Published in final edited form as:

Vaccine. 2010 November 16; 28(49): 7731–7736. doi:10.1016/j.vaccine.2010.09.065.

Forecasting the Economic Value of an Enterovirus 71 (EV71) Vaccine

Bruce Y. Lee, MD, MBA^{1,2,3}, Angela R. Wateska, MPH^{1,2,3}, Rachel R. Bailey, MPH^{1,2,3}, Julie H.Y. Tai, MD^{1,2,3}, Kristina M. Bacon, MPH^{1,2,3}, and Kenneth J. Smith, MD, MS¹

¹ Public Health Computational and Operations Research (PHICOR), School of Medicine, University of Pittsburgh, Pittsburgh PA

² Department of Biomedical Informatics, School of Medicine, University of Pittsburgh, Pittsburgh PA

³ Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh PA

Abstract

Enterovirus 71 (EV71) is a growing public health concern, especially in Asia. A surge of EV71 cases in 2008 prompted authorities in China to go on national alert. While there is currently no treatment for EV71 infections, vaccines are under development. We developed a computer simulation model to determine the potential economic value of an EV71 vaccine for children (<5 years old) in China. Our results suggest that routine vaccination in China (EV71 infection incidence 0.04%) may be cost-effective when vaccine cost is \$25 and efficacy $\geq 70\%$ or cost is \$10 and efficacy $\geq 50\%$. For populations with higher infection risk ($\geq 0.4\%$), a \$50 or \$75 vaccine would be highly cost-effective even when vaccine efficacy is as low as 50%.

Keywords

Enterovirus 71; Economics; Computer Simulation; Vaccine

1. Introduction

Enterovirus 71 (EV71) is a growing public health concern, especially in Asia. In 2008 China experienced a surge of EV71 cases prompting authorities to go on national alert. Outbreaks in Australia, Canada, Hong Kong, Japan, Malaysia and Taiwan have occurred. Manifestations of EV71 infection can range from fever, oral ulcerations, and benign skin lesions such as herpangina and hand, foot, and mouth disease (HFMD) to severe neurological complications and respiratory and cardiac conditions [1–2]. While EV71 can infect all ages, it more commonly and severely infects children 5 years of age and under since older individuals are more likely to have been exposed and developed humoral immunity previously [3]. With the exception of poliovirus, EV71 is the most clinically important infection of the enteroviruses, due to its potential to cause death and disability

Corresponding Author: Bruce Y. Lee, MD MBA, Public Health Computational and Operations Research (PHICOR), University of Pittsburgh 200 Meyran Avenue, Suite 200 Pittsburgh, PA, 15213, BYL1@pitt.edu, Phone:(412) 246-6934, FAX: (412) 246-6954.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

resulting from severe central nervous system disorders including meningitis, encephalitis, and acute flaccid paralysis similar to that found in paralytic poliomyelitis [4]. As of the year 2000, EV71 had been implicated in approximately 13 outbreaks in several regions throughout the world since its discovery in 1969 in California; however, it wasn't until 1997 that the prevalence of EV71 infection had increased significantly in Southeast Asia [1,4]. Outbreaks of HFMD mainly due to EV71 infection occurred recently in China in the years 2007, 2008, and 2009, with increasingly higher incidences and fatalities each subsequent year [5].

The recent outbreaks in China, as well as the propensity of the serotype EV71 to cause more severe complications, highlight the need for an effective EV71 vaccine. There is currently no effective treatment for EV71 infection. The successful poliovirus vaccines, both formaldehyde-inactivated and live attenuated, portend promise for an EV71 vaccine [6]. Several candidates for EV71 vaccination are under development including a recombinant VP1 protein vaccine, a formaldehyde-inactivated whole-virus vaccine, and an attenuated EV71 strain that contains determinants derived from the type 1 poliovirus vaccine strain [6–8].

Understanding a vaccine's potential economic value well before licensure can help guide investment in and development of the vaccine, identify appropriate target populations, establish appropriate price points and thereby improve the vaccine's chances for success [9]. In fact, a survey of policymakers and other decision makers in seven Southeast Asian countries found that the following factors are vital to guiding new vaccine introduction: disease burden, economic considerations such as the economic impact of the disease and potential cost savings of a vaccine, vaccine price and affordability, vaccine safety and performance, feasibility of local production, and other factors such as delivery, training, cold chain, and storage needs [10]. Therefore, we developed a computer simulation model to estimate the potential economic value of an EV71 vaccine for children 5 years and younger in China.

