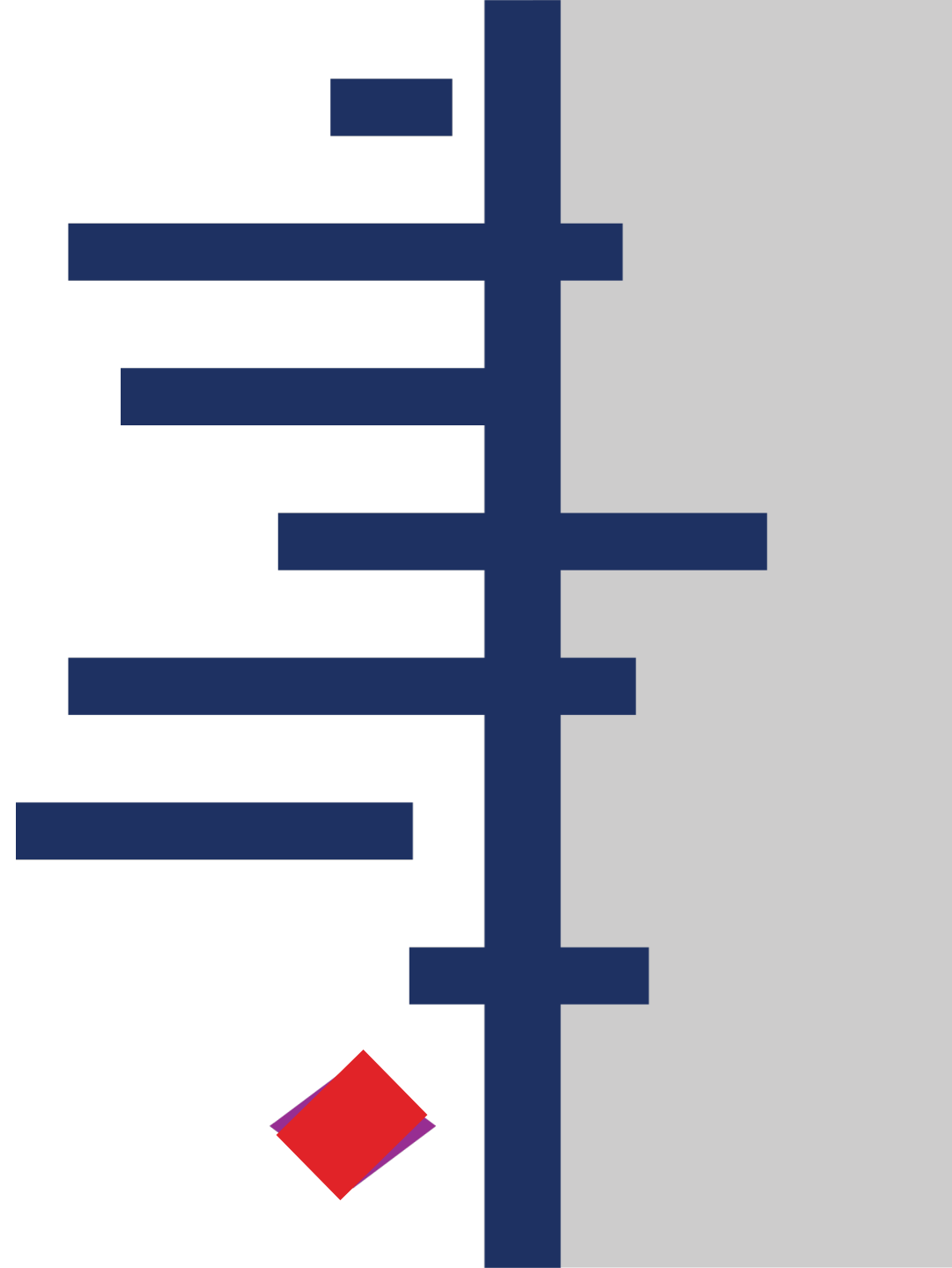


# Current evidence on HPV vaccine schedules

*Systematic review on the immunogenicity and efficacy of a single dose of HPV vaccine, different intervals between the first and second doses of HPV vaccine, and two doses in 15-18-year-olds*

Trusted evidence.  
Informed decisions.  
Better health.



