



Epidemiological Features of Hand, Foot and Mouth Disease Outbreaks among Chinese Preschool Children: A Meta-analysis

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Abstract

Background: Hand-foot-mouth disease (HFMD) is a widespread communicable disease and has caused large epidemics in many countries. This meta-analysis aimed to analyze and evaluate the epidemiological features of HFMD outbreaks in Chinese preschools.

Methods: Literature review was based on PubMed, Chinese National Knowledge Infrastructure (CNKI) and Wanfang databases from 2008 to 2015. The temporal, spatial and demographic parameters were summarized and analyzed.

Results: Overall, 19 studies with a total of 11269 HFMD cases were selected for data synthesis and analysis. April, May, June and July were detected as the peak months of HFMD outbreaks, with the pooled rate of 21% (95% CI: 12%-34%), 23% (95% CI: 19%-27%), 20% (95% CI: 17%-24%) and 11% (95% CI: 7%-15%). Urban areas were at a higher risk of suffering from HFMD outbreaks than rural areas, with the pooled rate of 65% (95% CI: 48%-78%) and 35% (95% CI: 22%-52%) respectively. The constituent ratio of children aged 37-48 months is the highest, accounting for 46% (95% CI: 39%-53%) of the total cases during HFMD outbreaks. The pooled rate of male cases (60%) was higher than that of female cases (40%).

Conclusion: Month, residence, age, and gender may be early risk factors for potential HFMD outbreaks. Before the advent of peak months from Apr to Jul each year, measures should be taken to prevent the HFMD outbreaks among preschool children in China. Preschools located in urban areas should take priority over special prevention. HFMD surveillance should preferentially focus on children aged 37-48 months, especially boys in preschools.

Keywords: Hand, Foot and mouth disease, Preschool, Outbreak, Meta-analysis, Prevention

Introduction

Hand, foot, and mouth disease (HFMD) is an acute communicable disease mostly happened to children. It is caused by viruses belonging to the Enterovirus genus, such as Coxsackievirus A16 (CA16) and Enterovirus71 (EV71) (1). Clinical symptoms usually include fever, malaise, rashes on hands and feet, and oral vesicles. Of note, severe and even life-threatening complications can

develop rapidly in young children, such as acute pulmonary edema, cardiopulmonary failure, aseptic meningitis, encephalitis and acute flaccid paralysis (2). HFMD is transmitted from person to person by direct contact with respiratory droplets, open and weeping skin vesicles, blister fluid from mouth, feces, or through exposing to a contaminated environment (3).

In the past three decades, HFMD epidemic has been continuously observed across the world. Recently, HFMD has become an increasing burden in the Asia-Pacific Region including Japan, Malaysia, Singapore, Viet, China etc. (4-8). In 2008 the largest Asia-Pacific pandemic was reported in China, posing a big threat to public health. Then, HFMD was designated as a C-class notifiable communicable disease by the Ministry of Health of China on 2 May 2008. The incidence of HFMD increased rapidly from 86.59/100,000 in 2009 to 203.16/100,000 in 2014 (9). HFMD has been responsible for 350-900 reported deaths annually, predominantly among young children, over the period of 2010-2012 (10). Currently, the nationwide mortality of HFMD remains the highest in all C-class communicable diseases, of which the proportion is over 90% in peak seasons (11).

HFMD outbreaks among Chinese preschool children occurred continuously since 2008 (12). A HFMD outbreak was defined in accordance with the criteria of the 2009 prevention and control guideline for HFMD issued by the Ministry of Health of the People's Republic of China: (1) 5 or more cases of HFMD in a school within 1 week; (2) 2 or more cases of HFMD in a classroom within 1 week (13). HFMD outbreaks among preschool children have become an important public health problem in China.

We performed a meta-analysis to evaluate the epidemiological features of HFMD outbreaks among preschool children. We assessed the spatio-temporal distribution of HFMD outbreaks, to identify early risk factors and provide reference for future surveillance and prevention. The results will be helpful to effectively contain the spread of HFMD.

Methods

Search strategy

We follow the preferred reporting items for meta-analysis of observational studies in epidemiology (MOOSE) (14). A systematic search strategy was developed by a research librarian and two study investigators, to ensure that all relevant studies under review were appropriate to use with preschool

children in China. PubMed, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases were queried from 2008 to 2015. The search was conducted by using the following free-text terms and medical subject headings: "hand foot and mouth disease", "HFMD", "outbreak", "preschool", "kindergarten", "daycare center", "nursery" and "China". In addition, Google and Google Scholar searches were conducted as a means of identifying pertinent gray literature.

