

Socioeconomic burden of hand, foot and mouth disease in children in Shanghai, China

Z. L. WANG^{1,2†}, A. M. XIA^{1†}, Y. F. LI¹, H. L. SU³, L. W. ZHAN³, Y. P. CHEN³,
Y. XI³, L. F. ZHAO³, L. J. LIU³, Z. Y. XU^{3*} AND M. ZENG^{1*}

¹ Department of Infectious Diseases, Children's Hospital of Fudan University, Shanghai, China

² Medical Affairs Department, Department of Infectious Diseases, Children's Hospital of Fudan University, Shanghai, China

³ Department of Infectious Diseases, Minhang District Center for Disease Control and Prevention, Shanghai, China

Received 24 March 2015; Final revision 20 May 2015; Accepted 16 June 2015;
first published online 10 July 2015

SUMMARY

In the near future, the inactivated enterovirus 71 (EV71) vaccine is expected to become available on the market in China. Since EV71 is a major cause of hand, foot and mouth disease (HFMD), the vaccine is expected to significantly reduce the number of cases, as well as the detrimental economic effect of the disease. However, for a national vaccination strategy to be developed, policy-makers need more information on the socioeconomic burden of EV71 HFMD infection. Based on the 2011 population data, we estimated the clinical and economic effect of EV71 HFMD infection in children aged 0–9 years in Shanghai, China. The annual cost related to HFMD is >US\$7.66 million for a population of 1.42 million children aged 0–9 years with an average cost of US\$208.2/case. The extrapolated cost for EV71 HFMD infection was US\$3.53 million, comprising 46.1% of the overall cost associated with HFMD. Around 97% of all of the HFMD-related expenses were paid for by the families creating a considerable economic burden. Our findings could provide the necessary recommendations on the most effective national EV71 vaccine implementation, as well as a baseline data for assessing the cost-effectiveness of the vaccine in China.

Key words: Economic burden; enterovirus 71 (EV71); hand, foot and mouth disease (HFMD).

INTRODUCTION

Hand, foot and mouth disease (HFMD) is a common, highly contagious disease found mostly in children. HFMD is caused by enteroviruses belonging to the species *Enterovirus A* and in rare cases to

Enterovirus B [1]. Both species are known to cause herpangina, a disease similar to HFMD, but with no skin lesions and limited to the posterior oral cavity. HFMD outbreaks occur worldwide and are often associated with coxsackievirus A16 and enterovirus 71 (EV71) [2]. Since the late 1990s, the most prevalent cause of large HFMD outbreaks in the Asia-Pacific region has been EV71. Some of the children experienced severe illness coupled with neurological and cardiopulmonary complications and in some cases death [3]. Since 2008, national outbreaks of EV71 HFMD have occurred throughout mainland China. As of 31

* Author for correspondence: Dr M. Zeng, Department of Infectious Diseases, Children's Hospital of Fudan University, 399 Wanyuan Road, Shanghai 201102, China.
(Email: zengmeigao@aliyun.com) [M.Z.]
(Email: xyz033@qq.com) [Z.Y.X.]

† These authors contributed equally to this work.

December 2014, more than 11.8 million cases of HFMD have been reported to the National Surveillance System in mainland China; which included a total of 3227 fatal cases [4]. HFMD has been ranked a top disease among nationally notifiable diseases since 2009. Shanghai has the highest gross domestic product and the largest population in China. The HFMD incidence rate in Shanghai was estimated at 1.6 cases/1000 in 2011, higher than the national level (1.2 cases/1000) [5, 6].

An inactivated EV71 vaccine with an efficacy of 90.0% against EV71-associated HFMD has been successfully developed in China and is expected to become available in the near future [7]. Currently, there is not enough information available regarding the socioeconomic burden of HFMD for policymakers to develop a nationwide strategy to vaccinate children in China. Therefore, we conducted a prospective study to evaluate the socioeconomic burden of HFMD on children and their families in Shanghai, China.