2. Methods

2.1. Model Structure

Figure 1 illustrates the general structure of the model, which was constructed using Tree Age Pro (TreeAge Software, Williamstown, MA) and represents the choice of whether a child (6 months to 5 years old) should receive EV71 vaccination from the payer perspective. The model followed the EV71 and vaccine related costs and effects for the remainder of the person's life. The target population (i.e., the age of individuals entering the model was children ranging from 6 months old (when children begin losing the benefits of maternal antibody protection and are able to generate an immune response) to 5 years old (since studies have suggested that children under the age of 5 have higher hospitalization and fatality rates and that the risk of EV71 infection drops substantially after age 5) [11–12]. The baseline risk was derived from the number of HFMD cases in China in 2009 and average population in China around 2008 as reported by UNICEF [5,13]. Sensitivity analyses explored the impact of varying this risk. Receiving the vaccine reduced the child's risk of infection by 1-vaccine efficacy. Vaccination also carried a risk of minor side effects such as fever, rash, and injection site pain. (The baseline scenarios fixed this risk at 50%. Sensitivity analyses found the model to be insensitive to varying this risk.)

EV71 infection could occur any time in the child's life. An infected individual then entered the outcomes subtree detailed in Figure 2. Infection could lead to any combination of the following outcomes: encephalitis, pulmonary edema, aseptic meningitis, myocarditis, acute flaccid paralysis, HFMD, and herpangina. Table 1 lists the probabilities of each outcome

and the respective sources. HFMD and/or herpangina alone did not require hospitalization and instead could be handled by outpatient treatment [12].

Each Monte Carlo simulation run sent 1000 hypothetical children through the model 1000 times for a total of 1,000,000 trial outcomes. For each run, we calculated the incremental cost-effectiveness ratio (ICER) of administering the vaccine versus not administering the vaccine using the equation:

$$ICER = \frac{Cost_{No\ EV71\ vaccination} - Cost_{EV71\ vaccination}}{Effectiveness_{No\ EV71\ vaccination} - Effectiveness_{EV71\ vaccination}}$$

Our model measured effectiveness in disability-adjusted life years (DALYs) where the DALY value for a particular condition is equal to the years of life lost (YLL) plus the years of life lost due to disability (YLD):

Disability Adjusted Life Year (DALY)=Years of life lost (YLL)+Years of life lost due to disability (YLD)

where YLL is equal to the life expectancy at the time of death and YLD for a particular condition is as follows:

$$YLD = \text{Disability weight (DW)} * \text{Length of illness in a given year}$$

Results from runs simulated are measured in cost per DALY averted. The World Health Organization's (WHO) Commission on Macroeconomics and Health classifies an intervention as "highly cost-effective" if the cost per DALY averted is less than the per capita gross national (GNI) or gross domestic product (GDP), "cost-effective" if it is between one and three times the GNI or GDP, and "cost-ineffective" if it is more than three times the GNI or GDP [14].

2.2 Data Inputs

Table 1 shows the cost (in 2010 US\$ and Chinese ¥), utility, and probability input distributions for our model. The durations of each outcome were based upon average hospitalization stays for each condition in the United States and have assumed beta distributions. This is likely an underestimation of the duration of each outcome as a patient will still experience residual illness despite leaving the hospital. The costs of the various EV71 outcomes came from an extensive literature search and the United States Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample [15–16]. A multiplier derived from the WHO-Choice Project converted U.S. hospital costs to China hospital costs [17–19]. Several studies have used a similar method to convert healthcare costs between countries with similar GDPs [20–21]. Since the error in using this method to convert U.S. costs to China costs is unclear, sensitivity analyses explored the effects of varying this multiplier by +/- 50%.

2.3 Sensitivity Analyses

Sensitivity analyses systematically varied the values of the following key variables:

- Vaccine cost: range \$10 to \$75,
- Patient age: range from less than one to 5 years old
- EV 71 risk: range 0.04% to 1%

- Vaccine efficacy: range 50%–90%
- US-China Cost conversion multiplier: range $\pm 50\%$

Since the model focuses on whether an individual should receive the vaccine, the risk of EV71 for the individual will reflect in part on the vaccine coverage of the population. As vaccine coverage increases, the risk of EV71 for the individual will decline. Ranging the EV71 risk would help decision makers understand how the economic value of the vaccine will change as this occurs.