## Systematic review of evidence

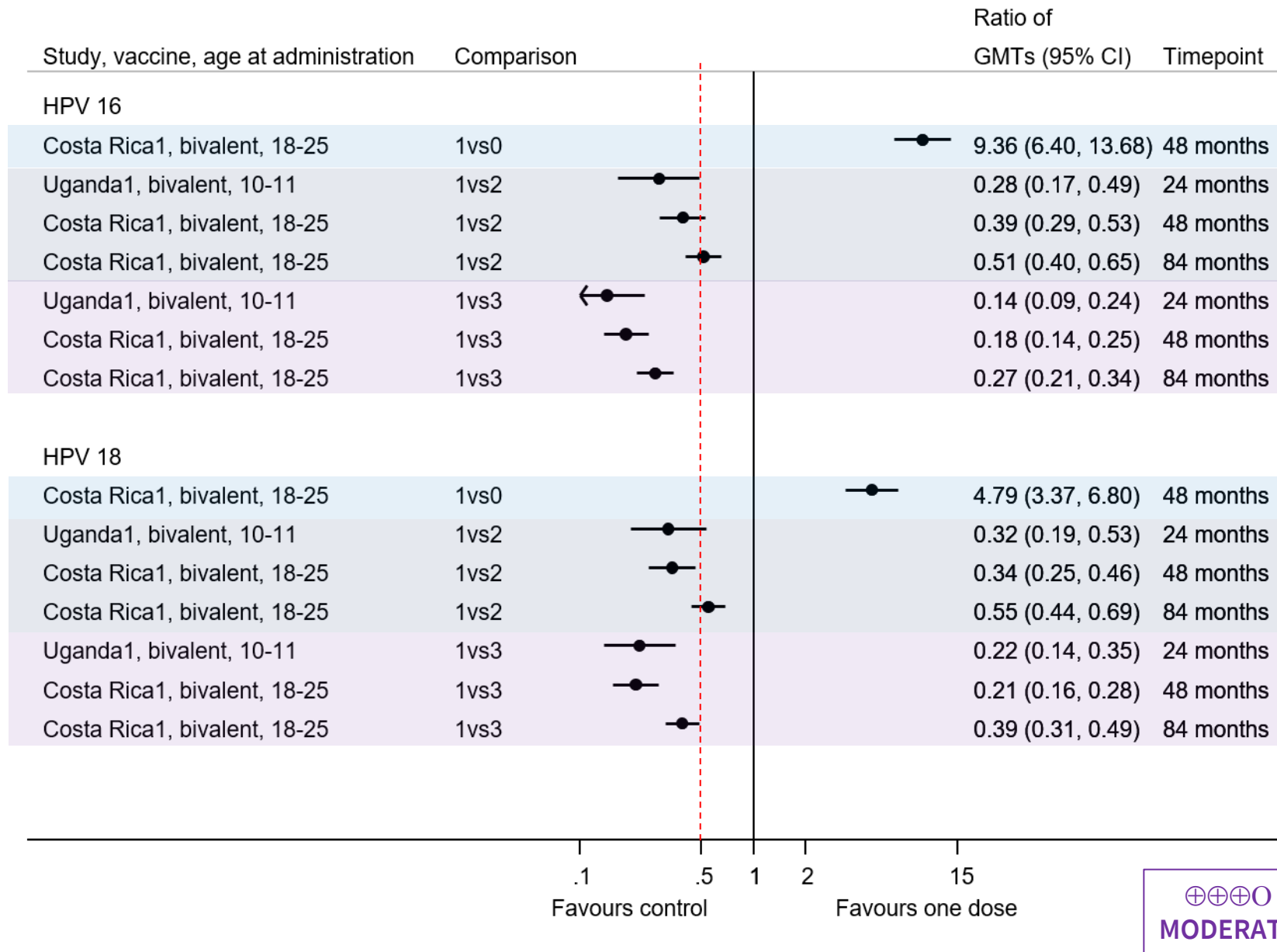
- Efficacy and effectiveness of one dose of HPV vaccine
  - One dose vs no vaccine
  - One dose vs two doses
  - One dose vs three doses
- Different intervals between the first and second doses of HPV vaccines
- Two doses of HPV vaccine in 15-18-year-olds
  - Two doses vs no vaccine
  - Two doses vs three doses