METHODS

Study setting and subjects of economic burden

A prospective study on the HFMD-associated economic burden was performed using the data collected from 15 June 2011 to 20 October 2011 by the Children's Hospital of Fudan University, Shanghai, China. Of all of the reported HFMD cases in Shanghai during the period, 30% of outpatients, 90% of inpatients and 95% of severe HFMD cases were treated at the hospital. Since 98% of HFMD cases and all severe cases occurred in children aged 0–9 years, only this age group was included in the study. The initial plan was to enrol 100 outpatients, 100 uncomplicated inpatients and 100 severe inpatients with confirmed central nervous system involvement. The study enrolment of HFMD cases was performed on Tuesdays and Thursdays every week. From 15 June 2011 to 20 August 2011, 5–6 outpatients and uncomplicated inpatients were enrolled per day. From 15 June 2011 to 20 October 2011, 2–3 severe cases were enrolled per day. The enrolled patients encompassed 11 of 18 districts of Shanghai. The survey on economic burden was part of the 2011 routine HFMD surveillance programme; therefore, this survey was exempt from ethical approval after the Ethics Committee of Children's Hospital of Fudan University reviewed this study.

Data collection

A written informed consent from the eligible child's parents was first obtained, followed by a questionnaire interview conducted by trained investigators. A structured questionnaire included questions on demographic data, clinical symptoms, course of illness, health-seeking behaviour, and information on medical and non-medical costs associated with HFMD infection. The face-to-face questionnaire interview was performed with the families at the first clinic visit or within 2 days after hospitalization. The families were given a form, 'List of expenditures related to HFMD' to complete. The goal of the form was to document all HFMD-related medical expenses and non-medical costs after enrolment. The families were provided with the pathogen test results 7 days after the onset of the disease followed by a survey related to the subsequent course of illness. The survey also included questions regarding HFMD expenditures included in the 'List of expenditures'. The same survey was conducted again by telephone 30 days after the onset of the disease. The medical cost of each enrolled inpatient was obtained using the Hospital Information System.

Data analysis and assessment of economic costs

The total HFMD-related cost was calculated by summing the medical cost (direct) and non-medical cost (indirect) [1]. Direct cost included hospital resource utilization and services such as professional consultation, medications, laboratory and imaging tests, medical procedures, bed usage and other material costs used during the hospital stay and clinical visits [2]. Indirect cost included family out-of-pocket costs for transportation to doctor, over-the-counter medications for sick children, additional food and lodging expenses for children and caregivers during hospital visits, expense for babysitting and housekeeping, and loss of work hours and earnings due the child's illness. The lost earnings were calculated based on work days lost multiplied by the 2011 average wage per day for local labourers in Shanghai (US\$22.3) [3].

The overall HFMD economic cost was calculated by multiplying mean cost per case by the number of patients in the specific group and summing all three costs. Our cost database included a total of 36 762 HFMD children aged <10 years reported to the Shanghai Municipal CDC in 2011. Of these, 35 208 (95.7%) were HFMD outpatients, 1250 (3.4%)

HFMD inpatients without complications, and the rest (354 cases, 0.09%) were severe HFMD inpatients with complications [5]. The average cost per HFMD case was calculated by dividing 36 762 cases by the total HFMD cost. The total cost was projected onto a population of 1 426 078 children aged 0–9 years in Shanghai.

The EV71 HFMD economic cost was based on the number of cases (the detection rate of EV71 multiplied by the total number of all three HFMD patient groups) multiplied by the average cost per HFMD case in the three patient groups. Variable data were presented as the means and ranges. All costs were converted from 2011 Chinese Yuan to 2011 US dollars using the official 2011 exchange rate on December 2011 (1 US\$ = 6.4588 CYN).

Statistical analysis

Data were double-entered using EpiData v. 3.1 (EpiData Association, Denmark). The groups were compared using SPSS statistical software v. 11.5 (SPSS Inc., USA). The continuous variables were presented as mean values with ranges, and the categorical variables were presented as absolute numbers and percentages. The two-sided Student's *t* test was used to analyse continuous data with a normal distribution. Otherwise, Wilcoxon's two-sided rank-sum test was implemented. To analyse the categorical data we used either contingency tables and the χ^2 or Fisher's test, as appropriate.