In addition, probabilistic sensitivity analyses explored the impact of varying all variables throughout the ranges in Table 1 simultaneously.

3. Results

Table 3 shows how the ICER values of vaccination vary with EV71 risk and vaccine efficacy for different vaccine costs. In general, as EV71 risk or vaccine efficacy increases or vaccine cost decreases, the vaccine becomes more cost-effective. The lightly shaded areas indicate where the vaccine is cost-effective (between one and three times the per capita GDP); the darker shaded areas show where the vaccine is highly cost effective (below one times the per capita GDP).

As can be seen, at the current EV71 risk (0.04%) in China, mass immunization is cost effective when vaccination costs $\leq \$25$. A \$10 vaccination would be cost effective when vaccine efficacy is $\geq 50\%$. A \$25 vaccination would also be cost-effective when vaccine efficacy is $\geq 70\%$. Figure 3 shows how the ICER varies with vaccine cost at the current EV71 risk (0.04%) in China at 70% vaccine efficacy. As risk levels move above 0.04%, \$10 vaccination becomes increasingly cost-effective.

When vaccine cost is \$50 or higher, mass immunization is not economically favorable at the current EV71 infection risk in China. However, targeted immunization for higher risk populations or groups may still be cost-effective. As Table 3 shows, the risk boundaries for a \$50 vaccination being cost-effective and highly cost effective are 0.07% and 0.4%, respectively. For \$75 vaccination, this risk threshold is 0.4%. As the EV71 risk moves above and beyond 0.07%, the vaccine becomes cost-effective. The ICER is highly sensitive to EV71 risk. In fact, when EV71 risk moves above 1.5% for a vaccine cost of \$10 and 70% efficacy, 3.5% for a vaccine cost of \$25 and 70% efficacy, and 5% for a vaccine cost of \$50 and 80% efficacy, the vaccine becomes economically dominant (saves costs as well as provides health benefits).

Our findings are robust (i.e., do not change significantly) to varying the US-China health care host multiplier by $\pm 50\%$. Therefore, even if our conversion of health care costs to those of China were much too high or low, the end results would not be substantially different.

4. Discussion

4.1 Study Implications

Given the number of HFMD cases in China in 2009 and the average population of China, the actual incidence of EV71 is quite low (around 0.04%). Therefore, current EV71 risk may not justify a vaccine that costs over \$25. However, adding a vaccine that costs less than \$25 (including administration costs) to China's routine immunization program may be worthwhile, assuming vaccine efficacy reaches the thresholds outlined by our study. The economic value of EV71 vaccination is quite sensitive to EV71 risk. Slight increases in

EV71 risk can make vaccination cost-effective even when the vaccine is more expensive and less efficacious.

Demonstrating the cost thresholds below which the vaccine is cost-effective can help manufacturers and purchasers (e.g. governments and third party organizations) determine suitable price points for the vaccine. As demonstrated, the vaccine remains cost-effective up to a vaccine cost of \$75, which may be encouraging news for manufacturers who are wed to prices in the \$0.12–\$8 range for other vaccines in developing countries [22]. Of course, research and development and manufacturing costs will also play a major role in determining whether EV71 vaccine is a worthwhile target for manufacturers. Better understanding of the relationship between a vaccine's price and its economic value can provide useful benchmarks [23].

Our study suggests that the cost-effectiveness of EV71 vaccine would be comparable to that of other pediatric vaccines in Asia. One study found that in middle-income Asian countries a \$2 and a \$60 rotavirus vaccine would have ICER's between \$15.32 and \$1364 per DALY avoided, respectively, from a payer perspective [24]. Another estimated that the ICER of an oral cholera vaccine ranges from \$1,353 to \$2,999 per DALY avoided for all countries (except in Indonesia where the ICER ranges from \$10,632 to \$23,415) [25]. A third study exploring the cost-effectiveness of catch-up HBV vaccination in China reported ICER's ranging from economic dominance to almost \$3000 per DALY avoided depending on the population [26].