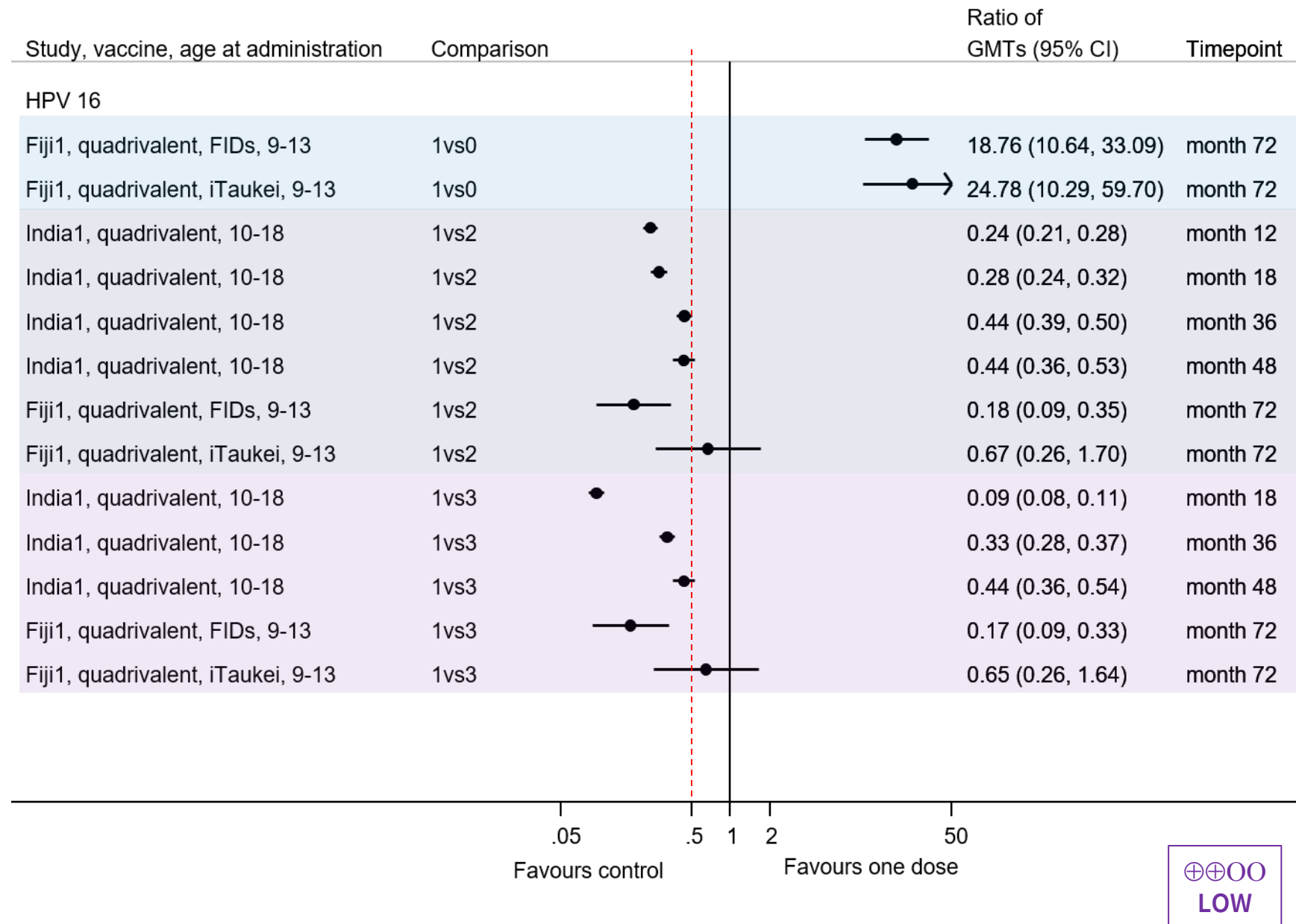
## Included studies on one dose HPV vaccine