RESULTS

Characteristics of study subjects

At enrolment, a total of 300 children were included in the study. The final number of 30-day questionnaire surveys collected after the follow-up was 269 (89.7%) representing 96 outpatients, 85 inpatients, and 88 severe inpatients. The remaining 31 (10.3%) surveys were excluded from this study because of parents' refusal to provide all the relevant information or loss of follow-up. The male:female ratio in our study was 1.6:1. The median age was 2.8 years (range 0.5–9.0 years). The ratio of migrant cases to local cases was 2.1:1. A total of 163 (60.6%) patients had government medical insurance coverage. No fatal case occurred during the study period. Enterovirus typing using a commercial real-time RT-PCR kit (Da An Gene Co. Ltd, China) showed 160 (59.5%) cases positive for EV71, 30 (11.2%) for coxsackievirus A16, and 79

(29.4%) either positive for other enteroviruses or negative. EV71 accounted for 38.5% of outpatients, 48.2% of uncomplicated inpatients, and 93.2% of severe inpatient cases.

Social impact of HFMD on children and their parents

The social impact of HFMD on children and their parents was determined using information on the frequency of hospital visits, inpatient hospitalization days, and loss of work days within a 1-month period from the initial onset of HFMD (Table 1). The child was considered cured if all HFMD-associated symptoms were resolved. There was no difference in the impact of frequency of hospital visits between HFMD outpatients and uncomplicated inpatients (1.8 vs. 2.3, $P = 0.21$), and severe inpatients (1.8 vs. 2.4, $P = 0.89$). The hospitalization duration was significantly shorter in uncomplicated HFMD inpatients than in severe cases (2.8 days vs. 4.6 days, $P < 0.05$). The mean number of lost work days for parents of children with severe HFMD was significantly longer than that of parents of uncomplicated inpatients (15.5 days vs. 6.5 days, $P < 0.05$) and of outpatients (15.5 vs. 2.6, $P < 0.05$). The parents of children with uncomplicated HFMD lost significantly more work days than the parents of outpatients (6.5 days vs. 2.6 days, $P < 0.05$).

Average direct and indirect costs per case

The mean direct cost per case for outpatients, ordinary uncomplicated inpatients, and severe inpatients was US\$56.7, US\$550.3 and US\$1524.6, respectively ($P < 0.001$). The mean indirect cost per case for outpatients, ordinary uncomplicated inpatients, and severe inpatients was US\$108.6, US\$309.5 and US\$645.0, respectively ($P < 0.001$). Around 50% of the indirect cost was incurred by parents missing work.

Taking the direct and indirect costs into consideration, the mean total cost of HFMD per case for outpatients, ordinary uncomplicated inpatients, and severe inpatients was US\$165.3, US\$859.8 and US\$2169.6, respectively. The indirect costs presented 65.7%, 36.0% and 29.7% of the total cost in outpatients, uncomplicated inpatients, and severe inpatients, respectively.

The total economic cost attributed to HFMD and EV71 HFMD

For 2011, we determined the average total cost per case for all reported HFMD cases aged 0–9 years.

Table 1. *Social impact and economic costs in HFMD outpatients and inpatients with/without complications in 2011*