In China, the reported incidence of HFMD cases escalated significantly from 2007 to 2009. The year 2007 experienced 83,344 reported cases with 17 deaths [5]. In 2008, when HFMD became a notifiable disease, the number of reported cases increased to 488,955 with 126 fatalities [5]. The following year, reported cases ballooned to 614,901 with 200 deaths just within the months of March to June [5]. The epidemic affected certain regions more than others. In 2008 and 2009, while the case fatality rate for China was about 0.03%, Fuyang City in Anhui Province experienced a case fatality rate of 0.3% [5,27]. Our simulation runs with a 0.07% incidence corresponded closest to the situation in Fuyang City, suggesting that mass vaccination with a \$50 EV71 vaccine would be cost-effective at vaccine efficacy $\geq 70\%$.

EV71 is growing problem throughout Asia. In 1998, Taiwan suffered an outbreak that resulted in 129,106 reported cases of HFMD/herpangina and 78 fatalities [11]. Since a Sarawak, Malaysia, outbreak in 1997, the number of cases in Asia has substantially exceeded those in other parts of the world [28–29]. The Sarawak outbreak certainly was not the first appearance of EV71 in Asia. Outbreaks manifested in Japan in 1973 and Hong Kong and Hubei in China in the years 1985 and 1987, respectively [1].

However, the first known appearance of EV71 was outside Asia in California in the United States in 1969. Over the ensuing decade, EV71 cases arose in different parts of the US but no fatalities were reported [1,4]. Australia faced an outbreak in 1972 but also saw no fatalities [4,30]. In Europe, outbreaks also mainly occurred in the 1970's in Sweden, Bulgaria, Hungary, and France with fatalities in Bulgaria and Hungary [4,31–33]. The incidence in Europe has remained relatively low compared to Asia; however, in 2007, the Netherlands experienced a surge of infections with 58 reported cases, prompting renewed surveillance efforts in the region [28].

Vaccines under development include an attenuated EV71 strain that contains determinants derived from the type 1 poliovirus strain as well as a recombinant VP1 protein vaccine and a formaldehyde-inactivated whole-virus vaccine that are in the animal experimental stage [6–8]. Given the very early stages of development for an EV71 vaccine, it remains to be seen if

one is produced, it will be successful. Proven effectiveness in mice does not necessarily confer immunity in humans. Although we have demonstrated a vaccine relatively low in efficacy can still be beneficial, it is of paramount importance to ensure the vaccine is safe and provides long lasting protection in humans. If production of an EV71 vaccine occurs, it will be among the first group of vaccines to be developed for an infectious disease circulating primarily in developing countries. It has been suggested producing the vaccine in one developing country could be utilized by other neighboring countries in order to make the vaccines more affordable for everyone [34].

4.2 Limitations

Computer simulation models are by definition, simplistic versions of real life scenarios and cannot account for every possible occurrence that could result from an infection with EV71. One of the purposes of this study is to outline the relationship between EV71 risk and economic value of the vaccine. Although EV71 risk will likely decline as vaccine coverage increases, the relationship exact relationship is unclear, especially since the transmission dynamics of EV71 in China have not yet been well characterized. Elucidating this relationship would require a population-wide transmission model.

Despite the side effects of vaccination set at a relatively high rate of 50% in the model, we still assumed the side effects to be minimal. Data inputs for the probabilities of outcomes from EV71 largely came from literature surrounding the 1998 outbreak in Taiwan due to limited available data regarding the outbreaks in China. Our model focused on the highest risk age group, i.e., children five years and younger. However, older individuals may be candidates for catch-up vaccination as well to ensure that the entire population is protected. Finally, outcome cost data was a gross approximation with respect to the conversion of US costs to China costs.

4.3 Conclusion

Our study favors universal EV71 vaccination of children in China at the current incidence of EV71 at vaccine price points \$25 and lower. For higher vaccine costs, nationwide incidence would have to be higher for routine immunization to be cost-effective as vaccination for a 5 and under population is cost-ineffective at these prices at the present incidence in China. Areas such as the southeastern provinces of Guangdong, Zhejiang, and Anhui, and more specifically, Fuyang City could potentially benefit from a reactive EV71 vaccination following close surveillance by the health ministry and the Chinese Center for Disease Control and Prevention. Intervention at an earlier stage in these epidemics could have prevented the large number of fatalities. Vaccination is highly cost-effective at a threshold risk of 0.4% across all price points; therefore if areas were to reach this level, it would be of great benefit to vaccinate even with a vaccine at lower efficacy of 50%. The last decade has indicated EV71 may become endemic in various regions in East Asia [34]. Developing a vaccine in advance for potential future epidemics would be advised for policymakers and global health leaders. Future studies may include a population-wide transmission model to better understand the transmission dynamics of EV71 in China and the resulting potential relationship between coverage and individual EV71 risk.

