temperature-disease relationship
Nonlinear association
Modification effect
Multisite study

ABSTRACT

Background: Hand, foot and mouth disease (HFMD) is a rising public health issue in the Asia-Pacific region. Numerous studies have tried to quantify the relationship between meteorological variables and HFMD but with inconsistent results, in particular for temperature. We aimed to characterize the relationship between temperature and HFMD in various locations and to investigate the potential heterogeneity.
Methods: We retrieved the daily series of childhood HFMD counts (aged 0–12 years) and meteorological variables for each of 143 cities in mainland China in the period 2009–2014. We fitted a common distributed lag nonlinear model allowing for over dispersion to each of the cities to obtain the city-specific estimates of temperature-HFMD relationship. Then we pooled the city-specific estimates through multivariate meta-regression with city-level characteristics as potential effect modifiers.
Results: We found that the overall pooled temperature-HFMD relationship was shown as an approximately inverted V shape curve, peaking at the 91th percentile of temperature with a risk ratio of 1.30 (95% CI: 1.23–1.37) compared to its 50th percentile. We found that 68.5% of the variations of city-specific estimates was attributable to heterogeneity. We identified rainfall and altitude as the two main effect modifiers.
Conclusions: We found a nonlinear relationship between temperature and HFMD. The temperature-HFMD relationship varies depending on geographic and climatic conditions. The findings can help us deepen the understanding of weather-HFMD relationship and provide evidences for related public health decisions.

1. Introduction

Hand, foot and mouth disease (HFMD) is a worldwide childhood infectious disease caused by Enterovirus. Although HFMD is normally characterized by mild symptoms of febrile illness and rashes (World Health Organization, 2011), some patients can develop severe central nervous system complications and even fatal cardiopulmonary failure (Sabanathan et al., 2014). Over the last few decades, a series of large HFMD epidemics, accompanied by abnormally high rates of severe and fatal cases, have occurred in countries of the Asia-Pacific region (Chan et al., 2003; Ho et al., 1999; Van Tu et al., 2007; Zhang et al., 2010). In mainland China, HFMD is one of the leading infectious diseases in children and is also responsible for hundreds of reported deaths every year since it has been made statutorily notifiable in May 2008 (Xing et al., 2014). Given its threat to children and the potential for its emergence as a leading cause of enterovirus-related CNS disease after poliomyelitis, HFMD has raised huge public health concerns in the Asia-Pacific region (Regional Emerging Diseases Intervention Center, 2009).

It is well accepted that weather plays an important role in the transmission of many infectious diseases (Kuhn et al., 2005). Epidemiologists have performed a large amount of studies trying to quantify the relationships between meteorological variables and HFMD. Among them, the temperature-HFMD relationship is the most controversial one. Earlier studies normally assumed a simple linear relationship. A study in Northern Thailand (Samphutthanon et al., 2014) showed that the relationship with temperature was negative, whereas studies in Hong

Abbreviations: HFMD, hand, foot and mouth disease; TSR, time series regression; DOW, day of week; LR, likelihood ratio; AIC, Akaike information criterion.

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http://dx.doi.org/10.1016/j.envint.2016.11.021
0160-4120/

Kong (Ma et al., 2010) and mainland China (Chen et al., 2015; Feng et al., 2014; Li et al., 2014; Wei et al., 2015; Wu et al., 2014; Zhang et al., 2016) found a positive relationship. More recent studies relaxed the linear assumption to allow for non-linear relationship. A study in Singapore (Hii et al., 2011) suggested the presence of a threshold and a J-shape relationship; by contrast, studies in Japan (Onozuka and Hashizume, 2011), Taiwan (Chang et al., 2012), South Korea(Kim et al., 2016) and mainland China (Xu et al., 2015; Zhu et al., 2015) showed that the risk of HFMD increased below moderately hot temperature but declined at extremely hot temperatures, with an approximately inverted V shape. The inconsistency of findings can be partly attributable to the diversity of methodologies and data sources, but it also implies that the temperature-HFMD relationship might be modified by some location-specific variables. The heterogeneity across studies is still poorly understood which hinder a more comprehensive characterization of the temperature-HFMD relationship.

The majority of previous studies are based on single-site analysis, which prevent the modelling and assessment of heterogeneous relationships. A more sophisticated approach is the use of two-stage multisite study (Dominici, 2002) in which data from multiple sites are analyzed, and then the site-specific results are pooled and evaluated potential effect modifiers. To the best of our knowledge, there are only three published papers focusing on the heterogeneity of temperature-HFMD relationship (Zhu et al., 2016; Zhu et al., 2015). However, all of them were conducted on a small scale, with limited between-site variability, and very few variables were studied to explain the heterogeneity.