Variables	Outpatients (<i>N</i> = 96) mean (range)/per case	Uncomplicated inpatients (<i>N</i> = 85) mean (range)/per case	Severe inpatients (<i>N</i> = 88) mean (range)/per case
Social impact			
Frequency of hospital visits/days of hospitalization	1·8 (1–5)/0	2·3 (1–7)/2·8 (0·5–9)	2·4/(1–5)/4·6 (2–14)
Lost work days for parents	2·6 (0·5–15)	6·5 (1–16)	15·5 (4–82)
Direct costs (US\$)			
Clinic visits	51·5 (11·5–216·8)	55·1 (0–185·8)	63·4 (0–278·7)
Hospitalization	0	491·8 (247·7–2167·6)	1453·3 (387·1–8901·4)
Follow-up visits	5·3 (0·00–61·9)	3·4 (0–46·4)	7·9 (0–199·7)
Total direct costs (US\$)	56·7 (12·5–278·7)	550·3 (252·4–2263·6)	1524·6 (415·2–8947·8)
Indirect costs (US\$)			
Transportation	19·2 (0–154·8)	65·2 (0–510·9)	122·2 (0–577·5)
Additional food supplements and non-prescription remedy for child	11·7 (0–99·1)	61·1 (0–1114·8)	64·1 (0–990·9)
Additional food and lodging expenses for parents or caregivers	8·9 (1·1–232·4)	35·3 (0–247·7)	89·5 (0–666·1)
Additional expenses for non-family caregivers	5·4 (0–154·8)	2·9 (0–61·9)	23·5 (0–557·4)
Lost earnings by parental lost work days	58·0 (0–334·5)	145·0 (22·3–356·8)	345·7 (89·2–1828·6)
Total indirect costs (US\$)	108·6 (1·08–387·2)	309·5 (4·6–1345·5)	645·0 (4·6–1574·9)
Total economic costs (US\$)	165·3 (36·0–626·3)	859·8 (288·7–2494·1)	2169·6 (737·7–10450·0)
Insurance reimbursement (US\$)			
Total costs covered by health insurance	2·7 (0–44·9)	70·3 (0–492·3)	119·2 (0–1265·6)
Total costs paid by family out-of-pocket expenses	162·6 (31·0–610·9)	789·5 (288·7–2494·1)	2050·4 (737·7–10450·0)
Proportion of reimbursement	1·6% (0–32·2%)	8·2% (0–40·9%)	5·5% (0–56·4%)

The corresponding total annual cost was US \$5819882·4 for 35 208 outpatients, US\$1074750 for 1250 uncomplicated inpatients, and US\$768038·4 for 354 severe inpatients. The finalized estimation of the total economic cost was US\$7662670·8 for 36 812 HFMD cases. The average cost per HFMD case was US\$208·2. The cost for HFMD outpatients and inpatients accounted for 76·0% and 24·0% of the total economic cost, respectively.

A total of 163 (163/269, 60·6%) patients had medical insurance. Of the 163 children, 58 (60·4%) outpatients, 57 (67·1%) uncomplicated inpatients, and 48 (54·5%) severe inpatients had at least one type of medical insurance coverage. The types of insurance available were urban medical insurance (73/163, 44·8%), the new rural cooperative medical insurance (59/163, 36·2%), and commercial insurance or other type (31/163, 19·0%). However, the average proportion of health insurance coverage accounted for 1·6%, 8·2% and 5·5% of the total cost in all three patient groups. The total cost paid for by the family was US \$5724820·8 for 35 208 outpatients, US\$986875 for 1250 uncomplicated inpatients, and US\$725841·6 for 354 severe inpatients. Overall, the total cost paid

for by the family was US\$7437537·4, accounting for 97·1% of the total cost of HFMD.

EV71 HFMD was confirmed in 39·75% of mild cases, in 47·36% of uncomplicated inpatients, and in 92·09% of inpatients with severe complications [5]. Using these numbers in combination with the total annual cost of HFMD, we were able to estimate a total annual cost of US\$2313403·2 (US\$5819882·4 × 39·75%) for outpatients, US\$509001·6 (US\$1074750 × 47·36%) for uncomplicated inpatients, and US\$707286·6 (US\$768038·4 × 92·09%) for severe inpatients. The final estimation of the total economic cost attributed to EV71 HFMD was US\$3529691·4 for children aged <10 years, comprising 46·1% of the overall HFMD cost. The EV71 HFMD associated cost represented 65·5% and 34·5% of the total economic cost in outpatients and inpatients, respectively.