- No published RCTs were identified evaluating one dose
- 35 non-randomised studies, including:
  - 22 retrospective, 4 prospective, 3 cross-sectional
  - 3 post-hoc analyses of RCTs
  - 3 case-control studies
- 10 studies on bivalent, 23 quadrivalent, 1 study mixed quadrivalent/nonavalent HPV vaccine
- Outcomes reported: GMTs, seroconversion, CIN1/2/3+, genital warts, HPV infection

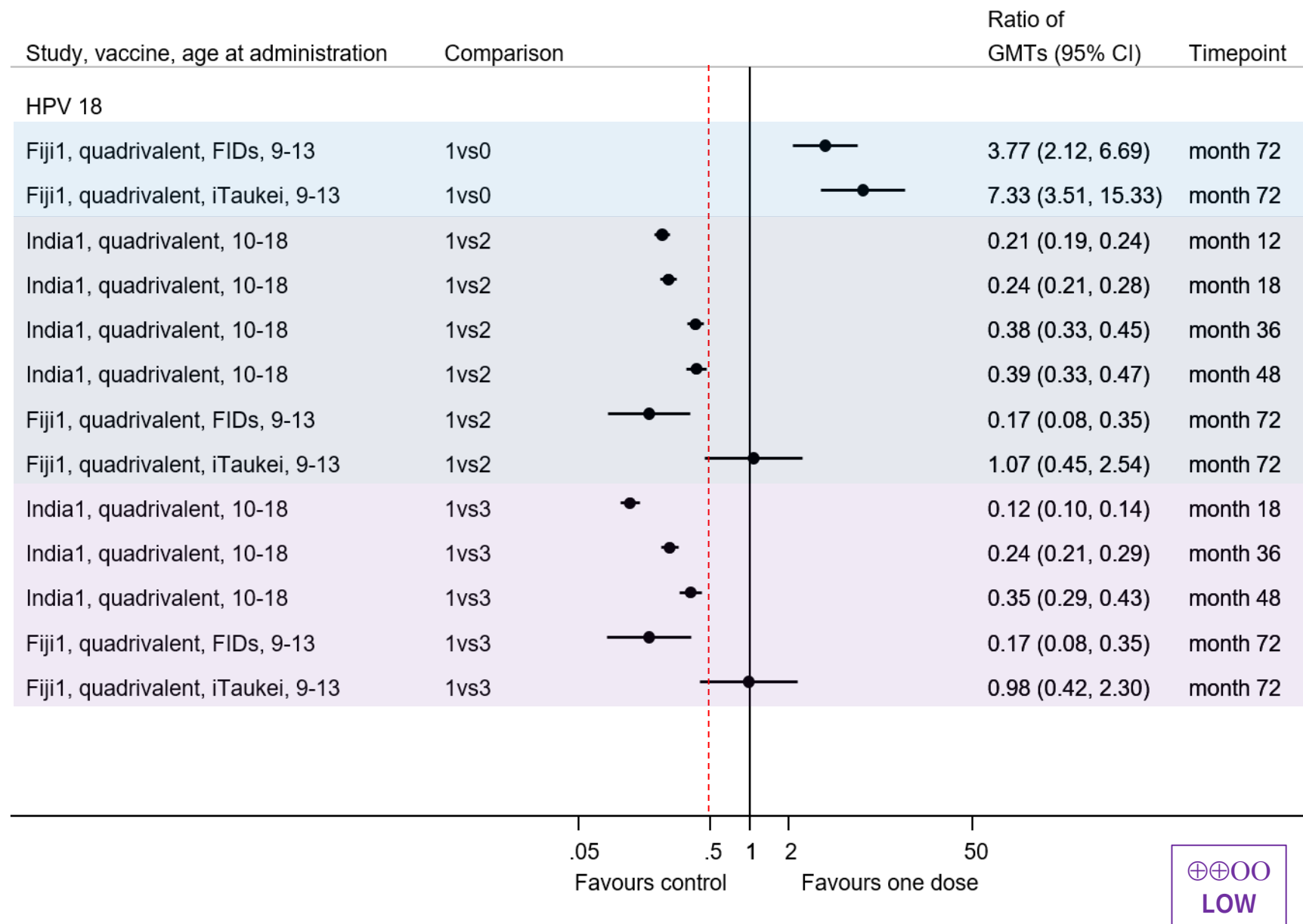
# GMTs for HPV 16 and 18 over 84 months following one dose bivalent HPV vaccine versus no vaccine, two doses, or three doses.



