

Disease burden of enterovirus 71 in rural central China: A community-based survey

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Abbreviations: EV71, enterovirus 71; HFMD, hand, foot and mouth disease; DALYs, disability-adjusted life years; NRCMS, the New Rural Cooperative Medical Scheme; YLLs, years of life lost resulting from mortality; YLDs, years of life lost resulting from disability or morbidity; TAPQOL, The TNO-AZL Preschool Children Quality of Life; PYs, person-years

In recent years, the epidemics of hand, foot, and mouth disease (HFMD) centered in the Asian-Pacific region have been characterized by high morbidity and mortality. Enterovirus 71 (EV71) infections were responsible for the majority of the infections leading to severe cases of HFMD and death. This is a community-based survey aimed to estimate the disease burden of EV71 in rural central China, especially for HFMD. From 2011 to 2013, demographic and socio-economic data were gathered from 343 ill children and their parents using a structured questionnaire. We quantified the health burden of disease resulting from EV71 infection in disability-adjusted life years (DALYs). Among 343 cases, 303 had confirmed HFMD, 6 presented with herpangina, 25 presented with respiratory symptoms, and 9 presented with non-specific symptoms. The number of severe cases was 47 (including 1 death) and all of these presented with HFMD. The total cost per patient for severe HFMD, mild HFMD, herpangina, respiratory disease, and non-specific disease was \$2149.47, \$513.22, \$53.28, \$31.95, and \$39.25, respectively. The overall cost of EV71-related diseases as a proportion of local farmers' per capita net income ranged from 0.18% for those with non-specific disease to 187.12% for those with severe HFMD. The loss of DALYs for the 5 forms of disease were 3.47, 1.76, 1.07, 1.44, 1.22 person-years per 1000 persons, respectively. This study provides data on cost of treatment and health burden for diseases caused by EV71, which can be used in the evaluation of EV71 vaccine cost-effectiveness.

Introduction

Enterovirus 71 (EV71), a species of the Enterovirus genus within the family Picornaviridae,¹ was one of the major causative agents of outbreaks of hand, foot, and mouth disease (HFMD) or herpangina throughout the world.^{2–6} Besides, EV71 infection has been associated with an array of other clinical diseases, including aseptic meningitis, encephalitis, poliomyelitis-like paralysis, neurogenic pulmonary edema, and myocarditis.^{7,8} Although most EV71-associated illness is mild and self-limiting, some cases lead to life-threatening illness or death. In the past decade, EV71 has accounted for more than 6 billion cases and more than 2000 deaths, affecting in particular infants and young children.⁹ According to the national enhanced surveillance system in China, there were approximately 2 million cases of HFMD and resulting 500–900 deaths each year, during the period of 2008 to 2012.¹⁰ Most of the severe or fatal cases occurred in children

under 3 years of age and were associated with EV71 infection.^{11,12} In addition to the pain and suffering of children, these EV71-associated events resulted in increased medical expenses, lost productivity, and other costs to society while significantly impacting social and economic development.

However, data on the economic and health burden of EV71 infection are scarce. This study aimed to use a standard prevalence-based cost-of-illness method to estimate the direct and indirect costs of EV71-associated diseases and its health burden using disability-adjusted life years (DALYs). DALYs, which represent the sum of years of life lost resulting from mortality (YLLs) and years of life lost resulting from disability or morbidity (YLDs), were first used in 1996 when Harvard University and the World Health Organization (WHO) jointly conducted the Global Burden of Disease study.¹³ Since then, DALYs have been used widely across the world to estimate burden of disease at the international, national, and local levels.^{14–16}

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Results

Characteristic of enrolled patients

We investigated 343 cases of disease caused by EV71 infection. Of these cases, 303 were confirmed as HFMD, 6 were herpangina, 25 involved respiratory symptoms, and 9 involved non-specific symptoms, such as There were 47 severe HFMD cases, including 1 death. The average age of children at the time of illness was 28.01 months (SD 17.13). The male to female ratio was 1.86:1. Detailed demographic and clinical characteristics of all patients are shown in Table 1.