Inclusion and exclusion criteria

Inclusion criteria for studies were as follows: (1) published in Chinese or English; (2) including information about epidemiology of HFMD outbreaks. (3) Studies including HFMD outbreaks that occurred in preschool settings rather than at other places. Studies were excluded if they met the following criteria: (1) not an original study, such as review papers; (2) case series which reported less than 3 outbreaks; (3) If the study was reported in duplicate, the article published with more cases were included.

Study selection

Two reviewers reviewed the studies respectively, screening article titles and abstracts for possible inclusion. If the information is not sufficient enough to make a decision on whether the study should be included or not, the full text of the article was further reviewed. The results were checked and discussed by two reviewers to agree upon a final list of included studies.

Data extraction and analysis

Data from eligible studies were extracted separately by two reviewers. For each included study, we extracted the following data from original publications: authors, year of publication, study location (province and city), study period, residence (urban or rural area), number of HFMD outbreaks in each month, age of the patients, total number of HFMD cases and number of HFMD outbreaks in each study. Disagreements between the two reviewers during data extraction were reconciled by a third investigator.

A published systematic meta-analysis technique was used to calculate the pooled parameters of HFMD

outbreaks from all eligible studies. Meta-analysis was carried out by using the software in R version 3.2.1, downloaded from the Comprehensive R Archive Network (CRAN, <https://cran.r-project.org/>). Proportion was automatically selected as a summary statistic in R software to enable forest plots. Pooled proportion and 95% confidence intervals were obtained by random or fixed effects model determined by I^2 . Pooled rate was gotten from pooled proportion multiplied by 100%.

We assessed the temporal, spatial and demographic distribution trends of HFMD outbreaks, with respect to month, region, age and gender, etc. For monthly distribution analysis, proportion represents the ratio of the number of HFMD outbreaks in targeted months to the total number of outbreaks in a year. For regional distribution analysis, proportion represents the ratio of the number of HFMD outbreaks in urban or rural areas to the total number of outbreaks. For age distribution analysis, proportion represents the ratio of the number of HFMD cases in each age group to the total number of HFMD cases. In addition to age distribution, impact of gender was also analyzed as part of the demographic distribution assessment. Proportion represents the ratio

of the number of boy or girl cases to the total number of HFMD cases.

The statistical heterogeneity across the studies was estimated by the Chi-square based Q test ($P < 0.10$ indicating statistical significance). The I^2 statistic for each analysis was calculated. Subgroup analyses were conducted to investigate the source of high heterogeneities (15). Finally, the random effect model would be used if the heterogeneities could not be reduced by subgroup analyses. Egger's test was used to assess the publication bias, and a P -value of < 0.05 was considered as statistically significant (16).

Results

Literature search and studies characteristics

The results of the study selection process are shown in Fig. 1. The initial electronic search strategy identified 176 studies for review. In total, 51 potentially relevant articles were selected for full-text assessment. After a detailed evaluation, 19 original studies (17-35) remained for the final meta-analysis. A manual search of the reference lists of these studies did not yield any new eligible studies. Table 1 provides a descriptive summary of the included studies.

Table 1: Characteristics of included studies

<i>First author</i>	<i>Published year</i>	<i>Study period</i>	<i>Study location</i>	<i>Number of HFMD cases</i>	<i>Number of HFMD outbreak</i>
Li M (17)	2012	2011	Licheng	266	45
Kong ZF (18)	2014	2012	Ninhai	861	153
Wang RQ (19)	2013	2009	Changping	103	7
Zhang ZW (20)	2014	2012	Dongguan	130	7
Li Z (21)	2013	2012	Jinan	734	214
Tian L (22)	2011	2009	Shanghai	2993	672
Wang LJ (23)	2013	2010	Beijing	83	24
Ye ZW (24)	2014	2012	Zhuhai	1203	148
Xv JJ (25)	2013	2012	Yancheng	804	75
Chen HQ (26)	2010	2009	Jinan	87	5
Gu YG (27)	2010	2009	Jinin	127	28
Hu QP (28)	2015	2012	Pudong	462	79
Wang J (29)	2013	2010	Shanghai	219	40
Zhang CD (30)	2013	2010-2011	Lianyungang	225	52
Zhao ZR (31)	2013	2010-2011	Maanshan	1874	291
Xiong JG (32)	2012	2010	Dongguan	190	16
Li JY (33)	2012	2010	Foshan	345	65
Wang JP (34)	2013	2010	Yidu	137	27
Liu Y (35)	2015	2009-2013	Dandong	426	80