DISCUSSION

The need for an effective anti-EV71 vaccine for prevention and control of the EV71 HFMD outbreaks is urgent in China. Inactivated EV71 vaccines with high efficacy and safety have been shown to reduce

the prevalence of EV71 HFMD during the two large-scale phase 3 clinical trials conducted in China. EV71 vaccine is expected to become part of the routine child immunization schedule soon [7, 8]. Several factors should be considered before the introduction of a new vaccine on a national scale. These include the burden of disease, the economic impact of the disease and potential cost savings of vaccine implementation, vaccine price and affordability, the cost-effectiveness of the strategies, and other factors [9]. The results of this study demonstrated a significant economic burden arising from HFMD for both children and their families.

Based on the 2011 HFMD epidemiological data, the extrapolated annual costs incurred by HFMD in children aged <10 years were estimated to be >US \$7.66 million. Of particular note, >97% of the costs incurred due to HFMD were out-of-pocket family expenditures. If a novel anti-HFMD vaccine is to be introduced into the national immunization programme, without financial assistance from the government, then the vaccine pricing should take into account the burden of out-of-pocket costs. Based on the prevalence of EV71 infection and the number of HFMD cases in all patient groups, the extrapolated costs of EV71 HFMD in children aged <10 years in Shanghai reached US\$3.53 million, accounting for 46.1% of the overall cost associated with HFMD.

The study did not take into account the costs incurred by public health intervention and surveillance when estimating the total cost. According to previous studies conducted in Taiwan, symptomatic EV71 infection can manifest as HFMD (70%), herpangina (10%) or other febrile diseases (20%) [10]. Currently, herpangina is not listed as a notifiable disease in Shanghai. We have observed that the annual activity of herpangina is parallel with HFMD in children in Shanghai. In Shanghai, kindergarten children with herpangina have to stay at home in isolation until the illness is resolved. Therefore, the actual EV71 herpangina economic burden is beyond our estimation. Future massive immunization against EV71 HFMD in a 200 000 birth cohort (in 2014) in Shanghai children will be a cost-saving endeavour if the cost of vaccine is <US\$15 and the effectiveness of the vaccine is 90% after two doses.

The results showed that the average HFMD cost per child aged <10 years was US\$208.2. The average costs for HFMD outpatients amounted to 24.4%, 126.8% and 305.2% of the average monthly income for each patient group based on the monthly income

of a local labourer in Shanghai. Insurance covered only 1.6%, 8.2% and 5.5% of the total cost for outpatients, uncomplicated inpatients, and severe inpatients, respectively. Compared to childhood influenza and rotavirus diarrhoea, the average cost of HFMD was significantly higher than that of seasonal influenza in Shanghai in 2011–2012 (US\$154.8) [11]. The HFMD costs per outpatient case and per inpatient case were significantly greater than those of rotavirus diarrhoea in eastern China in 2006–2007 (US\$61.84 for outpatients and US\$684.2 for inpatients) [12]. The current price for a single dose of rotavirus vaccine is around US\$24, and the coverage rate for a single dose of rotavirus vaccine was around 41% in children aged ≤ 2 years in Shanghai in 2014. Thus, it is possible to price EV71 vaccine at the similar level as that of a rotavirus vaccine.

In addition to the substantial economic burden caused by HFMD, this disease also resulted in significant societal impact on the children and their parents. Parents lost an average of 2.6, 6.5 and 15.5 work days for taking care of outpatients, uncomplicated inpatients, and severe inpatients, respectively. However, the actual number of lost work days and lost earnings may be an underestimation since we did not consider parents whose children although healthy, could not go to either childcare centre or school due to their closure as way of preventing the disease. Based on the active surveillance of the Shanghai Municipal CDC, 1190 clusters or outbreaks of HFMD were detected in kindergartens or schools in 2011 [5]. As a result, 1357 schools and 70 kindergarten centres were closed for 2 weeks in accordance with the National Public Health intervention policies for HFMD prevention and control. Usually, each kindergarten class has about 20 children, and each kindergarten centre has about 200 children. Thus, the number of families affected by the HFMD outbreaks in the kindergartens is estimated to be 41 140 ($1357 \times 20 + 70 \times 200 = 41140$). Nevertheless, it is hard to estimate the number of days 'bystander' parents have to take off since the majority of preschool-age children are cared for by grandparents, and only a small number of professional parents have to look after their children themselves.

