Supplementary

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

Contents

Uncertainty regarding test-negatives

As mentioned in the main text, we linked national HFMD surveillance data and virological surveillance records from all 31 provinces to account for the uncertainty regarding the percentage of test-negatives that were EV71/CA16-HFMD. We considered 51 scenarios (web-only supplementary Figure S2) according to assumptions regarding: 1) the percentage of test-negatives that were mild cases during 2010-2012; 2) the respective percentage of mild test-negatives that were EV71/CA16-HFMD during 2010-2013; 3) the respective percentage of fatal/severe test-negatives that were EV71/CA16-HFMD during 2010-2013.

On assumption 1), we considered three possibilities: a) the percentage of test-negatives that were mild cases was the same as that of test-positives, b) all test-negatives were fatal/severe cases, c) all test-negatives were mild cases. Notably, if the number of fatal/severe cases in any possibility exceeded the number of fatal/severe cases registered in national surveillance system, the excess would be classified as mild cases.

To consider the uncertainty regarding the respective percentage of mild test-negatives that were EV71/CA16-HFMD in assumption 2), we considered five possibilities: a) none of mild test-negatives were EV71/CA16-HFMD, b) the percentage of mild test-negatives that were EV71/CA16-HFMD was the same as that of mild test-positives, c) all mild test-negatives were EV71-HFMD, d) all mild test-negatives were EV71/ CA16-HFMD, in which the respective percentage of EV71/CA16-HFMD was the same as that of mild test-positives (i.e. % of mild test-negatives that were EV71-HFMD = No. mild test-positives that were EV71-HFMD/ (No. mild test-positives that were EV71/CA16-HFMD), e) all mild test-negatives were CA16-HFMD.

We also considered five possibilities on assumption 3) regarding fatal/severe cases, similar with those on assumption 2).

Costs and QALY loss

A caregiver survey was previously conducted to measure the costs and health-related quality of life associated with HFMD in 2012-2013 [1]. As with the methodology of our previous paper [2], severity-specific costs and QALY loss of CA16-HFMD per birth were calculated by multiplying weighted costs and QALY loss of CA16-HFMD per case by risk of CA16-HFMD per birth. We calculated costs and QALY loss per case accounting for discounting, the age distribution of severity-specific CA16-HFMD cases in each province, and the severity-specific risk distribution among all the provinces (i.e. the probability that a given severity-specific HFMD case was from a certain province). Costs and QALY loss due to mild, severe, and fatal EV71-HFMD were also estimated by the same method. All costs were reported in Chinese Yuan during 2012-2013 but were inflated to 2017-2018 prices using China's annual consumer price index (health care) [3] before being converted to 2017 Euro (€, 1 € = 7.75 Chinese Yuan).

As adverse events due to monovalent EV71 vaccination reported in the phase III trials were usually mild and uncommon [4-6], we did not consider such events in our CEA of bivalent EV71/CA16 and monovalent EV71 vaccination. We also excluded the productivity loss due to premature death as done in our previous study.

Threshold vaccine cost (TVC)

Let VC_m and VC_{bi} denote the vaccine cost of monovalent EV71 vaccine and bivalent EV71/CA16 vaccine, respectively. Let C_1 and C_2 denote the cost due to EV71/CA16-HFMD per birth, Q_1 and Q_2 denote the QALY loss due to EV71/CA16-HFMD per birth, VE_1 and VE_2 denote the bivalent vaccine efficacy against EV71/CA16-HFMD, respectively. Let VE_m denote the monovalent vaccine efficacy against EV71-HFMD, and $\Delta VE_1 = VE_1 - VE_m$ denote the differential vaccine efficacy against EV71-HFMD between the two vaccines. The incremental cost-effectiveness ratio (ICER) of bivalent EV71/CA16 vaccination versus monovalent EV71 vaccination was calculated as:

$$\text{ICER} = \frac{\text{Cost with bivalent vaccination - Cost with monovalent EV71 vaccination}}{\text{Health utility with bivalent vaccination - Health utility with monovalent EV71 vaccination}}$$

$$= \frac{(VC_{bi} - VE_1 \times C_1 - VE_2 \times C_2) - (VC_m - VE_m \times C_1)}{(VE_1 \times Q_1 + VE_2 \times Q_2) - (VE_m \times Q_1)}$$

$$= \frac{(VC_{bi} - VC_m) - [(VE_1 - VE_m) \times C_1 + VE_2 \times C_2]}{(VE_1 - VE_m) \times Q_1 + VE_2 \times Q_2}$$

Hence, with a willingness-to-pay (WTP) threshold, TVC of bivalent EV71/CA16 vaccine was as below:

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

Table S1. The probability of each outcome corresponding to bivalent EV71/CA16 vaccination

EV71-HFMD	CA16-HFMD	Probability	
		Bivalent EV71/CA16 vaccination	**No vaccination**
No EV71-HFMD	No CA16-HFMD	$[1 - (1 - VE_1)\ P_1] * [1 - (1 - VE_2)\ P_2]$	$(1 - P_1) * (1 - P_2)$
	Mild CA16-HFMD	$[1 - (1 - VE_1)\ P_1] * [(1 - VE_2)\ P_{m2}]$	$(1 - P_1) * P_{m2}$
	Severe CA16-HFMD	$[1 - (1 - VE_1)\ P_1] * [(1 - VE_2)\ P_{s2}]$	$(1 - P_1) * P_{s2}$
	Fatal CA16-HFMD	$[1 - (1 - VE_1)\ P_1] * [(1 - VE_2)\ P_{f2}]$	$(1 - P_1) * P_{f2}$
Mild EV71-HFMD	No CA16-HFMD	$[(1 - VE_1)\ P_{m1}] * [1 - (1 - VE_2)\ P_2]$	$P_{m1} * (1 - P_2)$
	Mild CA16-HFMD	$[(1 - VE_1)\ P_{m1}] * [(1 - VE_2)\ P_{m2}]$	$P_{m1} * P_{m2}$
	Severe CA16-HFMD	$[(1 - VE_1)\ P_{m1}] * [(1 - VE_2)\ P_{s2}]$	$P_{m1} * P_{s2}$
	Fatal CA16-HFMD	$[(1 - VE_1)\ P_{m1}] * [(1 - VE_2)\ P_{f2}]$	$P_{m1} * P_{f2}$
Severe EV71-HFMD	No CA16-HFMD	$[(1 - VE_1)\ P_{s1}] * [1 - (1 - VE_2)\ P_2]$	$P_{s1} * (1 - P_2)$
	Mild CA16-HFMD	$[(1 - VE_1)\ P_{s1}] * [(1 - VE_2)\ P_{m2}]$	$P_{s1} * P_{m2}$
	Severe CA16-HFMD	$[(1 - VE_1)\ P_{s1}] * [(1 - VE_2)\ P_{s2}]$	$P_{s1} * P_{s2}$
	Fatal CA16-HFMD	$[(1 - VE_1)\ P_{s1}] * [(1 - VE_2)\ P_{f2}]$	$P_{s1} * P_{f2}$
Fatal EV71-HFMD	No CA16-HFMD	$[(1 - VE_1)\ P_{f1}] * [1 - (1 - VE_2)\ P_2]$	$P_{f1} * (1 - P_2)$
	Mild CA16-HFMD	$[(1 - VE_1)\ P_{f1}] * [(1 - VE_2)\ P_{m2}]$	$P_{f1} * P_{m2}$
	Severe CA16-HFMD	$[(1 - VE_1)\ P_{f1}] * [(1 - VE_2)\ P_{s2}]$	$P_{f1} * P_{s2}$
	Fatal CA16-HFMD	$[(1 - VE_1)\ P_{f1}] * [(1 - VE_2)\ P_{f2}]$	$P_{f1} * P_{f2}$

P_{m1}, P_{s1} and P_{f1} denote the national average risk of mild, severe and fatal EV71-HFMD per child, respectively.