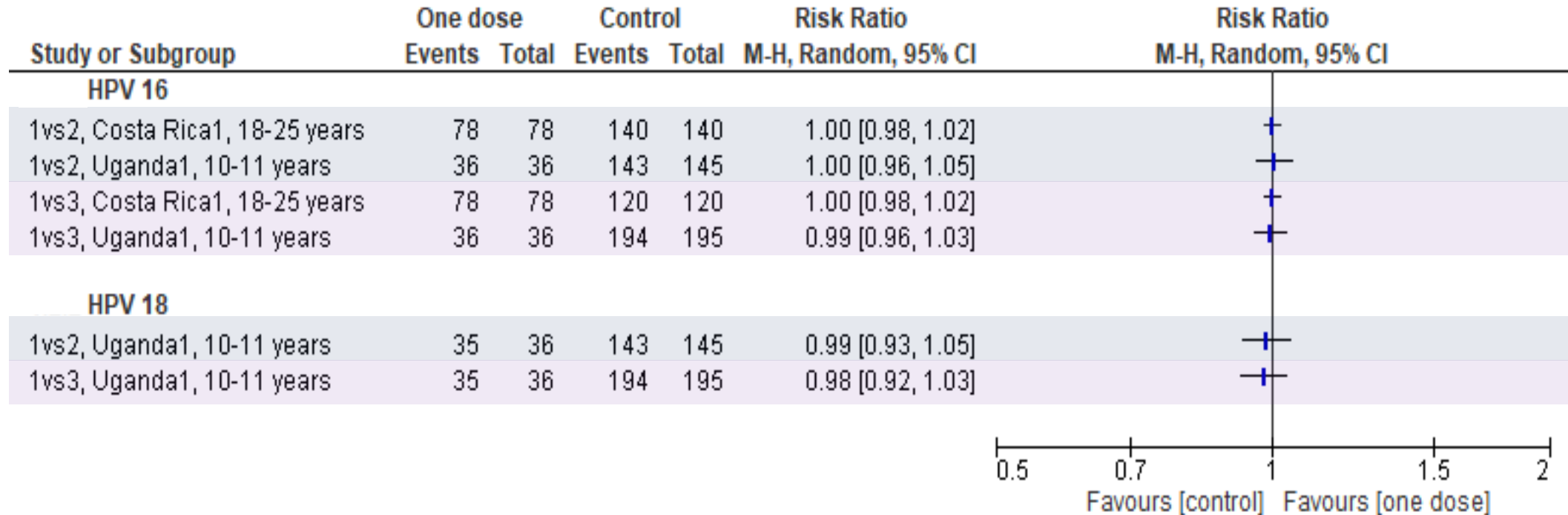
# GMTs for HPV 16 over 72 months following one dose quadrivalent HPV vaccine versus no vaccine, two doses, or three doses. FID= Fijians of Indian Descent; iTaukei= indigenous Fijians



# GMTs for HPV 18 over 72 months following one dose quadrivalent HPV vaccine versus no vaccine, two doses, or three doses. FID= Fijians of Indian Descent; iTaukei= indigenous Fijians