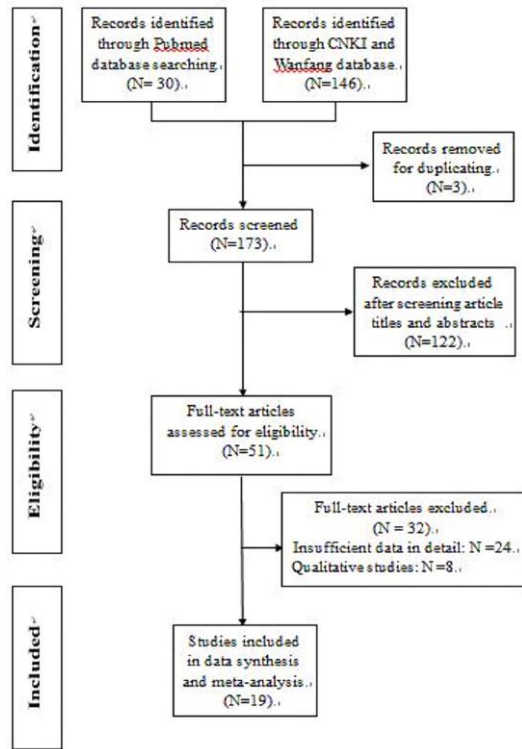


Fig. 1: Flowchart of study selection

Overall, 2028 HFMD outbreaks including total 11269 HFMD cases were analyzed. There was no evidence for publication bias using the Egger’s test.

Monthly distribution and peak months

The monthly distribution trends of HFMD outbreaks were investigated. The corresponding results are presented in Table 2. The pooled values of HFMD outbreaks from Jan to Dec were described in detail. HFMD outbreaks occurred year-round in China. During one year, the pooled rate of HFMD outbreaks was at the lowest level in Jan and Feb, with the numeral value of 2%. Then the rate began to increase in Mar and the numeral value was 7%. The pooled rate reached the highest level in the period of Apr to Jul, which was 21%, 23%, 20%, and 11% respectively. From Aug to Oct, the pooled rate remained the same (7%). In Nov the rate grew slightly to 8%. Finally, it dropped to 4% in Dec.

Peak months from Apr to Jul were observed. Over this consecutive period, the pooled rate of HFMD outbreaks was 72% (95% CI: 64%-79%), obviously higher than the sum of the rest months.

Table 2: Monthly distribution of HFMD outbreaks

Month	Pooled rate (%)	95% CI (%)	Heterogeneity (%)	P
January	2	1-5	0	0.78
February	2	1-4	0	0.89
March	7	4-12	33.20	0.14
April	21	12-34	79.10	<0.01
May	23	19-27	0	0.70
June	20	17-24	0	0.94
July	11	7-15	18.30	0.27
August	7	5-10	0	0.98
September	7	5-9	0	0.99
October	7	5-10	0	0.86
November	8	5-13	24.90	0.21
December	4	2-6	0	0.91

However, the heterogeneity was significant ($I^2=54.2\%$; $P=0.02$). To eliminate the heterogeneity between studies, subgroup analyses were conducted for sample size, geographical regions, and study year. Finally, geographical difference was found to be the heterogeneous source. Southern

China (sample 2) has higher pooled rate of HFMD outbreaks than Northern China (sample 1) during peak months, and the numeral value was 78% (95% CI: 70%-84%) and 61% (95% CI: 55%-66%) respectively (Fig. 2).

Regional Distribution in Urban and Rural Areas

As for urban areas, the pooled rate of HFMD outbreaks is high, with the numeral value of 65% (95% CI: 48%-78%). While in rural areas the rate

is lower, which was 35% (95% CI: 22%-52%). There was high heterogeneity between studies ($I^2=89.1\%$; $P<0.0001$) which could not be reduced by subgroup analyses. Therefore, the random effect model was used.