In this paper we fill this research gap by characterizing in more details the relationship between temperature and HFMD across various locations, and more importantly, exploring the reasons for the potential heterogeneity. Specifically, we conducted a two-stage multisite time series analysis based on data from 143 cities all across mainland China between 2009 and 2014. City-specific characteristics on multiple aspects, including geographic and climatic differences, social-economic status, health sources and other factors, were incorporated to study their modification effects on temperature-HFMD relationship.

2. Material and methods

2.1. Data sources

2.1.1. Daily series of HFMD counts and meteorological variables

We retrieved the surveillance data of reported clinical HFMD cases and meteorological variables in mainland China between 1 January 2009 and 31 December 2014.

We collected the reported clinical cases of HFMD from China Information System for Disease Control and Prevention. A clinical HFMD case is defined as a patient with papular or vesicular rashes on hands, feet, mouth or buttocks, with or without fever. All clinical cases were reported online within 24 h of diagnosis by use of a standardized form. More details of the surveillance data of HFMD have been described elsewhere (Xing et al., 2014). As over 99% of cases occurred among children under the age of 12 years (i.e. children in elementary school and below) according to our preliminary analysis, in this study we focused on the incidence of HFMD among children aged 0–12 years. The daily counts of HFMD clinical cases based on the date of onset of symptom were then aggregated at each of 293 cities in mainland China (Chen, 2009–2014). A city is defined as the main central urban area in each of the prefectures (i.e. prefectural-level city). A prefecture is an administration division ranking below a province and above a county in China's administrative structure, and a prefectural-level city corresponds to a middle to large size city in China.

We collected the daily monitoring data of meteorological variables, including mean temperature, mean relative humidity, mean air pressure, accumulated rainfall and sunshine hours, from China Meteorological Data Sharing Service System. We included 646 national ground meteorological stations which have daily records in the period 2009–2014. The missing values in the daily records were filled by different approaches depending on the nature of each meteorological variable. Specifically, for temperature, humidity and air pressure, the missing values were filled by the polynomial interpolation (Zeileis and Grothendieck, 2005); for sunshine hours and rainfall, the missing values were replaced by zero. However, the missing issue should be negligible given that the missing proportion is very small (<0.1%).

By matching, we finally restricted the analysis to the 143 cities for which data from a meteorological station within the city administrative boundaries was available. For two cities with multiple meteorological stations, the station which is closest to the city center was chosen.

2.1.2. City-specific characteristics

We collected the geographic, climatic and social characteristics for each of the 143 cities. We used the coordinates of city/station to represent their differences in geographic locations, and we calculated the arithmetic mean of daily monitoring data of meteorological variables (including temperature, relative humidity, air pressure, rainfall and sunshine hours) at each city/station to represent their climatic differences. We collected the city-specific social characteristics from the China city statistical yearbook (Chen, 2009–2014), including demographic variables (population density and population increase rate), economic variables (GDP per person and GDP increase), health resources (licensed physicians and hospital beds per 1000 persons), traffic (total travel passengers a year) and number of elementary school students per 1000 persons. Besides, an indicator variable based on the national standard of meteorological and geographic division (China Meteorological Administration, 2006) was also used to group the 143 cities into eight regions.

2.2. Statistical analysis

We implemented a two-stage multisite time series analysis to first obtain the city-specific estimates of temperature-HFMD relationship, and then to pool the multicity estimates and study the heterogeneity.

2.2.1. First-stage analysis

In the first-stage analysis, we fitted a common time series regression (TSR) (Peng and Dominici, 2008) to each of the 143 cities to relate the daily series of HFMD counts and mean temperature. Given that multiple previous studies suggest that the temperature-HFMD relationship can be nonlinear and also their association can be delayed because of the incubation period of infectious disease, we incorporated distributed lag nonlinear model (Gasparrini et al., 2010) into the TSR to allow for bi-dimensional exposure-lag-response relationship. We determined our specific model parameters based on prior knowledge, followed by a systematic sensitivity analysis to further evaluated our choices. See more technical details and discussions of our model choices and related sensitivity analysis in Appendix, Text A.1.

In summary, a quasi-Poisson regression model was adopted to allow for over dispersion. The bi-dimensional exposure-lag-response relationship between temperature and HFMD was described through a cross-basis function (Gasparrini et al., 2010), using natural cubic splines with 5 degrees of freedom (*df*) for the exposure-response relationship and natural cubic splines with 4 *df* for the lag-response relationship. The lag range of 4 to 14 days was used to represent the lag structure of temperature-HFMD relationship. The start lag and the lag interval were informed by the median incubation period of HFMD infections (4 days) (Ministry of Health of China, 2009) and a preliminary analysis (see Appendix, Text A.1, Section 4), respectively. To control for the unmeasured time-varying