P_{m2}, P_{s2} and P_{f2} denote the national average risk of mild, severe and fatal CA16-HFMD per child, respectively.

P_1 and P_2 denote the national average risk of EV71-HFMD and CA16-HFMD per child, respectively.

Table S2. The probability of each outcome corresponding to monovalent EV71 vaccination

EV71-HFMD	CA16-HFMD	Probability	
		Monovalent EV71 vaccination	No vaccination
No EV71-HFMD	No CA16-HFMD	$[1 - (1 – VE_m) P_1] * (1 - P_2)$	$(1 - P_1) * (1 - P_2)$
	Mild CA16-HFMD	$[1 - (1 – VE_m) P_1] * P_{m2}$	$(1 - P_1) * P_{m2}$
	Severe CA16-HFMD	$[1 - (1 – VE_m) P_1] * P_{s2}$	$(1 - P_1) * P_{s2}$
	Fatal CA16-HFMD	$[1 - (1 – VE_m) P_1] * P_{f2}$	$(1 - P_1) * P_{f2}$
Mild EV71-HFMD	No CA16-HFMD	$[(1 – VE_m) P_{m1}] * (1 - P_2)$	$P_{m1} * (1 - P_2)$
	Mild CA16-HFMD	$[(1 – VE_m) P_{m1}] * P_{m2}$	$P_{m1} * P_{m2}$
	Severe CA16-HFMD	$[(1 – VE_m) P_{m1}] * P_{s2}$	$P_{m1} * P_{s2}$
	Fatal CA16-HFMD	$[(1 – VE_m) P_{m1}] * P_{f2}$	$P_{m1} * P_{f2}$
Severe EV71-HFMD	No CA16-HFMD	$[(1 – VE_m) P_{s1}] * (1 - P_2)$	$P_{s1} * (1 - P_2)$
	Mild CA16-HFMD	$[(1 – VE_m) P_{s1}] * P_{m2}$	$P_{s1} * P_{m2}$
	Severe CA16-HFMD	$[(1 – VE_m) P_{s1}] * P_{s2}$	$P_{s1} * P_{s2}$
	Fatal CA16-HFMD	$[(1 – VE_m) P_{s1}] * P_{f2}$	$P_{s1} * P_{f2}$
Fatal EV71-HFMD	No CA16-HFMD	$[(1 – VE_m) P_{f1}] * (1 - P_2)$	$P_{f1} * (1 - P_2)$
	Mild CA16-HFMD	$[(1 – VE_m) P_{f1}] * P_{m2}$	$P_{f1} * P_{m2}$
	Severe CA16-HFMD	$[(1 – VE_m) P_{f1}] * P_{s2}$	$P_{f1} * P_{s2}$
	Fatal CA16-HFMD	$[(1 – VE_m) P_{f1}] * P_{f2}$	$P_{f1} * P_{f2}$

P_{m1}, P_{s1} and P_{f1} denote the national average risk of mild, severe and fatal EV71-HFMD per child, respectively.
P_{m2}, P_{s2} and P_{f2} denote the national average risk of mild, severe and fatal CA16-HFMD per child, respectively.
P_1 and P_2 denote the national average risk of EV71-HFMD and CA16-HFMD per child, respectively.

