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Original article

Cost-effectiveness of bivalent versus monovalent vaccines against hand, foot and mouth disease

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ABSTRACT

Objectives: Enterovirus 71 (EV71) and coxsackievirus A16 (CA16) were responsible for 43.3% (235 123/543 243) and 24.8% (134 607/543 243) of all laboratory-confirmed hand, foot and mouth disease (HFMD) cases during 2010–2015 in China. Three monovalent EV71 vaccines have been licensed in China while bivalent EV71/CA16 vaccines are under development. A comparative cost-effectiveness analysis of bivalent EV71/CA16 versus monovalent EV71 vaccination would be useful for informing the additional value of bivalent HFMD vaccines in China.

Methods: We used a static model parameterized with the national HFMD surveillance data during 2010–2013, virological HFMD surveillance records from all 31 provinces in mainland China during 2010–2013 and caregiver survey data of costs and health quality of life during 2012–2013. We estimated the threshold vaccine cost (TVC), defined as the maximum additional cost that could be paid for a cost-effective bivalent EV71/CA16 vaccine over a monovalent EV71 vaccine, as the outcome. The base case analysis was performed from a societal perspective. Several sensitivity analyses were conducted by varying assumptions governing HFMD risk, costs, discounting and vaccine efficacy.

Results: In the base case, choosing the bivalent EV71/CA16 over monovalent EV71 vaccination would be cost-effective only if the additional cost of the bivalent EV71/CA16 compared with the monovalent EV71 vaccine is less than €4.7 (95% CI 4.2–5.2). Compared with the TVC in the base case, TVC increased by up to €8.9 if all the test-negative cases were CA16-HFMD; decreased by €1.1 with an annual discount rate of 6% and exclusion of the productivity loss; and increased by €0.14 and €0.3 with every 1% increase in bivalent vaccine efficacy against CA16-HFMD and differential vaccine efficacy against EV71-HFMD, respectively.

Conclusions: Bivalent EV71/CA16 vaccines can be cost-effective compared with monovalent EV71 vaccines, if suitably priced. Our study provides further evidence for determining the optimal use of HFMD vaccines in routine paediatric vaccination programme in China. **D. Liu, Clin Microbiol Infect 2020;26:373**

Introduction

Hand, foot and mouth disease (HFMD), commonly affecting children under 5 years old, has been a serious threat to public health across Asia over the last two decades [1]. In China, HFMD has been a notifiable disease since May 2008 [2]. The national HFMD surveillance system registered about 12 million HFMD cases and

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2843 deaths during 2010–2015 [3]. Among all the laboratory-confirmed HFMD cases in 2010–2015, enterovirus 71 (EV71) and coxsackievirus A16 (CA16) accounted for 39.8% (194 445/488 231) and 26.9% (131 481/488 231) of mild cases; 73.3% (38 858/53 011) and 5.8% (3087/53 011) of severe cases; and 92.5% (1850/2001) and 1.9% (39/2001) of fatal cases, respectively [3]. As no specific treatment is available for HFMD at present, vaccination is the most promising intervention to prevent and control epidemics of HFMD [4].

Three monovalent EV71 vaccines have been licensed in China since December 2015 and are now commercially available in the China market [5,6]. Our previous work showed that routine paediatric vaccination with these monovalent EV71 vaccines are likely to be cost-effective if the cost for vaccinating per child is below €16.4–17.8 (the variation in cost is driven by differential vaccine efficacy estimates among the three vaccines) [7]. As of May 2019, monovalent EV71 vaccines have not yet been included in the routine paediatric vaccination programme in China, meaning that they are needed to be paid out-of-pocket by parents (the vaccines currently cost €21.7–24.3 per dose for two doses per child [8]). As such, vaccine coverage of these monovalent EV71 vaccines among children aged 6 months to 5 years ranges from <10% to 50% in different provinces [9]. Meanwhile, bivalent EV71/CA16 vaccines are under development and have been shown to induce potent protective immunity against both EV71 and CA16 in mice [10–12]. These bivalent vaccines have the potential to further reduce the health burden attributable to HFMD, though the resulting marginal reduction in severe and fatal cases might not be substantial compared to monovalent EV71 vaccines because CA16 accounts for a relatively small percentage of fatal and severe HFMD cases. Our objective in this study is to characterize the marginal cost and benefit of bivalent vaccines by comparing the cost-effectiveness of bivalent EV71/CA16 vaccination and monovalent EV71 vaccination.