Acknowledgments

This research was supported by the National Institute of General Medical Sciences Models of Infectious Agent Study (MIDAS) grant 1U54GM088491-0109 and the Vaccine Modeling Initiative (VMI) funded by the Bill and Melinda Gates Foundation. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Hsiung GD, Wang JR. Enterovirus infections with special reference to enterovirus 71. *J Microbiol Immunol Infect.* 2000; 33(1):1–8. [PubMed: 10806956]
2. Sawyer MH. Enterovirus infections: diagnosis and treatment. *Curr Opin Pediatr.* 2001; 13(1):65–9. [PubMed: 11176247]
3. Palacios G, Oberste MS. Enteroviruses as agents of emerging infectious diseases. *J Neurovirol.* 2005; 11(5):424–33. [PubMed: 16287683]
4. Ho M. Enterovirus 71: the virus, its infections and outbreaks. *J Microbiol Immunol Infect.* 2000; 33(4):205–16. [PubMed: 11269363]
5. Wong SS, et al. Human enterovirus 71 and hand, foot and mouth disease. *Epidemiol Infect.* 2010:1–19.
6. Ong KC, et al. Formaldehyde-inactivated whole-virus vaccine protects a murine model of enterovirus 71 encephalomyelitis against disease. *J Virol.* 2010; 84(1):661–5. [PubMed: 19864378]
7. Chen HL, et al. Expression of VP1 protein in the milk of transgenic mice: a potential oral vaccine protects against enterovirus 71 infection. *Vaccine.* 2008; 26(23):2882–9. [PubMed: 18450335]
8. Arita M, et al. Cooperative effect of the attenuation determinants derived from poliovirus sabin 1 strain is essential for attenuation of enterovirus 71 in the NOD/SCID mouse infection model. *J Virol.* 2008; 82(4):1787–97. [PubMed: 18057246]
9. Lee BY, Burke DS. Constructing target product profiles (TPPs) to help vaccines overcome post-approval obstacles. *Vaccine.* 2010; 28(16):2806–9. [PubMed: 19782109]
10. DeRoek D, et al. Policymakers' views regarding the introduction of new- generation vaccines against typhoid fever, shigellosis and cholera in Asia. *Vaccine.* 2005; 23(21):2762–74. [PubMed: 15780724]
11. Chang LY, et al. Risk factors of enterovirus 71 infection and associated hand, foot, and mouth disease/herpangina in children during an epidemic in Taiwan. *Pediatrics.* 2002; 109(6):e88. [PubMed: 12042582]
12. Ho M, et al. An epidemic of enterovirus 71 infection in Taiwan. Taiwan Enterovirus Epidemic Working Group. *N Engl J Med.* 1999; 341(13):929–35. [PubMed: 10498487]
13. UNICEF. Info by country: China Statistics. 2007 Jan 24. 2010]; Available from: http://www.unicef.org/infobycountry/china_statistics.html
14. Walker, D.; Beutels, P. WHO guide for standardization of economic evaluations of immunization programmes. Department of Immunization Vaccines and Biologicals; Geneva: 2008.
15. Agency for Healthcare Research and Quality. HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2007.
16. Pichichero ME, et al. Clinical and economic impact of enterovirus illness in private pediatric practice. *Pediatrics.* 1998; 102(5):1126–34. [PubMed: 9794944]
17. World Health Organization. Estimates of Unit Costs for Patient Services for China. Choosing Interventions that are Cost Effective. [cited 2/19/2010]; Available from: <http://www.who.int/choice/country/chn/cost/en/index.html>
18. World Health Organization. Estimates of Unit Costs for Patient Services for United States of America. Choosing Interventions that are Cost Effective. [cited 2/19/2010]; Available from: <http://www.who.int/choice/country/usa/cost/en/index.html>
19. Adam T, Evans DB, Murray CJ. Econometric estimation of country-specific hospital costs. *Cost Eff Resour Alloc.* 2003; 1(1):3. [PubMed: 12773218]
20. Goldie SJ, et al. Cost-effectiveness of HPV 16, 18 vaccination in Brazil. *Vaccine.* 2007; 25(33):6257–70. [PubMed: 17606315]
21. Hu D, et al. The costs, benefits, and cost-effectiveness of interventions to reduce maternal morbidity and mortality in Mexico. *PLoS One.* 2007; 2(1):e750. [PubMed: 17710149]
22. World Health Organization. Vaccine Management and Logistics: Vaccine Volume Calculator. 2009 Sept 13. 2010]; Available from: http://www.who.int/immunization_delivery/systems_policy/logistics/en/index4.html