Table S3**. Threshold vaccine cost (€) with different cost estimates and annual discount rates**

Scenario	**3% annual discount rate**		**6% annual discount rate**	
	Including productivity loss	**Excluding productivity loss**	**Including productivity loss**	**Excluding productivity loss**
1	4.7(4.2-5.2)	3.8(3.4-4.2)	4.4(3.9-4.9)	3.6(3.2-3.9)
2	6.9(6.1-7.7)	5.6(5.0-6.1)	6.5(5.8-7.2)	5.2(4.7-5.8)
3	4.7(4.2-5.2)	3.8(3.4-4.2)	4.4(3.9-4.9)	3.6(3.2-3.9)
4	7.9(7.0-8.8)	6.4(5.7-7.0)	7.5(6.6-8.4)	6.0(5.4-6.6)
5	12.3(10.9-13.7)	9.8(8.8-10.8)	11.6(10.3-13.0)	9.3(8.3-10.2)
6	4.8(4.3-5.3)	3.9(3.5-4.3)	4.5(4.0-5.0)	3.6(3.3-4.0)
7	7.0(6.2-7.8)	5.6(5.1-6.2)	6.6(5.9-7.3)	5.3(4.8-5.8)
8	4.8(4.3-5.3)	3.9(3.5-4.3)	4.5(4.0-5.0)	3.6(3.3-4.0)
9	8.0(7.1-9.0)	6.5(5.8-7.1)	7.6(6.7-8.4)	6.1(5.5-6.7)
10	12.4(11.0-13.8)	9.9(8.9-10.9)	11.7(10.3-13.1)	9.3(8.4-10.3)
11	4.7(4.2-5.2)	3.8(3.4-4.2)	4.4(3.9-4.9)	3.5(3.2-3.9)
12	6.9(6.1-7.7)	5.6(5.0-6.1)	6.5(5.8-7.3)	5.2(4.7-5.7)
13	4.7(4.2-5.2)	3.8(3.4-4.2)	4.4(3.9-4.9)	3.5(3.2-3.9)
14	8.0(7.1-8.9)	6.4(5.7-7.0)	7.5(6.6-8.3)	6.0(5.4-6.6)
15	12.3(10.9-13.7)	9.8(8.8-10.8)	11.6(10.3-13.0)	9.3(8.3-10.2)
16	4.8(4.3-5.4)	3.9(3.6-4.3)	4.5(4.0-5.0)	3.6(3.3-4.0)
17	7.1(6.3-7.8)	5.7(5.1-6.2)	6.6(5.9-7.4)	5.3(4.8-5.8)
18	4.8(4.3-5.4)	3.9(3.5-4.3)	4.5(4.0-5.0)	3.6(3.3-4.0)
19	8.1(7.2-9.0)	6.5(5.8-7.1)	7.6(6.7-8.4)	6.1(5.5-6.7)
20	12.4(11.0-13.8)	10.0(9.0-10.9)	11.7(10.4-13.1)	9.4(8.4-10.3)
21	6.1(5.5-6.6)	5.1(4.7-5.5)	5.4(4.9-5.9)	4.5(4.1-4.9)
22	8.3(7.5-9.1)	6.9(6.3-7.5)	7.5(6.8-8.3)	6.2(5.6-6.7)
23	6.1(5.5-6.6)	5.1(4.7-5.5)	5.4(4.9-5.9)	4.5(4.1-4.9)
24	9.3(8.4-10.2)	7.7(7.0-8.4)	8.5(7.6-9.4)	7.0(6.3-7.6)
25	13.6(12.2-15.1)	11.2(10.1-12.2)	12.6(11.3-13.9)	10.3(9.3-11.2)
26	4.9(4.4-5.4)	3.9(3.6-4.3)	4.6(4.1-5.1)	3.7(3.3-4.1)
27	6.9(6.1-7.7)	5.5(5.0-6.1)	6.5(5.8-7.2)	5.2(4.7-5.7)
28	4.9(4.4-5.4)	3.9(3.6-4.3)	4.6(4.1-5.1)	3.7(3.3-4.1)
29	7.8(6.9-8.7)	6.3(5.6-6.9)	7.4(6.6-8.2)	5.9(5.3-6.5)
30	11.6(10.2-13.0)	9.3(8.3-10.2)	11.0(9.7-12.3)	8.8(7.9-9.7)