Direct costs

The median of direct medical costs for severe HFMD, mild HFMD, herpangina, respiratory disease, and non-specific disease were \$1608.62, \$307.55, \$24.41, \$12.98, and \$19.46 respectively (Table 2), and accounted for 76.59%, 68.62%, 60.14%, 69.50%, and 72.32% in direct cost, respectively. The outpatient expenditures were highest for severe HFMD (\$54.22), followed by mild HFMD and herpangina with a median of \$44.79 and \$31.45, respectively. Hospitalization fees were reported only by severe HFMD cases or mild HFMD cases, with a median of \$1653.17 and \$441.78 respectively, of which the cost for drugs and tests accounted for 60.93% and 9.38%. Besides, the median of direct non-medical costs for severe HFMD, mild HFMD, herpangina, respiratory disease, and non-specific disease, were \$377.32, \$102.82, \$10.10, \$4.87, and \$17.03, respectively. Nutrition expenses comprised the largest portion of the direct non-medical cost, accounting for 45.28%, 50.68%, 71.25%, 61.17%, and 56.44% in direct non-medical cost of corresponding diseases. Statistically significant differences were noticed in both the direct medical and non-medical cost among the different EV71-associated diseases ($P < 0.001$), and the cost of severe HFMD was the highest. The median of direct medical and non-medical costs for all cases were \$319.42 and \$105.10, respectively.

Indirect costs

The estimated loss for severe HFMD, mild HFMD, herpangina, respiratory disease, and non-specific disease was \$153.17,

\$62.19, \$12.69, \$10.94, and \$15.73, respectively, and the costs between the different diseases were significantly different ($P < 0.001$). The median of indirect cost for all cases was \$62.19 (Table 2).

Overall cost of illness

The overall economic burden of EV71-related diseases and their impact on a household were illustrated in Table 2. The median of overall cost for severe HFMD, mild HFMD, herpangina, respiratory disease, and non-specific disease were \$2149.47, \$513.22, \$53.28, \$31.95, and \$39.25, respectively. The overall cost of EV71-related diseases as a proportion of local farmers' per capita net income (\$1914.10 for Ganyu and \$2121.55 for Sheyang) ranged from 0.18% for those with non-specific disease to 187.12% for those with severe HFMD. The economic burden and proportion of costs in annual family income were significantly different among the 5 diseases (Table 2).

Burden of disease

In 343 cases, 25 (7.29%) children with EV71-associated disease presented no disability because of mild symptoms. One child (0-year-old male) was dead because of severe HFMD, resulting in a number of DALY of 32.34 person-years (PYs) recommended by the WHO.¹⁷ Furthermore, 317 children presented different degrees of temporary disability which was attributed to EV71-associated disease. The loss of DALYs caused by this situation was 0.62 PYs and the average intensity of burden for the 317 children was 1.96 PYs per 1000 persons. We noticed significant differences of disease burden among the different EV71-associated diseases ($P < 0.001$), of which the degree of severe HFMD was the highest while herpangina was the lowest (Table 3).

Nationally, there were 1,828,377 HFMD cases and 252 deaths in 2013 in China.¹⁸ According to the study reported by Xing et al,¹⁰ the proportion of severe cases was 1.1% in all HFMD cases, of which EV71 accounted for 45% of mild, 80% of severe, and 93% of fatal cases. Thus, the cost-of-illness for EV71-associated disease in China was estimated to be over \$450 million in 2013 based on the national data. Moreover, considering the number of HFMD cases and deaths in China, we

Table 1. Demographic and clinical characteristics of patients infected with EV71 (%)

	HFMD*	Herpangina	Respiratory disease	Non-specific disease	Total
Sex					
Male	202 (58.90)	4 (1.17)	11 (3.21)	6 (1.75)	223 (65.01)
Female	101 (29.44)	2 (0.58)	14 (4.08)	3 (0.87)	120 (34.99)
Age (months)					
6–36	241 (70.26)	5 (1.46)	17 (4.96)	7 (2.04)	270 (78.72)
37–72	57 (16.62)	1 (0.29)	8 (2.33)	2 (0.58)	68 (19.82)
73–	5 (1.46)	0 (0.00)	0 (0.00)	0 (0.00)	5 (1.46)
Disease severity					
Severe	47 (13.70)	0 (0.00)	0 (0.00)	0 (0.00)	47 (13.70)
Mild	256 (74.64)	6 (1.75)	25 (7.29)	9 (2.62)	296 (86.30)
Total	303 (88.34)	6 (1.75)	25 (7.29)	9 (2.62)	343(100.00)

*HFMD = hand, foot, and mouth disease.