In this study, a very small portion of costs was reimbursed by health insurance. In China, the medical costs incurred during an outpatient visit are usually not covered by the medical insurance; the native Shanghainese children had government insurance covering 50% of the outpatient visit medical fees. Moreover, some medication prescribed by doctors

cannot be covered by insurance; thus, parents have to pay these expenses themselves. For inpatient children, a portion of medical costs incurred by IVIG use, special medications, hospital food and bed usage by the caregivers in the wards are not covered by insurance. The provincial medical insurance usually covers the medical cost accrued in the local household registration province. If a migrant child seeks medical care in Shanghai, the local medical insurance does not cover the medical cost or will only cover few expenses. Thus, migrant children in Shanghai should be the primary target population to receive the EV71 vaccine to reduce the economic burden of HFMD on their families.

Our study has several limitations. First, the study analysed data from only 1 year. Considering that the disease prevalence varies with each year, the burden associated with EV71 HFMD may vary as well. Thus, continuous surveillance studies over longer periods of time are needed to evaluate the effect of the disease on the economic burden. Second, the follow-up surveys were self-reported and may be subject to recall bias regarding costs. Finally, our hospital is located in an economically developed city in eastern China. Therefore, our results most likely cannot be projected to less developed areas of the country.

Despite the study's limitations, we strongly believe that our findings could not only provide a baseline for assessing the cost-effectiveness of the upcoming EV71 vaccine in China, but help policy-makers formulate the EV71 vaccination strategy and set an appropriate price.

ACKNOWLEDGEMENTS

We thank collaborators from Minhang District Center for Disease Control and medical workers from the Children's Hospital of Fudan University for their assistance with field investigation and laboratory testing. The study site, enrolled patients, and the data of medical costs were provided by Children's Hospital of Fudan University.

This study received no financial support.

DECLARATION OF INTEREST

None.

REFERENCES

1. **Tapparel C, et al.** Picornavirus and enterovirus diversity with associated human diseases. *Infection Genetics and Evolution* 2013, **14**: 282–293.
2. **Solomon T, et al.** Virology, epidemiology, pathogenesis, and control of enterovirus 71. *Lancet Infectious Diseases* 2010; **10**: 778–790.
3. **Ooi MH, et al.** Clinical features, diagnosis, and management of enterovirus 71. *Lancet Neurology* 2010; **9**: 1097–1105.
4. **China CDC.** National Incidence and death cases of notifiable infectious diseases, 2008–2014 (<http://www.chinacdc.cn>). Accessed 12 March 2015.
5. **Xu ZY, et al.** The population-based health effect of hand, foot and mouth disease in children in Shanghai. *Pediatric Infectious Disease Journal* 2014; **33**: 448–452.
6. **Xing W, et al.** Hand, foot, and mouth disease in China, 2008–12: an epidemiological study. *Lancet Infectious Diseases* 2014; **4**: 308–318.
7. **Zhu FC, et al.** Efficacy, safety, and immunology of an inactivated alum-adjunct enterovirus 71 vaccine in children in China: a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**: 2024–2032.
8. **Zhu F, et al.** Efficacy, safety, and immunogenicity of an enterovirus 71 vaccine in China. *New England Journal of Medicine* 2014; **370**: 818–828.
9. **DeRoeck D, et al.** Policymakers' views regarding the introduction of new-generation vaccines against typhoid fever, shigellosis and cholera in Asia. *Vaccine* 2005; **23**: 2762–2774.
10. **Chang LY, et al.** Transmission and clinical features of enterovirus 71 infections in household contacts in Taiwan. *Journal of the American Medical Association* 2004; **291**: 222–227.
11. **Jin H, et al.** Hospital-based study of the economic burden associated with rotavirus diarrhea in eastern China. *Vaccine* 2011; **29**: 7801–7806.
12. **Wang XS, et al.** Socio-economic impact of influenza in children: a single-centered hospital study in Shanghai. *Chinese Journal of Epidemiology* 2015; **36**: 27–30.