Methods

Model

We adapted a previous model that we constructed to estimate the cost-effectiveness of routine paediatric vaccination using monovalent EV71 vaccines [7], which was parameterized with national HFMD surveillance data in 2010–2013 [13], virological surveillance records from all 31 provinces in mainland China in 2010–2013 [7], and caregiver survey data about costs and health-related quality of life of lab-confirmed HFMD patients in 2012–2013 [14]. In this new analysis, we assumed that children were vaccinated at 6 months old with vaccine coverage c and vaccine protection to at least 5 years old under one of two possible vaccination programs of (1) a bivalent EV71/CA16 vaccine with constant vaccine efficacy VE_1 against EV71-related HFMD (EV71-HFMD) and VE_2 against CA16-related HFMD (CA16-HFMD); (2) a monovalent EV71 vaccine with constant vaccine efficacy VE_m against EV71-HFMD (Fig. 1; Tables S1 and S2). Moreover, we assumed that there was no cross-protection between the two viruses (Fig. S1) [15,16]. We only considered children aged 6 months to 5 years old because 90% (10 741 149/11 933 033), 94% (102 672/108 738) and 96% (2724/2843) of mild, severe and fatal HFMD cases registered in 2010–2015 occurred in this age group [3,7,13], which is also the age group currently recommended for monovalent EV71 vaccination [17].

Disease burden

The methodology used to estimate disease burden of EV71-HFMD and CA16-HFMD (written as EV71/CA16-HFMD hereafter) was conceptually the same as that in our previous study [7]. Following the methodology in our previous paper, to account for the uncertainty regarding the percentages of test-negatives that were EV71/CA16-HFMD in the national surveillance data, we used virological surveillance records from all 31 provinces to supplement national surveillance data and considered 51 scenarios (Fig. S2) (please see supplementary material, Uncertainty regarding test-negatives, for details).

We assumed that in the absence of vaccination, the long-term average risk of mild, severe and fatal EV71/CA16-HFMD in future birth cohorts would be identical to that registered by the national surveillance system between 2010 and 2013. The national average risk of mild, severe and fatal serotype-specific HFMD were estimated as the sum of the number of that disease in all 31 provinces in 2010–2013 divided by the total number of new births during the same years (Table 1).

Vaccine efficacy

A meta-analysis using a random-effect model showed an overall 1-year efficacy of monovalent EV71 vaccines of 95% (90–98%) [18–21]. As such, we assumed that VE_m, VE_1 and VE_2 were all 95% in the base case scenario. For sensitivity analysis, we assumed that both VE_1 and VE_2 varied between 70% and 100%, i.e. the differential vaccine efficacy against EV71 between the two vaccines, $\Delta VE_1 = VE_1 - VE_m$, varied between −25% and 5%.

Costs, QALY loss and cost-effectiveness

We estimated costs and quality-adjusted life-year (QALY) loss per birth due to EV71/CA16-HFMD using the same methodology as in our previous paper (please see supplementary material, Costs and QALY loss) [7]. We calculated the threshold vaccine cost (TVC) for bivalent EV71/CA16 vaccine compared to monovalent EV71 vaccine as the outcome in our analysis. TVC was defined as the maximum additional cost that could be paid for a cost-effective bivalent EV71/CA16 vaccine compared to the monovalent EV71 vaccine. Given a particular societal willingness-to-pay (WTP) threshold, the TVC was calculated as follows:

$$TVC = \Delta VE_1 \times (\text{WTP threshold} \times Q_1 + C_1) + VE_2 \times (\text{WTP threshold} \times Q_2 + C_2) \quad (1)$$

where C_1 and Q_1 denoted the costs and QALY loss due to EV71-HFMD per birth, and C_2 and Q_2 denoted the costs and QALY loss due to CA16-HFMD per birth [14]. Choosing the bivalent EV71/CA16 vaccine over the monovalent EV71 vaccine would be cost-effective only if the bivalent vaccine cost was no more than TVC extra compared to that of the monovalent vaccine. In the base case analysis, as VE_1 was assumed to be equal to VE_m (i.e. $\Delta E_1 = 0$), TVC here was just $VE_2 \times (\text{WTP threshold} \times Q_2 + C_2)$ (please see supplementary material, Threshold vaccine cost (TVC), for details).

In the base case, a WTP threshold of one gross domestic product per capita (GDPpc; €7698 in 2017) was applied because it is commonly used in China [22,23]. A societal perspective was used (including parent/caregiver out-of-pocket costs and productivity losses), and costs and health utilities were discounted at a rate of 3% per annum. All costs were reported in Chinese Yuan during 2012–2013 but were inflated to 2017–2018 prices using China's annual consumer price index (healthcare) [24], before being converted to 2017 Euro (1 euro = 7.75 Chinese Yuan).