Table 2. Direct medical and non-medical costs for EV71-related disease (Median (IQR))

Disease category	No.	direct costs			Overall cost of illness	Percent of per capita net income* (%)
		Direct medical costs	Direct non medical costs	Indirect costs		
HFMD (severe)	47	1608.62 (1061.91–2255.61)	377.32 (237.84–668.62)	153.17 (98.47–188.11)	2149.47 (1650.90–3087.17)	112.30 (86.25–161.29)
HFMD (mild)	256	307.55 (98.06–421.02)	102.82 (59.92–164.96)	62.19 (35.54–88.84)	513.22 (232.15–683.06)	26.81 (12.13–35.69)
Herpangina	6	24.41 (14.75–47.04)	10.10 (3.04–21.29)	12.69 (6.84–22.29)	53.28 (36.91–79.10)	2.78 (1.93–4.13)
Respiratory disease	25	12.98 (4.87–18.47)	4.87 (1.01–15.57)	10.94 (5.36–20.98)	31.95 (17.31–50.58)	1.67 (0.90–2.64)
Non-specific disease	9	19.46 (5.81–198.58)	17.03 (3.64–88.88)	15.73 (4.10–52.69)	39.25 (28.64–338.54)	2.05 (1.50–17.69)
Total	343	319.42 (70.90–491.40)	105.10 (40.87–203.86)	62.19 (26.22–96.60)	535.39 (141.91–772.94)	27.97(7.41–40.38)
Kruskal-Wallis χ^2		157.464	135.904	118.920	159.921	160.043
P value [#]		<0.001	<0.001	<0.001	<0.001	<0.001

*1 US dollar = 6.1653 RMB (exchange rate on June 30, 2013). The per capital annual net income of local farmers per capita in Ganyu and Sheyang prefectures, respectively, were \$1914.10 and \$2121.55 in 2013.

[#]Kruskal-Wallis test was used for continuous variables that were not normally distributed.

estimated the DALYs attributable to EV71 infection were more than 9251.28 PYs for the year 2013.

Discussion

Research on the burden of disease can not only evaluate the severity and predict the prevalence trend of the disease, but also be essential for determining high-risk populations, quantifying the damage of major risk factors for health, and optimizing the allocation of health resources. At present, the study of EV71 mainly focused on the investigation of outbreak,¹⁹ the analysis of severe cases,²⁰ the surveillance of molecular epidemiology,²¹ and the evaluation of EV71 vaccine efficacy.^{22,23} This study, based on 2 large-scale phase 3 clinical trials of an inactivated EV71 vaccine, we estimated the economic and health burden of EV71 associated-disease using the TAPQOL questionnaire to provide valuable information for both those researching the cost-effectiveness analysis of EV71 vaccine and those who make policies regarding the plan or allocation of health resources.

From 2008 to 2012, there were more than 7.2 million cases of HFMD reported to the national enhanced surveillance system in China and the estimated incidence of HFMD was 1.2 per 1000 PYs.¹⁰ EV71 infection accounted for more than 45% of all cases and 93% of fatal cases. Thus, the burden of EV71-related disease should not be neglected. The results of our study showed that the cost of severe HFMD, mild HFMD, herpangina, respiratory disease, and non-specific disease were \$2149.47, \$513.22, \$53.28,

\$31.95, and \$39.25, respectively, and accounting for 101.32%, 25.87%, 2.65%, 1.67%, and 2.05% of local farmers' per capita net income, respectively. The cost of EV71-associated HFMD was significantly higher than other diseases associated with EV71; furthermore, the cost of severe HFMD was higher than that of mild HFMD. This result indicated that we should focus more on preventing severe HDMD and deaths caused by EV71 infection. Overall cost-of-illness due to EV71-associated disease was estimated at more than \$0.45 billion annually in China, significantly higher than the total cost of rotavirus gastroenteritis in the European pediatric population.²⁴