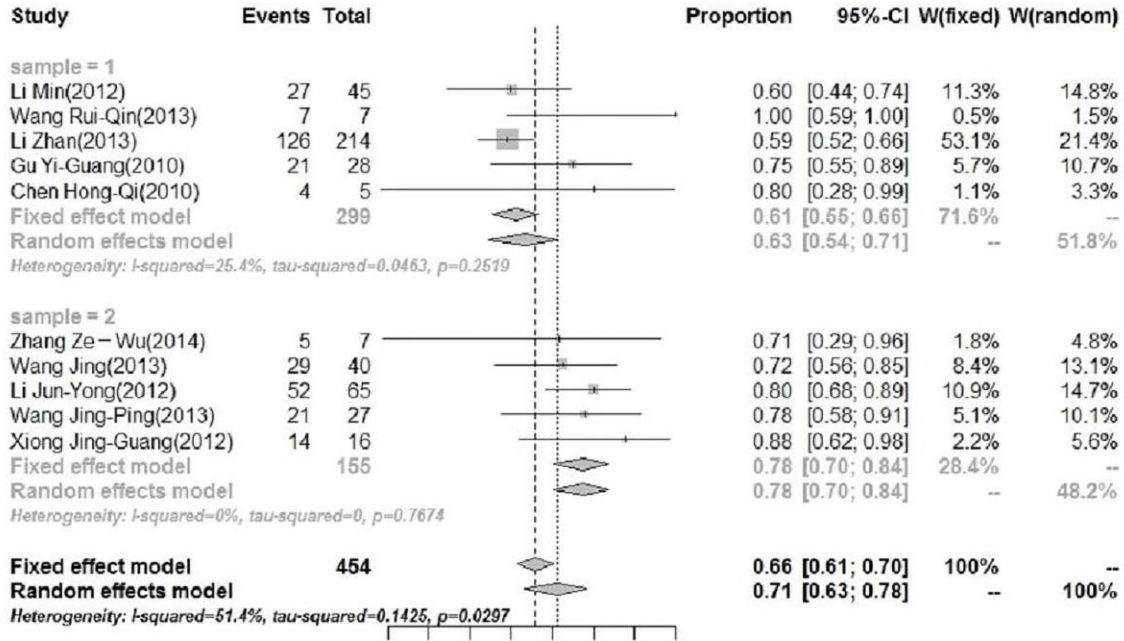


Fig. 2: Monthly distribution of HFMD outbreaks in the period of April to July

Age distribution Trends

All the HFMD cases in each study were divided into four age groups, including 0-36 months, 37-48 months, 49-60 months and 61-72 months. Significant differences were observed between each age group. The pooled rate of HFMD cases was the highest in the age group 37-48 months and the numeral value was 46% (95% CI: 39%-53%). Next was the age group 49-60 months, with the pooled rate of 28% (95% CI: 25%-33%). As for the age group 61-72 months, the pooled rate was relatively low, which was 14% (95% CI: 10%-19%). The lowest was the age group 0-36 months, with the pooled rate of 9% (95% CI: 5%-15%).

Impact of gender

In addition to age distribution, impact of gender was also analyzed as part of the demographic distribution assessments. The pooled rate of male

cases was 60% (95% CI: 59%; 61%). Fig. 3 shows the forest plot of meta-analysis for boys. The pooled rate of female cases was 40% (95% CI: 39%-41%). The male-to-female ratio was 1.5:1.

Discussion

In China, recurring outbreaks of HFMD among preschool children is a major public health concern. To the best of our knowledge, this is the first meta-analysis to identify epidemiological features of HFMD outbreaks in preschools across China. Month, region, age, and gender might be used as risk indicators for HFMD outbreaks. This will provide guidance for HFMD prevention and help to reduce outbreaks of HFMD in preschools.

In temperate climate, HFMD outbreaks usually occur in warmer months of the year, whereas in tropical areas, HFMD epidemics increase in wet

season (36). For example, in the USA, outbreaks of HFMD typically occur during summer and autumn months (37). In Taiwan, seasonal variations in HFMD incidence were observed, of which an incidence peak occurred in the summer months (38). In our study, outbreaks of HFMD

peaked in late spring and summer months from Apr to Jul, similar to that found in other temperate regions.

Such peak month pattern might be partly explained by climatic factors, such as temperature and humidity.