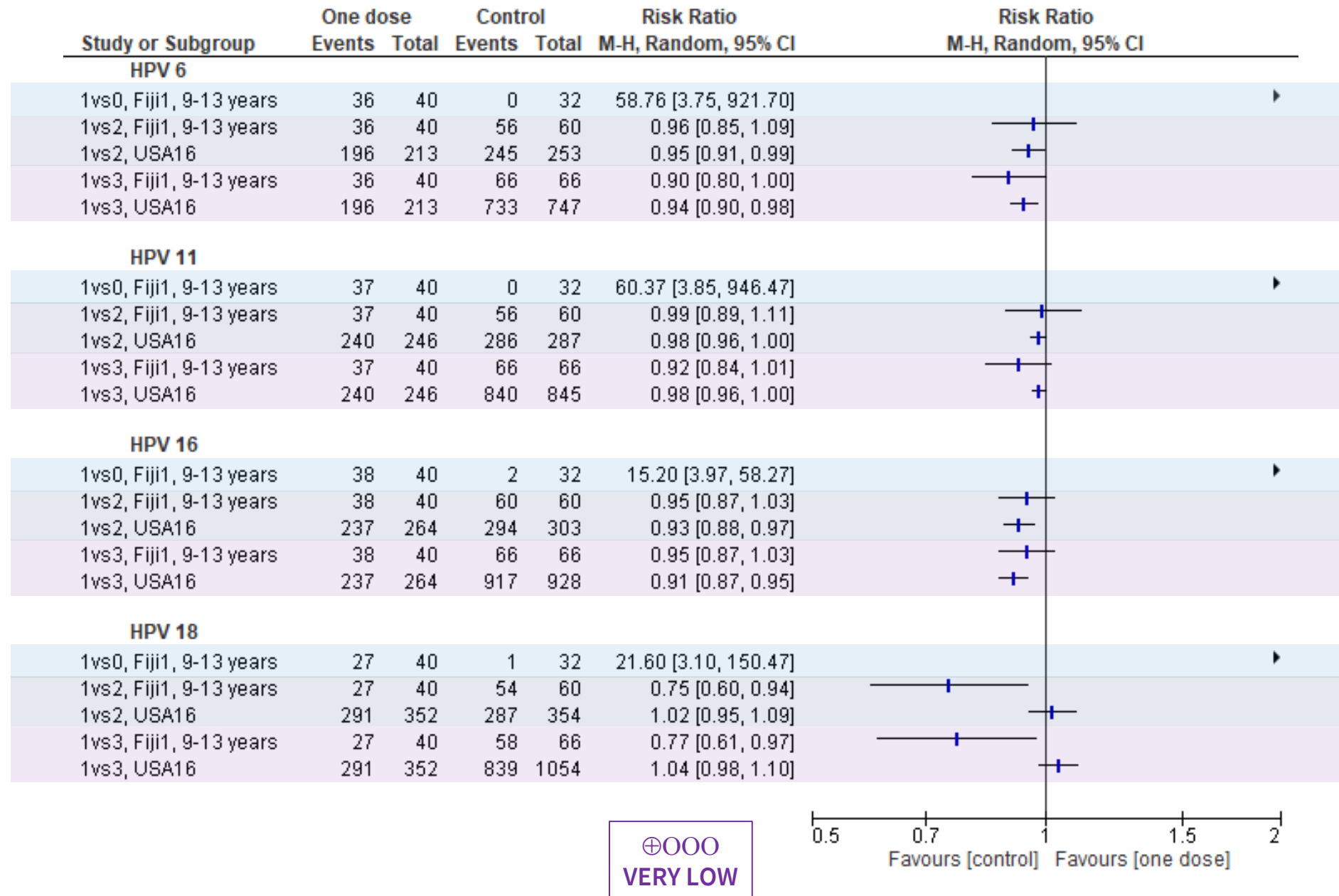


**Seropositivity to HPV 16 and 18 over 48 months following one dose bivalent HPV vaccine versus two doses, or three doses.**



⊕⊕⊕⊕  
LOW

# Seropositivity to HPV 6, 11, 16 and 18 over 4-6 years following one dose quadrivalent HPV vaccine versus no vaccine, two doses, or three doses.