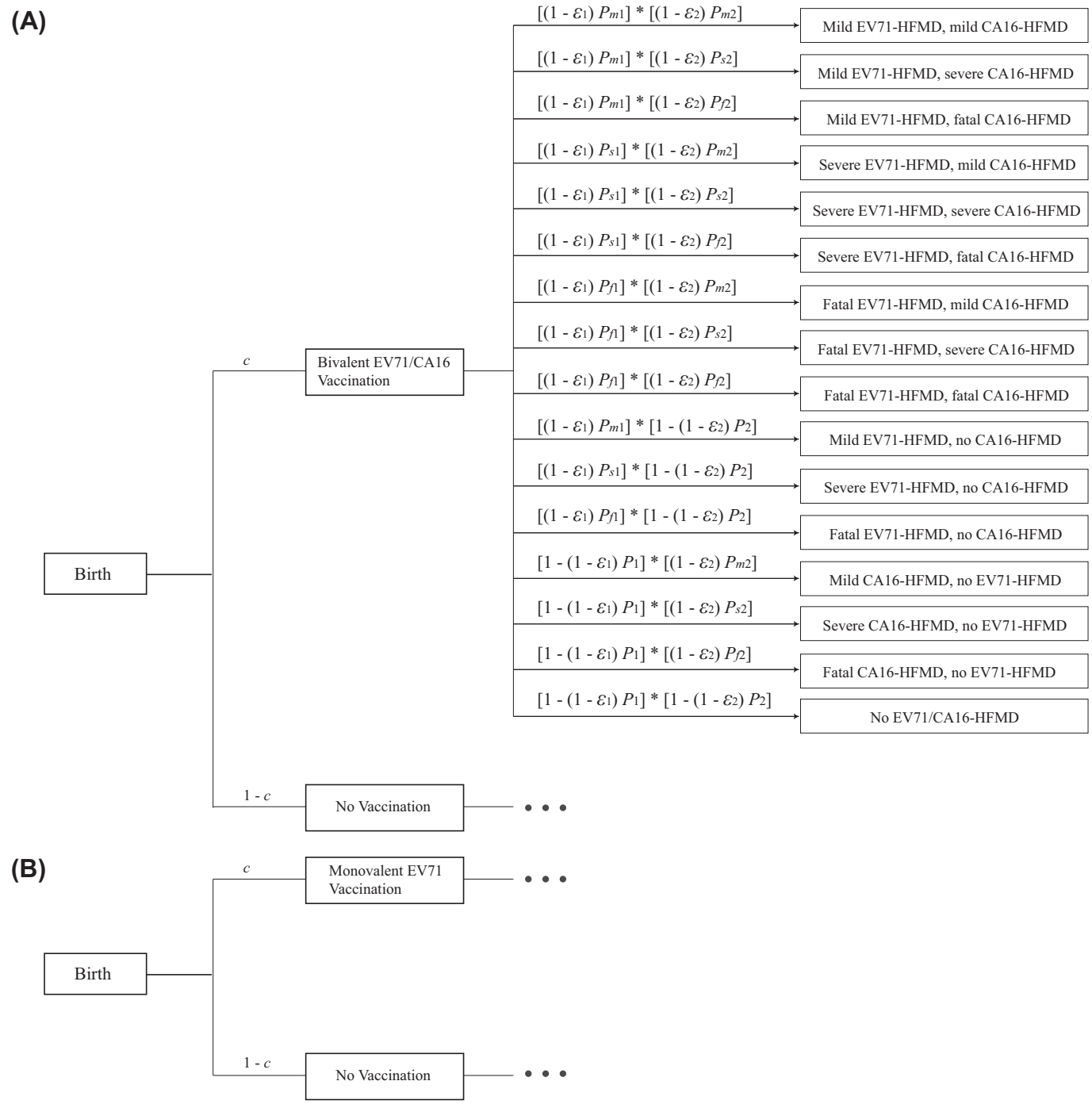

Fig. 1. Model structure. A birth cohort was assumed to be vaccinated by one of the two vaccination strategies: (A) bivalent EV71/CA16 vaccination with a vaccine coverage c and vaccine efficacy VE_1 against EV71-HFMD and VE_2 against CA16-HFMD; (B) monovalent EV71 vaccination with a vaccine coverage c and vaccine efficacy VE_m against EV71-HFMD. The timeframe was assumed to be 6 months to 5 years old. The ellipses indicated the same outcomes as bivalent EV71/CA16 vaccination. P_{m1}, P_{s1} and P_{f1} denote the national average risk of mild, severe and fatal EV71-HFMD per birth; P_{m2}, P_{s2} and P_{f2} denote the national average risk of mild, severe and fatal CA16-HFMD per birth; P_1 and P_2 denote the national average risk of EV71-HFMD and CA16-HFMD per birth; ε_1 and ε_2 denote the proportion of EV71-HFMD and CA16-HFMD prevented by each vaccination strategy, respectively. Therefore, ε_1 and ε_2 are (1) respectively equal to VE_1 and VE_2 under bivalent EV71/CA16 vaccination; (2) respectively equal to VE_m and 0 under monovalent EV71 vaccination; (3) both equal to 0 under no vaccination (see Tables S1 and S2 for detailed outcome probabilities). HFMD, hand, foot and mouth disease.