23. Lee BY, McGlone SM. Pricing of New Vaccines. *Human Vaccines*. 2010; 6(8):619–626. [PubMed: 20861678]
24. Podewils LJ, et al. Projected cost-effectiveness of rotavirus vaccination for children in Asia. *J Infect Dis*. 2005; 192(Suppl 1):S133–45. [PubMed: 16088797]
25. Jeuland M, et al. Cost-effectiveness of new-generation oral cholera vaccines: a multisite analysis. *Value Health*. 2009; 12(6):899–908. [PubMed: 19824189]
26. Hutton DW, So SK, Brandeau ML. Cost-effectiveness of nationwide hepatitis B catch-up vaccination among children and adolescents in China. *Hepatology*. 2010; 51(2):405–14. [PubMed: 19839061]
27. Chinese Center for Disease Control and Prevention and the Office of the World Health Organization in China. Report on the hand, foot and mouth disease outbreak in Fuyang City, Anhui Province and the prevention and control in China, May 2008. 2/15/2010; Available from: <http://www.wpro.who.int/NR/rdonlys/res/591D6A7B-FB15-4E94-A1E9-1D3381847D60/0/HFMDCCDC20080515ENG.pdf>
28. van der Sanden S, et al. Epidemiology of enterovirus 71 in the Netherlands, 1963 to 2008. *J Clin Microbiol*. 2009; 47(9):2826–33. [PubMed: 19625480]
29. Podin Y, et al. Sentinel surveillance for human enterovirus 71 in Sarawak, Malaysia: lessons from the first 7 years. *BMC Public Health*. 2006; 6:180. [PubMed: 16827926]
30. Gilbert GL, et al. Outbreak of enterovirus 71 infection in Victoria, Australia, with a high incidence of neurologic involvement. *Pediatr Infect Dis J*. 1988; 7(7):484–8. [PubMed: 2841639]
31. Blomberg J, et al. Letter: New enterovirus type associated with epidemic of aseptic meningitis and/or hand, foot, and mouth disease. *Lancet*. 1974; 2(7872):112. [PubMed: 4136956]
32. Shindarov LM, et al. Epidemiological, clinical, and pathomorphological characteristics of epidemic poliomyelitis-like disease caused by enterovirus 71. *J Hyg Epidemiol Microbiol Immunol*. 1979; 23(3):284–95.
33. Nagy G, et al. Virological diagnosis of enterovirus type 71 infections: experiences gained during an epidemic of acute CNS diseases in Hungary in 1978. *Arch Virol*. 1982; 71(3):217–27. [PubMed: 6285858]
34. Xu J, et al. EV71: an emerging infectious disease vaccine target in the Far East? *Vaccine*. 2010; 28(20):3516–21. [PubMed: 20304038]

Figure 1.
Structure of Enterovirus 71 Model

Figure 2.
Enterovirus 71 Infection Outcomes Subtree

Figure 3.
Change in incremental cost-effectiveness ratio (ICER) by vaccine cost at 0.04% risk and 70% vaccine efficacy