In this study, we used the TNO-AZL Preschool Children Quality of Life (TAPQOL) questionnaire scores to derive the disability weights for EV71-associated disease.²⁵ TAPQOL is a generic, non-disease specific and multidimensional quality-of-life tool for measuring parents' perceptions of health-related quality of life in preschool children, with an acceptable reliability and validity.²⁶⁻²⁸ In general, an ideal disability weight would have been generated specifically from the EV71 infection population using any of the standard techniques. However, there were no such disability weights available. We chose to derive disability weights from TAPQOL scores for EV71 infection because the TAPQOL was exclusively used in measuring the health-related quality of life of preschool children. The total health burden for 318 patients with EV71 infection was 32.96 PYs, of which the disease burden of 317 non-death cases was 0.62 PYs and the per capita number of DALYs lost was 1.96 PYs per 1000 persons. This level was similar to the disease burden of rotavirus diarrhea

Table 3. The disease burden of EV71-related diseases (DALY per 1000 persons)

Disease category	Number	Mean DALY/1000 persons (95% CI)	F value	P value
HFMD (severe)	46	3.47 (2.71, 4.32)	9.772	<0.001
HFMD (mild)	233	1.76 (1.57, 1.99)		
Herpangina	6	1.07 (0.44, 1.64)		
Respiratory disease	24	1.44 (0.96, 1.96)		
Non-specific disease	8	1.12(0.33, 2.14)		
Total	317	1.96 (1.74, 2.12)		

that was reported by the WHO, but higher than the level of burden of other common infectious diseases in children, such as Japanese encephalitis, measles, and chicken pox.²⁹

Though, total national costs of \$450 million and the DALYs of 9251.28 due to EV71 infection in 2013 was estimated in this study. It is still probably an underestimation of the real burden owing to several limitations: first, the national system of infectious diseases reporting and monitoring only report clinical diagnosed HFMD, while other diseases caused by EV71 such as herpangina, respiratory disease, and non-specific disease have not been incorporated into this surveillance system. Our estimations have been based on HFMD as the only disease caused by EV71 infection; second, the number of death cases in our study was very small, so information for the cost of death cases were insufficient. Since the death cases have a great influence on the estimation of the total economic and health burden, the estimation could be biased. However, in developing countries, conducting burden-of-disease assessments was always challenging, with very few published studies focusing on childhood diseases,³⁰ leading to large information gaps and limited evidence for national health policy decisions. On the other hand, the economic considerations and disease burden were vital for guiding new vaccine introduction for the pediatric population.³¹ Our study provides the first comprehensive assessment of the economic and health burden of EV71 infection in China.

Recently, the number of HFMD cases and severe cases has increased annually in China,²⁰ with more than 90% of these severe cases caused by EV71.²¹ EV71-associated disease has brought a heavy burden to ill children, their families, and the society. There has been increasing interest in how to effectively control EV71-associated disease and reduce the disease burden. The development of a vaccine, which is seen as the most effective preventive measure, has progressed rapidly. Three biological product companies have completed the phase III clinical trial of EV71 inactivated vaccine and the results show that the vaccine is safe and effective.^{23,32,33} Our findings suggest that more financial resources should be invested toward the prevention and management of EV71-associated disease, especially the severe HFMD. The department of health administration and government should reduce the disease burden of patients through various measures such as improving medical cost reimbursement, optimizing methods for diagnosis or treatment of EV71-associated disease. Meanwhile, data from this study are crucial to evaluating the cost-effectiveness of EV71 vaccine in the future.

Methods

Study design

The study was based on 2 phase 3 clinical trials of an EV71 vaccine that had been reported.^{23,33} The surveillance and definition of EV71-associated disease was referred to in these trials. We investigated 343 cases due to EV71 infection, which were reported between 2011 and 2013 by the Ganyu and Sheyang prefecture Centers for Disease Control and Prevention.

We developed and translated a questionnaire for illness children. This questionnaire documented demographic and socioeconomic data for these ill children and their parents. These data included age and sex of the ill children, education and occupation of their parents, family size, the illness and its effects on health status, health insurance status, characteristics of household income, work absences, days of patient care provided by household members, and household expenses. Health insurance was categorized as insured or uninsured. Insured was defined as someone who was covered by the New Rural Cooperative Medical Scheme (NRCMS).

All patients' parents or guardians were interviewed to collect the epidemiologic data, and they were confirmed as having an EV71 infection with a laboratory assay. Then, each case was classified as HFMD, herpangina, respiratory diseases, or non-specific illness.