Uncertainty analysis

Scenario sensitivity analyses were conducted by varying assumptions governing HFMD risk, costs, discounting and vaccine efficacies, as follows: (1) the estimated risk of EV71/CA16-HFMD in the 51 scenarios generated by the three assumptions mentioned above; (2) inclusion or exclusion of productivity loss of parents/caregivers in estimating costs; (3) discount rate at 3% or 6% per annum; (4) variation in ΔVE_1 and VE_2 as mentioned above. In addition, we conducted probabilistic sensitivity analysis by varying HFMD risk, costs and QALY loss due to EV71/CA16-HFMD

Table 1
Model parameters and their sources

	Base case	Uncertainty analysis	Distribution	Source
Lifetime risk (per 100 000 births)				
EV71-Mild	3088	2932–7077[a]	Dirichlet distribution	National HFMD surveillance data and virological surveillance records from all 31 provinces in mainland China between 2010 and 2013 [7,13]
EV71-Severe	83.4	75–107[a]		
EV71-Fatal	3.13	3.04–3.53[a]		
CA16-Mild	2,162	2083–6228[a]		
CA16-Severe	6.6	5.8–37.3[a]		
CA16-Fatal	0.07	0.07–0.54[a]		
Costs (per case, excluding productivity loss, €)				
EV71-Mild	693.8		Bivariate normal distribution	Caregiver survey data about costs and health-related quality of life of lab-confirmed HFMD patients between 2012 and 2013 [14]
EV71-Severe	2851.8			
EV71-Fatal	2392.8			
CA16-Mild	360.6			
CA16-Severe	2433.7			
CA16-Fatal	2264.4			
Costs (per case, including productivity loss, €)				
EV71-Mild	761.0		Bivariate normal distribution	Caregiver survey data about costs and health-related quality of life of lab-confirmed HFMD patients between 2012 and 2013 [14]
EV71-Severe	2970.8			
EV71-Fatal	2567.3			
CA16-Mild	419.4			
CA16-Severe	2552.5			
CA16-Fatal	2422.4			
Costs (per birth, excluding productivity loss, €)				
EV71-Mild	5.73		Bivariate normal distribution	Caregiver survey data about costs and health-related quality of life of lab-confirmed HFMD patients between 2012 and 2013 [14]
EV71-Severe	2.41			
EV71-Fatal	0.06			
CA16-Mild	3.02			
CA16-Severe	0.16			
CA16-Fatal	0.001			
Costs (per birth, including productivity loss, €)				
EV71-Mild	7.37		Bivariate normal distribution	Caregiver survey data about costs and health-related quality of life of lab-confirmed HFMD patients between 2012 and 2013 [14]
EV71-Severe	2.52			
EV71-Fatal	0.07			
CA16-Mild	3.97			
CA16-Severe	0.17			
CA16-Fatal	0.001			
QALY loss (per case)				
EV71-Mild	0.006		Bivariate normal distribution	Caregiver survey data about costs and health-related quality of life of lab-confirmed HFMD patients between 2012 and 2013 [14]
EV71-Severe	0.01			
EV71-Fatal	30.4			
CA16-Mild	0.005			
CA16-Severe	0.01			
CA16-Fatal	30.4			
QALY loss (per 10 000 births)				
EV71-Mild	1.12	–	Bivariate normal distribution	Caregiver survey data about costs and health-related quality of life of lab-confirmed HFMD patients between 2012 and 2013 [14]
EV71-Severe	0.12	–		
EV71-Fatal	9.53	–		
CA16-Mild	0.83	–		
CA16-Severe	0.01	–		
CA16-Fatal	0.23	–		
Vaccine efficacy				
VE_1	95%	70–100%	Uniform distribution	Assumed
VE_2	95%	70–100%	Uniform distribution	Assumed
VE_m	95%	–		Vaccine efficacy reported in phase III trials of three monovalent EV71 vaccines [19–21]
ΔVE_1 ($=VE_1 - VE_m$)	0%	−25–5%	Uniform distribution	Assumed
Discount rate per annum	3%	3% or 6%		Assumed
Willingness-to-pay threshold	one GDPpc	–		Assumed

GDPpc, gross domestic product per capita; HFMD, hand, foot and mouth disease; QALY, quality-adjusted life-year.
[a] Values for uncertainty analysis were the estimating risk of EV71-HFMD and CA16-HFMD in all the 51 scenarios in Fig. S2.

across the 51 test-negative scenarios described above. See Table 1 for details.