31	5.0(4.5-5.6)	4.1(3.7-4.4)	4.7(4.2-5.2)	3.8(3.4-4.1)
32	5.0(4.5-5.6)	4.1(3.7-4.5)	4.7(4.2-5.2)	3.8(3.4-4.2)
33	8.0(7.1-8.9)	6.4(5.7-7.0)	7.5(6.7-8.3)	6.0(5.4-6.6)
34	11.8(10.4-13.1)	9.4(8.4-10.3)	11.1(9.8-12.5)	8.9(8.0-9.8)
35	4.9(4.3-5.4)	3.9(3.6-4.3)	4.6(4.1-5.1)	3.7(3.3-4.1)
36	6.9(6.1-7.7)	5.5(5.0-6.1)	6.5(5.8-7.2)	5.2(4.7-5.7)
37	4.9(4.4-5.4)	3.9(3.6-4.3)	4.6(4.1-5.1)	3.7(3.3-4.1)
38	7.8(6.9-8.7)	6.3(5.6-6.9)	7.4(6.6-8.2)	5.9(5.3-6.5)
39	11.6(10.2-13.0)	9.3(8.3-10.2)	11.0(9.7-12.3)	8.8(7.9-9.7)
40	5.1(4.5-5.6)	4.1(3.7-4.5)	4.7(4.2-5.2)	3.8(3.4-4.2)
41	7.1(6.3-7.9)	5.7(5.1-6.3)	6.6(5.9-7.4)	5.3(4.8-5.8)
42	5.1(4.5-5.6)	4.1(3.7-4.5)	4.7(4.2-5.2)	3.8(3.5-4.2)
43	11.8(10.5-13.2)	9.4(8.5-10.4)	11.1(9.8-12.4)	8.9(8.0-9.8)
44	6.8(6.2-7.4)	5.8(5.3-6.3)	6.0(5.4-6.6)	5.1(4.7-5.5)
45	8.8(7.9-9.6)	7.4(6.8-8.0)	7.9(7.1-8.7)	6.6(6.0-7.2)
46	6.8(6.2-7.4)	5.8(5.3-6.3)	6.0(5.4-6.6)	5.1(4.6-5.5)
47	9.7(8.8-10.7)	8.1(7.5-8.8)	8.8(7.9-9.7)	7.3(6.6-7.9)
48	13.6(12.2-15.0)	11.1(10.1-12.1)	12.4(11.1-13.8)	10.1(9.2-11.1)
49	4.6(4.1-5.2)	3.8(3.4-4.1)	4.3(3.9-4.8)	3.5(3.2-3.8)
50	4.6(4.1-5.1)	3.8(3.4-4.1)	4.3(3.9-4.8)	3.5(3.2-3.8)
51	12.9(11.4-14.3)	10.3(9.3-11.3)	12.2(10.8-13.6)	9.7(8.8-10.7)

The threshold vaccine cost listed here were all calculated with a willingness-to-pay threshold of one GDP per capita and with VE_m, VE_1 and VE_2 all being 95%.

Figure S1. Comparison of the cumulative incidence predicted in the dynamic model with and without cross-protection. The dynamic model presented here is a two-strain SIR model adapted from the TSIR model used in Takahashi et al [7]. The duration of cross-protection varied between 0 days (i.e. dynamic model without cross-protection) and 90 days. We estimated the cumulative incidence with an infectious period of 7 days and 14 days for both EV71-HFMD and CA16-HFMD, respectively. The cumulative incidence predicted by the model with cross-protection was very similar with those predicted by the model without cross-protection. With an infectious period of 7 days, the cumulative incidence of EV71-HFMD predicted by the dynamic model ranged from 96,436.7 to 99,303.9 per 100,000 with the duration of cross-protection ranging from 90 days to 0 days. And the cumulative incidence of EV71-HFMD ranged from 96,728.9 to 99,303.7 per 100,000 with the duration of cross-protection ranging from 90 days to 0 days and an infectious period of 14 days. For CA16-HFMD, this ranged from 96,500.0 to 99,326.4 per 100,000 with an infectious period of 7 days, and from 96,787.9 to 99,326.3 per 100,000 with an infectious period of 14 days.