Cost Inputs for Model

Table 1

Description (units)	Mean US\$ ^a	Mean China ¥ ^b	Range or Standard Deviation		Distribution Type	Source
Hospitalization and outpatient visits						
Encephalitis						
Age<1	795.53 ^{a,2}	1,670.61 ^{b,2}	207.84 ^{a,1}	436.46 ^{b,1}	Gamma	[15]
Age>1	468.22 ^{a,2}	983.26 ^{b,2}	118.19 ^{a,1}	248.20 ^{b,1}	Gamma	[15]
Myocarditis						
Age<1	724.90 ^{a,2}	1522.29 ^{b,2}	763.22 ^{a,1}	1,602.76 ^{b,1}	Gamma	[15]
Age>1	388.35 ^{a,2}	815.53 ^{b,2}	202.34 ^{a,1}	424.92 ^{b,1}	Gamma	[15]
Aseptic meningitis						
Age<1	146.75 ^{a,2}	308.17 ^{b,2}	21.98 ^{a,1}	46.15 ^{b,1}	Gamma	[15]
Age>1	161.54 ^{a,2}	339.23 ^{b,2}	19.82 ^{a,1}	41.62 ^{b,1}	Gamma	[15]
Pulmonary edema						
	280.5 ^{a,2}	589.05 ^{b,2}	52.26 ^{a,1}	109.75 ^{b,1}	Gamma	[15]
Acute flaccid paralysis						
	481.80 ^{a,2}	1011.78 ^{b,2}	55.36 ^{a,1}	116.26 ^{b,1}	Gamma	[15]
Hand foot and mouth disease						
	4.76 ^a	10.00 ^b	-	-	Gamma	[16]
Herpangina						
	6.48 ^a	13.61 ^b	-	-	Gamma	[16]
Side effect from vaccine						
	1.65 ^a	3.47 ^b	1.46–8.26 ^a	3.07–17.35 ^b	Triangular	[33]

^aUS \$^bChina ¥¹Standard deviation²Median

Table 2

Utility and Probability Inputs for Model

Description (units)	Mean	Range	Distribution Type	Source
Disability Weights				
Encephalitis	0.615	0.613–0.616	Triangular	[34]
Pulmonary edema	0.252	0.201–0.300	Triangular	[34]
Aseptic meningitis	0.615	0.613–0.616	Triangular	[34]
Myocarditis	0.252	0.201–0.300	Triangular	[34]
Acute flaccid paralysis	0.369 ^I	-	-	[34]
Hand foot and mouth disease	0.056 ^I	-	-	[34]
Herpangina	0.056 ^I	-	-	[34]
Probabilities (%)				
Encephalitis	26.4	7.2–39.2	Beta	[12, 35–36]
Pulmonary edema	10.0	7.1–11.5	Beta	[12, 35, 37]
Aseptic meningitis	5.1	2.5–7.1	Beta	[12, 35–36, 38–39]
Myocarditis	0.98	0.67–1.3	Beta	[12, 35]
Acute flaccid paralysis	2.2	0.51–4.4	Beta	[12, 35–36, 38–39]
Hand foot and mouth disease	67.3	45.4–97.4	Beta	[36, 38–39]
Herpangina	8.8	6.1–10.3	Beta	[36, 38–39]
Side effects	50			Assumed
Mortalities under the following conditions				
CNS events	26.5	-	-	[36]
Cardiopulmonary events	59.3	-	-	[37]

^I Values obtained from World Health Organization's Global Burden of Disease Update did not have ranges associated with them.

Table 3

Incremental cost-effectiveness ratio (ICER) values for Enterovirus 71 vaccination in Pediatric Population (Ages 1 to 5 years old) in China at Baseline Healthcare Costs

EV71 Risk	Vaccine Efficacy				
	50%	60%	70%	80%	90%
Vaccination Cost \$10					
0.04% (Baseline)	4,763	4,485	3,169	3,393	3,605
0.07%	2,966	2,186	2,399	1,892	1,780
0.1%	2,519	1,960	1,332	998	1,131
Vaccination Cost \$25					
0.04% (Baseline)	10,293	10,899	7,306	6,277	6,625
0.07%	8,548	5,750	4,927	4,542	3,671
0.1%	4,111	3,672	3,384	3,378	2,451
0.4%	1,040	900	855	654	569
Vaccination Cost \$50					
0.04% (Baseline)	21,149	17,437	18,361	17,441	13,129
0.07%	15,826	9,632	8,444	8,994	8,435
0.1%	9,246	9,505	7,958	6,641	6,151
0.4%	2,325	2,163	1,677	1,326	1,102
0.7%	1,483	1,035	947	779	709
1%	828	802	625	576	461
Vaccination Cost \$75					
0.04% (Baseline)	51,873	38,400	27,249	23,013	19,513
0.07%	15,181	14,144	12,269	9,983	10,181
0.1%	13,392	12,118	11,072	10,391	8,273
0.4%	3,637	3,217	2,620	2,379	2,038
0.7%	2,021	1,981	1,335	1,245	1,100
1%	1,203	1,231	921	814	628

Light grey: Cost-effective ($\leq 3X$ China's GDP per capita) Dark grey: Highly cost-effective ($\leq$ China's GDP per capita)