Results

Base case analysis

In the base case analysis, choosing a bivalent EV71/CA16 vaccine over a monovalent EV71 vaccine would be cost-effective only if the cost of the bivalent vaccine was no more than €4.7 (95% CI €4.2–5.2) higher than that of the monovalent EV71 vaccine. Moreover, bivalent EV71/CA16 vaccination would be cost-effective compared to no vaccination if the total costs of bivalent EV71/CA16 vaccination per birth were no more than €22.0 (21.1–23.0).

The number of mild CA16-HFMD cases was 300 and 30 000 times higher than that of severe and fatal cases (Fig. 2A). Consequently, the risk of mild CA16-HFMD cases was the most important driving factor of the TVC (Fig. 3) even though the costs and QALY loss per episode due to severe and fatal CA16-HFMD were higher than those of mild CA16-HFMD. The costs and QALY loss

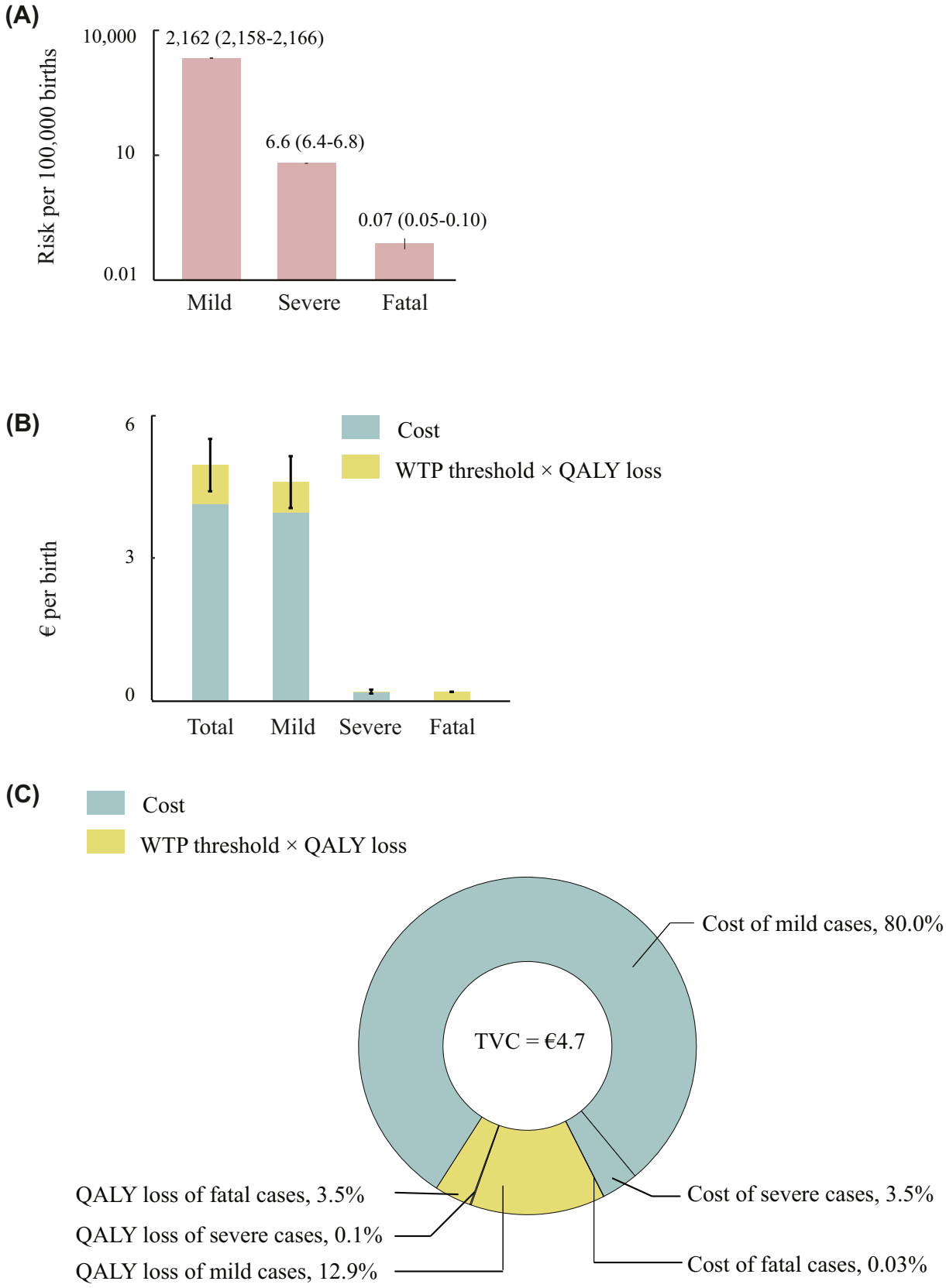

Fig. 2. Estimated risk, costs, and QALY loss attributable to CA16-HFMD in the base case. In the base case, both vaccines are equally efficacious against EV71-HFMD. The error bars show the 95% CIs. (A) The estimated national average risk of CA16-HFMD per 100 000 births. (B) Estimated costs and QALY loss due to CA16-HFMD per birth. Costs were inflated to 2017–18 prices before being converted to Euro. The estimated costs due to mild, severe and fatal CA16-HFMD per birth were €3.97 (3.50–4.43), €0.17 (0.13–0.22) and €0.001 (0.001-0.002), respectively. The estimated QALY loss (times WTP threshold) due to mild, severe and fatal CA16-HFMD per birth were €0.63 (0.49–0.78), €0.006 (0.004–0.007) and €0.17 (0.17–0.17), respectively. (C) Percentage breakdown of estimated costs and QALY loss due to CA16-HFMD per birth. HFMD, hand, foot and mouth disease; QALY, quality-adjusted life-year; WTP threshold, willingness-to-pay threshold, defined as one gross domestic product per capita (€7698 in 2017) in the base case.