Figure S2. Estimating the percentage of mild and fatal/severe cases that were EV71/CA16-HFMD. Fifty-five scenarios were generated by three assumptions regarding: 1) the percentage of test-negatives that were mild cases (the rhombus branching point); 2) the percentage of mild test-negatives that were EV71/CA16-HFMD (the branching point in light green shades); 3) the percentage of fatal/severe test-negatives that were EV71/CA16-HFMD (the branching point in light blue shades). When all test-negatives were estimated as EV71/CA16-HFMD, there were three possibilities: a) all mild test-negatives were EV71-HFMD (the third column); b) all mild test-negatives were EV71/CA16-HFMD, and the percentage of mild test-negatives that were EV71/CA16-HFMD was the same as that of mild test-positives (i.e. % of mild test-negatives that were EV71-HFMD = No. mild test-positives that were EV71-HFMD/ No. mild test-positives that were EV71/CA16-HFMD; the fourth column); 3) all mild test-negatives were CA16-HFMD (the fifth column). The same is true of the percentage that all fatal/severe test-negatives were EV71/CA16-HFMD. The scenario colored in purple (scenario 1) was the base case in our analysis. The risk of EV71/CA16-HFMD in the three scenarios colored in blue were identical to each other, and so were the three scenarios colored in grass green. Thus, there were only 51 unique scenarios generated in our study.

Figure S3. Comparative cost-effectiveness of bivalent EV71/CA16 versus monovalent EV71 vaccination with different vaccine efficacies. A, B, C and D correspond to situations where VE_1 are 70%, 80%, 95% and 100%, respectively. TVC is calculated with a willingness-to-pay threshold of GDP per capita (€7,698 in 2017) and an annual discount rate of 3%. The 51 test-negative scenarios are listed along y-axis from bottom to top in the same ascending order of TVC as that in Figure 3.

Figure S4. Estimated risk, costs, and QALY loss attributable to EV71-HFMD and CA16-HFMD in the base case. The error bars show the 95% CIs, but they are not apparent in some cases. (A) The estimated national average risk of EV71-HFMD and CA16-HFMD per 100,000 births. The risk of mild EV71/CA16-HFMD were 3,088 (95% CI: 3,084-3,093) and 2,162 (2,158-2,166) per 100,000 births; the risk of severe EV71/CA16-HFMD were 83.4 (82.7-84.2) and 6.6 (6.4-6.8) per 100,000 births; and the risk of fatal EV71/CA16-HFMD were 3.13 (2.99-3.28) and 0.07 (0.05-0.10) per 100,000 births. (B) Estimated costs and WTP threshold times QALY loss due to EV71/CA16-HFMD per birth. The estimated costs of mild EV71-HFMD and CA16-HFMD per birth were €7.37 (6.58-8.17) and €3.97 (3.50-4.44); the estimated costs of severe EV71-HFMD and CA16-HFMD were €2.52 (2.33-2.71) and €0.17 (0.13-0.22); and the estimated costs of fatal EV71-HFMD and CA16-HFMD were €0.07 (0.04-0.10) and €0.001 (0.001-0.002). The estimated WTP threshold times QALY loss were €0.86 (0.77-0.96) and €0.64 (0.49-0.78) for mild EV71-HFMD and CA16-HFMD; €0.09 (0.09-0.10) and €0.006 (0.004-0.008) for severe EV71-HFMD and CA16-HFMD; €7.33 (7.33-7.33) and €0.17 (0.17-0.17) for fatal EV71-HFMD and CA16-HFMD.

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