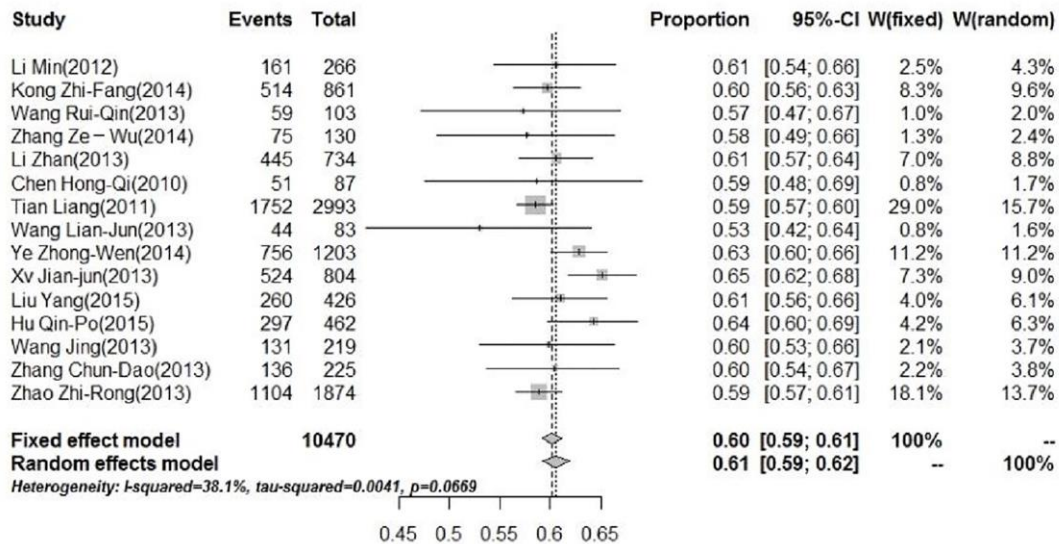


Fig. 3: Forest plot of the constituent ratio for male cases

In Japan, higher temperature could influence the increase of HFMD incidence (39). In addition, sentinel surveillance in Belgium has shown that HFMD viruses were more active in summer months when the temperature is high (40). A Singapore study pointed out that a maximum daily temperature above 32 °C and rainfall up to 75 mm was expected to increase the HFMD incidence (36). In China, the average temperature and humidity are relatively high in the period of Apr to Jul. The environment is warm and damp, which are conducive to the survival of enteroviruses and the transmission of HFMD (41-43). Considering the peak month pattern of HFMD outbreaks, we recommend that during the period of Apr-Jul each year, routine epidemiological surveillance should be strengthened among preschool children.

The difference in HFMD incidence between urban and rural areas has also been discussed in other studies. The rural region in Taiwan had the

least incidences of severe HFMD cases (38). Children living in urban areas and in rural areas accounted for 70.5% and 29.5% of the severe HFMD cases respectively (44). In our study, HFMD outbreaks occurred more in urban preschools than those in rural areas. High population density and the congregation of migrant children might be two underlying causes. Previous studies have proved a correlation between the density of children and the incidence of HFMD (45, 46). In urban areas of China, preschool children commonly congregate in limited space, which provides an available reservoir for the rapid transmission of the virus. Additionally, urban areas in China accommodate lots of migrant children. Migrant children were at significantly high risk of developing HFMD (47). Migrant children had a higher HFMD attack rate than permanent residents (48). Terrible sanitation, tardy care, and poor educational environment may result in the susceptibility of migrant

children. We suggest that public health measures of controlling HFMD outbreaks should better focus on urban areas preferentially.

Age has been identified as a risk factor for HFMD infection in previous studies. Data from Asia countries showed that HFMD incidence rate varies widely even within the narrow 0- to 5-yr age-band. A serologic survey in Singapore children showed that seropositivity to EV71 increases rapidly from age 2 to 5 yr (49). In Malaysia, HFMD incidence was the highest in children <2 yr and decreased with age (50). An 8-year study of epidemiologic features of EV71 infection in Taiwan found that younger children (< 4 yr of age) are at an apparently increased risk for HFMD infection (51). In China, younger children less than 5 yr accounted for the majority of sporadic cases (52-54). Our study confirmed the impact of age on HFMD infection but paid more attention to the differences between each age group among preschool children in HFMD outbreaks. In our study, children aged 37-48 months appeared to be the most susceptible age group during HFMD outbreaks. We recommend that special preventive measures should be taken in the future to protect this age group of children.

Another interesting finding in our study was that gender might be a risk factor of HFMD outbreaks among preschool children. The male-to-female ratio was 1.5:1. In a report from Singapore, there was a male predominance of HFMD cases, with a male-to-female ratio between 1.3:1 and 1.6:1 (55). In Taiwan, during the enterovirus outbreak in 2008, the male-to-female ratio was 1.6:1 (56). These findings might suggest susceptibility at the host genetic level. However, the reasons are unclear and deserve further research.

Conclusion

Month, residence, age and gender might be early risk factors for potential HFMD outbreaks. To control future HFMD outbreaks among preschool children, prevention measures should be taken before the advent of peak months from Apr to Jul each year. Those preschools located in

urban areas should take priority over preventing and controlling the disease. Further professional protection should be given to high-risk children 37-48 months old, especially preschool boys. We hope that data from China could help other countries to improve the quality of HFMD prevention.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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