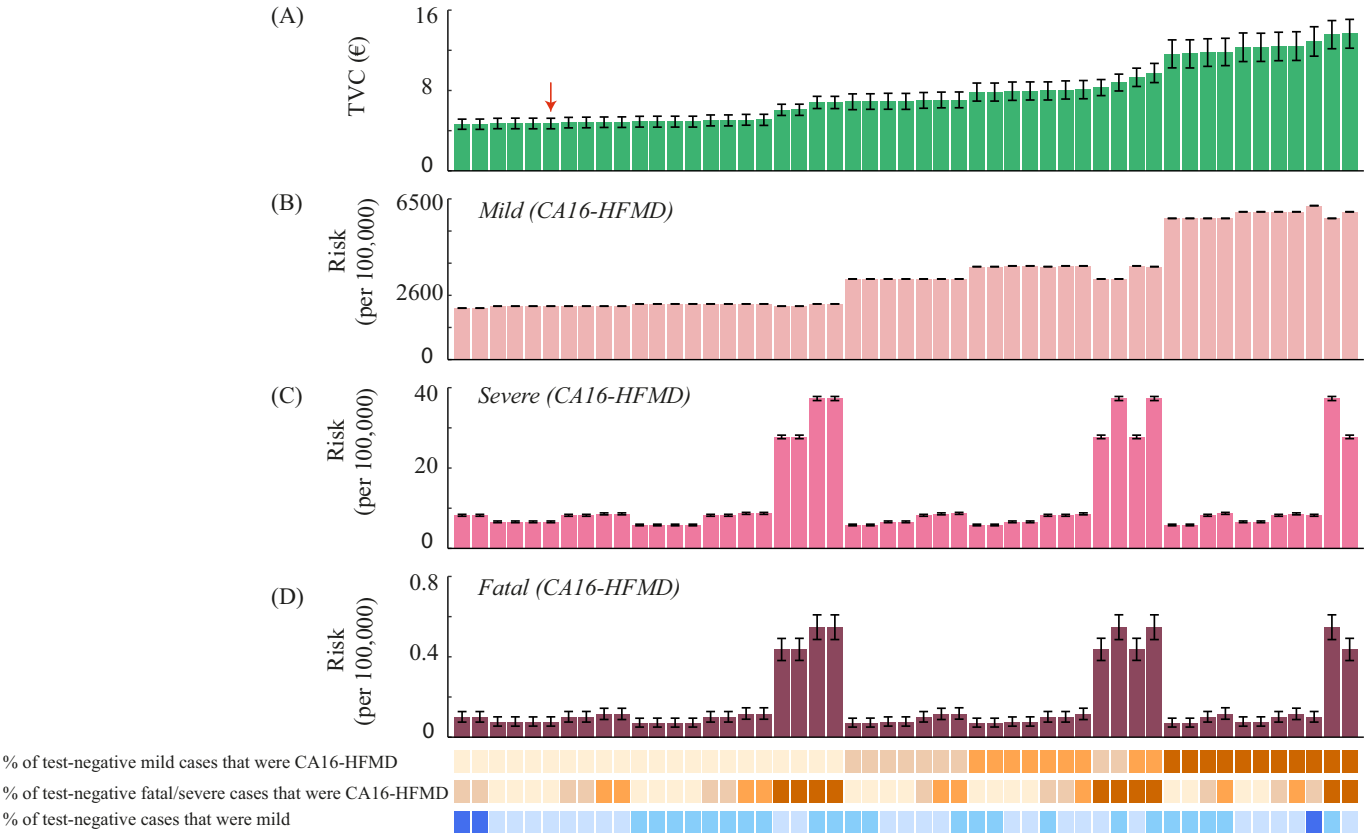

Fig. 3. Comparative cost-effectiveness of routine paediatric bivalent EV71/CA16 versus monovalent EV71 vaccination. TVC was calculated with a societal willingness-to-pay threshold of one GDPpc, an annual discount rate of 3% and $VE_m = VE_1 = VE_2 = 95\%$. (A) TVC (€) of the 51 scenarios regarding HFMD risk from Fig. S2 are listed along the *x*-axis in ascending order. The square grids in blue and orange at the bottom indicate the assumptions regarding the percentage of test-negative cases that were mild during 2010–2012 (bottom row) and the percentage of test-negative severe/fatal and mild cases that were CA16-HFMD (middle and top row) in each scenario, where darker shades correspond to higher percentage. The red arrow indicates the base case (scenario 1). (B–D) The risk of mild, severe, and fatal CA16-HFMD listed along the x-axis in ascending order of TVC. The error bars show the 95% CIs, but in some cases they are not apparent for the risk of mild and severe CA16-HFMD. Fig. 3A and B have a similar trend, indicating that the TVC depends mainly on the risk of mild CA16-HFMD. The percentage of mild test-negatives that were CA16-HFMD (top row of the square grids) also has a similar trend to Fig. 3A. HFMD, hand, foot and mouth disease.

attributable to mild CA16-HFMD were the main constituents of the TVC, accounting for 80% (€3.77/€4.7) and 13% (€0.61/€4.7), respectively (Fig. 2B and C).

Uncertainty analysis

Compared to the base case scenario (scenario 1), the TVC increased by (1) 46–87% (€2.2–4.1/€4.7) if the percentage of mild test-negatives that were EV71/CA16-HFMD was the same as that of mild test-positives (scenarios of the 2nd column in Fig. S2); (2) 66–107% (€3.1–5.0/€4.7) if all the mild test-negatives were EV71/CA16-HFMD (scenarios of the 4th column in Fig. S2); 3) 147–190% (€6.9–8.9/€4.7) if all the mild test-negatives were CA16-HFMD (scenarios of the 5th column in Fig. S2). Compared to TVC with an annual discount rate of 3% and the inclusion of productivity losses in the cost estimate, TVC decreased by (1) 5.3% (€0.65/€12.3) – 11.5% (€0.78/€6.8) if the annual discount rate was 6%; (2) 14.7% (€1.00/€6.8) – 20.5% (€2.39/€11.6) if productivity losses were excluded; (3) 24.4% (€3.14/€12.9) – 25.6% (€1.56/€6.1) if the annual discount rate was 6% and productivity losses were excluded (Table S3).

Generally, TVC increased by (WTP threshold × $Q_1 + C_1$) / 100 and (WTP threshold × $Q_2 + C_2$) / 100 with every 1% increase in ΔVE_1 and VE_2, respectively. Hence, TVC increased monotonically with ΔVE_1 and VE_2, and was more sensitive to ΔVE_1 than VE_2. By fixing other parameters to their base case values, TVC increased by (1) €0.18–€0.30 for every 1% increase in ΔVE_1 among all the 51 scenarios; (2) €0.05–€0.14 for every 1% increase in VE_2 among all the 51 scenarios (Fig. S3).

Additionally, we have built an online app to enable the readers to explore all the possible TVC results corresponding to different assumptions governing HFMD risk, costs, discounting and vaccine efficacies (https://diliu-hku.shinyapps.io/shinyapp_cea_hfmd/).

Discussion

Our study is the first to compare the cost-effectiveness of a bivalent EV71/CA16 vaccine to that of a monovalent EV71 vaccine for reducing the burden of HFMD in China. In the base case analysis, our results suggest that choosing bivalent EV71/CA16 vaccination over monovalent EV71 vaccination could be cost-effective if the cost of bivalent EV71/CA16 vaccination per birth was no more than €4.7 (95% CI €4.2–5.2) above that of monovalent EV71 vaccination.