Case definitions

EV71-associated disease included HFMD, herpangina, respiratory diseases, and non-specific illness—eg, febrile illness, viral exanthema,—which were caused by EV71 virus (positive either for EV71 isolation or at least 2 consecutive EV71-specific RNA tests). HFMD was defined as the presence of fever with papulovesicular rash (occasionally maculopapular without vesicular lesion) on the palms, soles, knees, or elbows.⁹ Severe HFMD was defined as symptoms and signs of HFMD and more than one of the following: high fever ($\geq 39^{\circ}\text{C}$), shortness of breath, irritability, seizures, aseptic meningitis, encephalitis, pneumonia, pulmonary edema, or myocarditis. Herpangina was defined as the presence of fever with oral ulcers on the anterior tonsillar pillars, as well as the soft palate, buccal mucosa, or uvula. Respiratory disease was defined as the presence of 2 or more of the following symptoms: cough, runny nose, sore throat, rhonchi, or rales, or one of these symptoms in the presence of fever. Non-specific illness was defined as fever alone or other circumstances that do not fit the above 4 categories. All cases were confirmed by using laboratory pathogen detection methods. Laboratory confirmed EV71-associated disease was defined as a case with a positive result for EV71 RNA on a real-time polymerase chain reaction assay or a positive result for EV71 on viral isolation.

Costs

The direct medical costs of each patient were obtained from the medical records of the local hospital or from the local office of the NRCMS, which included both outpatient and inpatient costs.³⁴ Direct medical costs included hospitalization expenditures, nursing, prescription drugs, laboratory tests, examination fees, and other expenses directly related to diagnosis and treatment. Direct non-medical costs included parents' out-of-pocket payments for transportation, food, lodging, and miscellaneous expenses associated with family members visiting patients at the hospital, including the extra nutrition fee spent by parents or other relatives and friends, and with the expenses of seeking and obtaining medical care.

Indirect costs were the monetary values of the following: lost days of school, lost days of work for pay, and other days lost by

either the parents or any other household member who provided care to the children during an episode of illness.³⁵ We used the human capital approach to estimate these indirect costs.^{36,37} Because most subjects were less than 6 years old, the cost of school days lost was negligible. We set the value of workdays lost by a parent or other household member as the individual's monthly wages divided by 30 days. We then calculated the total economic cost of work days lost as the product of this average daily loss times and the number of work days lost. To value "other" days (caregiver and household member days lost other than worker) we used a local farmers' per capita daily wage (the per capita net income of local farmers divided by 365 days) for patients or household members older than 15 years old. Household total days lost are the total work days lost and the total "other" days lost.

Disability-adjusted life years burden of disease

DALYs have 2 components: (1) YLLs and (2) YLDs. Because there was only one death in our cohort, we calculated the DALYs lost due to mortality using the value recommended by the WHO. The YLDs were estimated based on the severity of the disease (disability weight) and the length of time lived with that disease and any accompanying disability. We used the base case recommended by Murray and Lopez with $C = 0.1658$, $r = 0.03$ and $\hat{a} = 0.04$.³⁸ For the absence of disability weights for EV71-associated disease, we used the TNO-AZL Preschool Quality of Life Questionnaire (TAPQOL) to assess health-related quality of life of all ill children as well as the same number of healthy children of the same age.²⁵ Based on the TAPQOL results, the disability weight for each ill child was calculated from the ill child's scale score divided by the mean scale score of all healthy children.

Ethical approval

This study was approved by the ethics committee of the Jiangsu Centers for Disease Control and Prevention (CDC). Before subjects were enrolled in the study, written informed consent was obtained from the parent(s) or guardian(s) of each subject.

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Statistical analysis

A parallel and double entry method was used to input data using Epidata 3.1. Microsoft Excel 2010 and SPSS 18.0 statistical software were used for analysis in this study. Descriptive statistics were employed to illustrate the characteristics of all patients in the study. Individual categories of categorical variables are presented as frequencies and percentages, continuous variables as median and interquartile range. Difference by diseases was investigated. We used the Kruskal–Wallis test for continuous variables that were not normally distributed or one-way analysis of variance for the normally distributed variables. P values of <0.05 were considered significant. All costs were discounted by the rate of 5% and expressed in United States dollars using the June 30, 2013 exchange rate of 6.1653 RMB.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Authors' Contributions

All authors contributed to the implementation of the study, including substantial contributions to the study design, data collection, study supervision, data interpretation, statistical analysis, manuscript drafting, or revision of the report. All authors had full access to all data. All authors reviewed and approved the final version of the report.

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