Our results show that in the base case, bivalent EV71/CA16 vaccine could prevent 70% (2162/3088), 8% (6.6/83.4) and 2% (0.07/3.13) more mild, severe and fatal cases than monovalent EV71 vaccine by preventing CA16-HFMD cases. This is in line with our results indicating that the risk of mild CA16-HFMD is the most important determinant of the comparative cost-effectiveness of bivalent EV71/CA16 vaccine versus monovalent EV71 vaccine.

Therefore, an apparent change in risk of mild CA16-HFMD cases might affect the comparative cost-effectiveness of bivalent EV71/CA16 vaccines versus monovalent EV71 vaccines. However, about 33% (162 305/488 231) of mild HFMD cases in China were caused by other enteroviruses in 2010–2015 [3] and the incidence of mild HFMD cases attributable to other enteroviruses, especially CA6, has been increasing in recent years [25–27]. As such, the TVC under which the bivalent EV71/CA16 vaccine would be cost-effective compared with monovalent EV71 vaccine may vary significantly with the changing aetiology of HFMD in China.

Given that bivalent EV71/CA16 vaccines are still undergoing clinical trials, their vaccine efficacies remain unknown. Nonetheless, our results will be useful to vaccine manufacturers for understanding the market value and potential return on investment of a bivalent vaccine, as well as the way it depends not only on its vaccine efficacy but also those of the monovalent EV71 vaccines. They are also useful to purchasers (e.g. China's National Health Commission) when a vaccine eventually becomes available. Our results demonstrate that TVC is more sensitive to the differential vaccine efficacy against EV71 (ΔVE_1) than the vaccine efficacy against CA16 (VE_2). If the current bivalent vaccine is successful in clinical trials and licensure, the reported efficacy figures can be used to generate more precise estimates.

Our study has several limitations [7]. First, we have likely underestimated the economic and health burden of EV71/CA16-HFMD (and potentially cost-effectiveness of a bivalent vaccine) because not all HFMD cases have been registered in the national surveillance data. Second, we assumed that the long-term incidence of EV71/CA16-HFMD in the future would be similar to that estimated from national surveillance data between 2010 and 2013, whereas the aetiology of HFMD in China may significantly change over time. Third, we did not account for adverse events of vaccination and productivity losses due to premature death, which respectively could decrease and increase the TVC. Fourth, we assumed that the vaccine protection is at least 5 years for both the monovalent and bivalent vaccines. If the bivalent EV71/CA16 vaccine efficacies or monovalent EV71 vaccine efficacy or both wane within the 5-year time period, the TVC would also change. Wei et al. reported similar 2-year vaccine efficacy to 1-year vaccine efficacy of Vigoo monovalent EV71 vaccine against EV71-HFMD [21,28]. While there are no data about the vaccine efficacy of bivalent vaccines, their results provide partial support for our assumption that bivalent vaccine efficacy does not decrease greatly within 5 years. Finally, we assumed that there is no cross-protection among EV71, CA16 and other enteroviruses. Although Takahashi et al. reported that EV71 and CA16 might provide around 7 weeks of cross-protection against each other, the results from Pons-Salort and Grassly implied that such level of cross-protection is sufficiently low such that the epidemic dynamics of the different HFMD serotypes can be regarded as independent of each other [15,16].

Studies have shown that a national introduction of highly effective bivalent EV71/CA16 vaccines would have the potential to greatly reduce the incidence of EV71/CA16-HFMD in the long run. Takahashi et al. [15] simulated the 10-year effect following introduction of a 100% effective bivalent EV71/CA16 vaccine nationwide in China and found that a vaccine coverage of 90% led to almost no EV71/CA16-HFMD cases from 6 years after its introduction. Similarly, Pons-Salort and Grassly simulated the effect of introducing a 100% effective bivalent EV71/CA16 vaccine in Japan, and showed that a similar coverage led to almost no EV71/CA16-HFMD cases from 2 years after its introduction [16].

The Chinese national routine paediatric vaccination programme was last expanded in 2007 when measles, mumps and rubella vaccine, epidemic encephalitis vaccine, meningococcal meningitis vaccine and hepatitis A vaccine were added to the programme (with the oral polio vaccine replaced by inactivated polio vaccine in 2016) [29]. Since then, China has increased its GDPpc substantially from €2646 to €7698 and hence has the financial resources to expand its national vaccination programme to improve population health as well as productivity. Given that HFMD is the most prevalent notifiable infectious disease in China for children under 5 years, HFMD vaccines should be amongst the top candidates for inclusion into the programme.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.06.029.

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