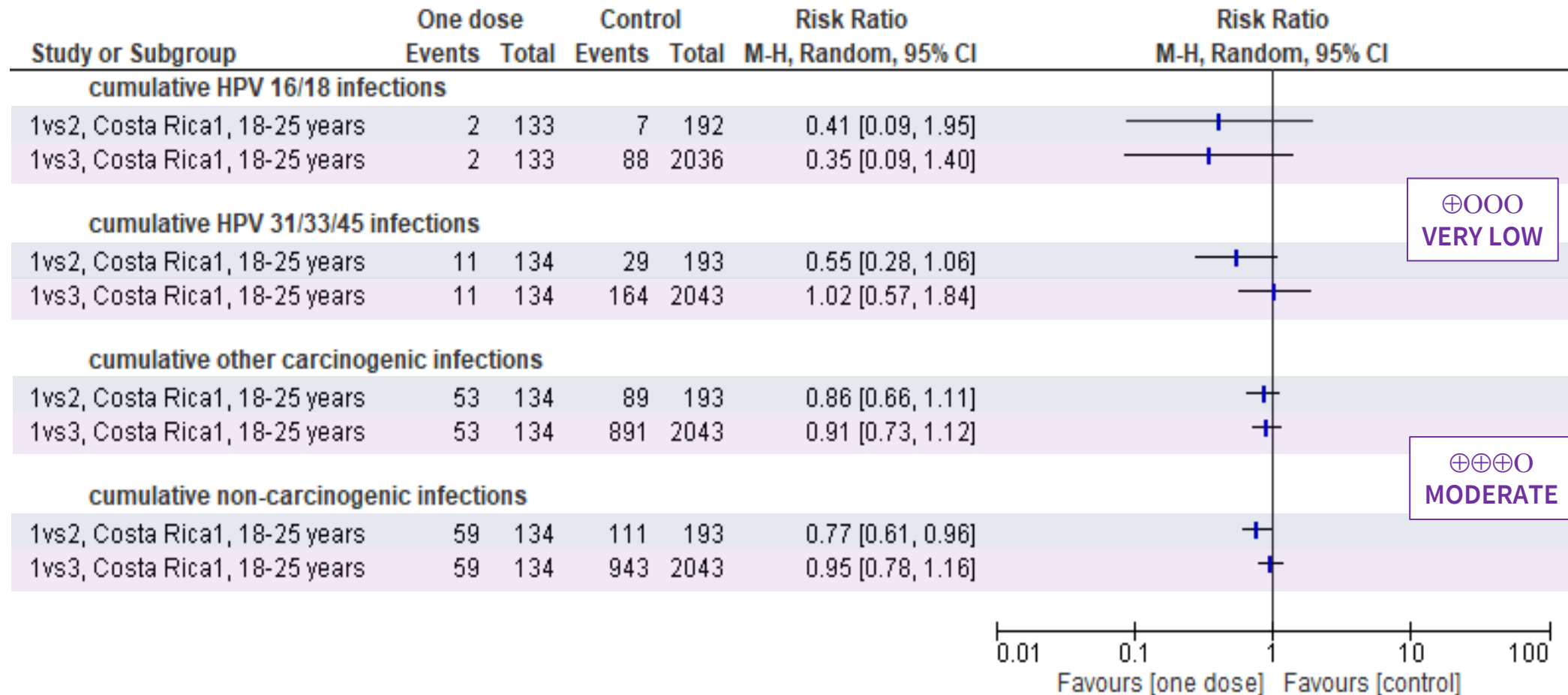


## CIN2+ following one dose quadrivalent HPV vaccine versus two doses

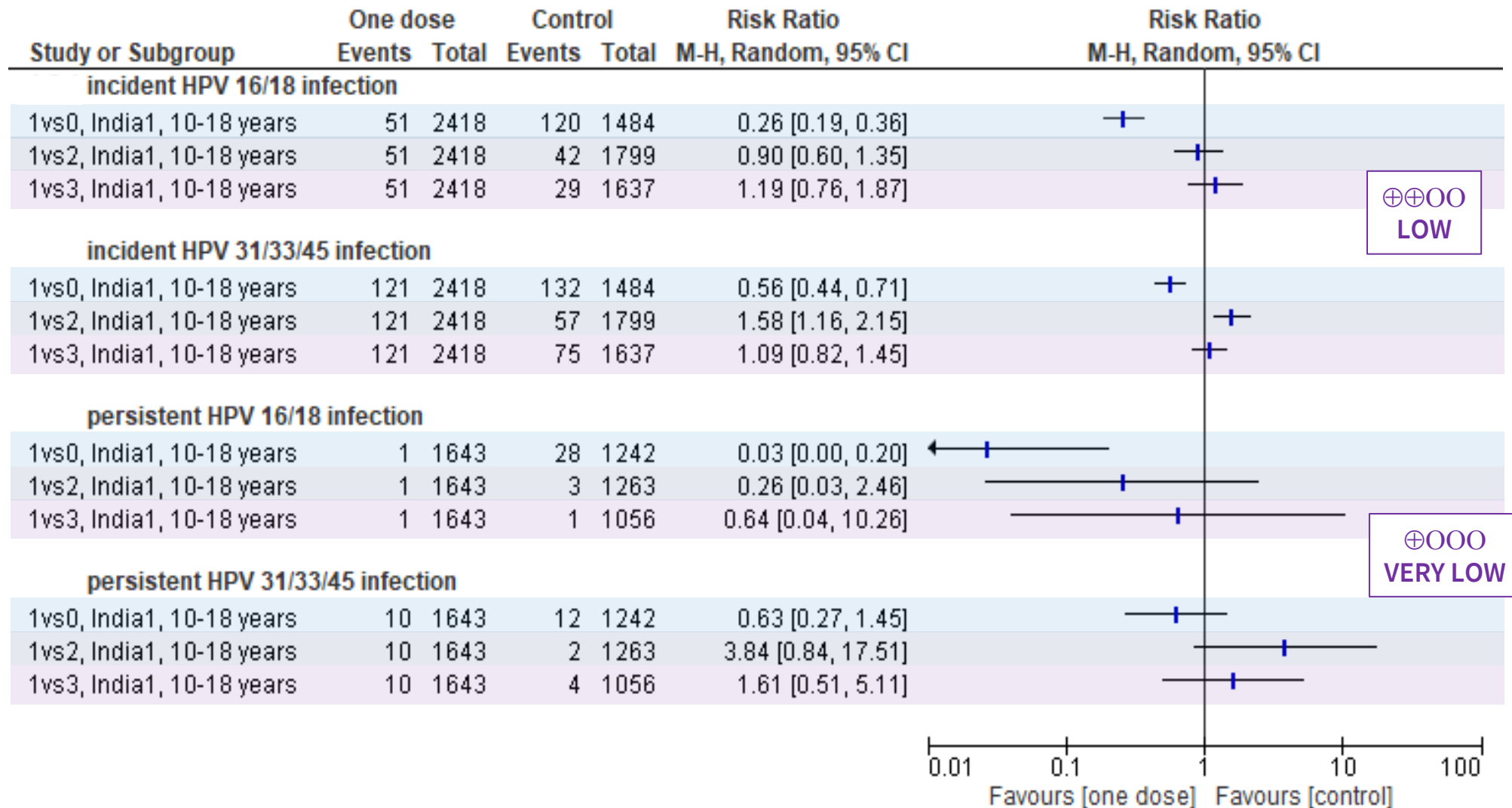
- Denmark<sup>3</sup> (<16 years) – adjusted for maternal education and attained age:
  - CIN2+ (**IRR 1.00, 95% CI 0.61 to 1.64**)
  - CIN3+ (IRR 0.89, 95% CI 0.53 to 1.52)
- Australia<sup>4</sup> (<15 years) – adjusted for age, area of residence, and socioeconomic status:
  - CIN2+ (**HR 0.94, 95% CI 0.73 to 1.21**)
  - CIN3+ (HR 0.64, 95% CI 0.35 to 1.16)



## Cumulative HPV infections over 7 years following one dose bivalent HPV vaccine versus two or three doses; unadjusted estimates



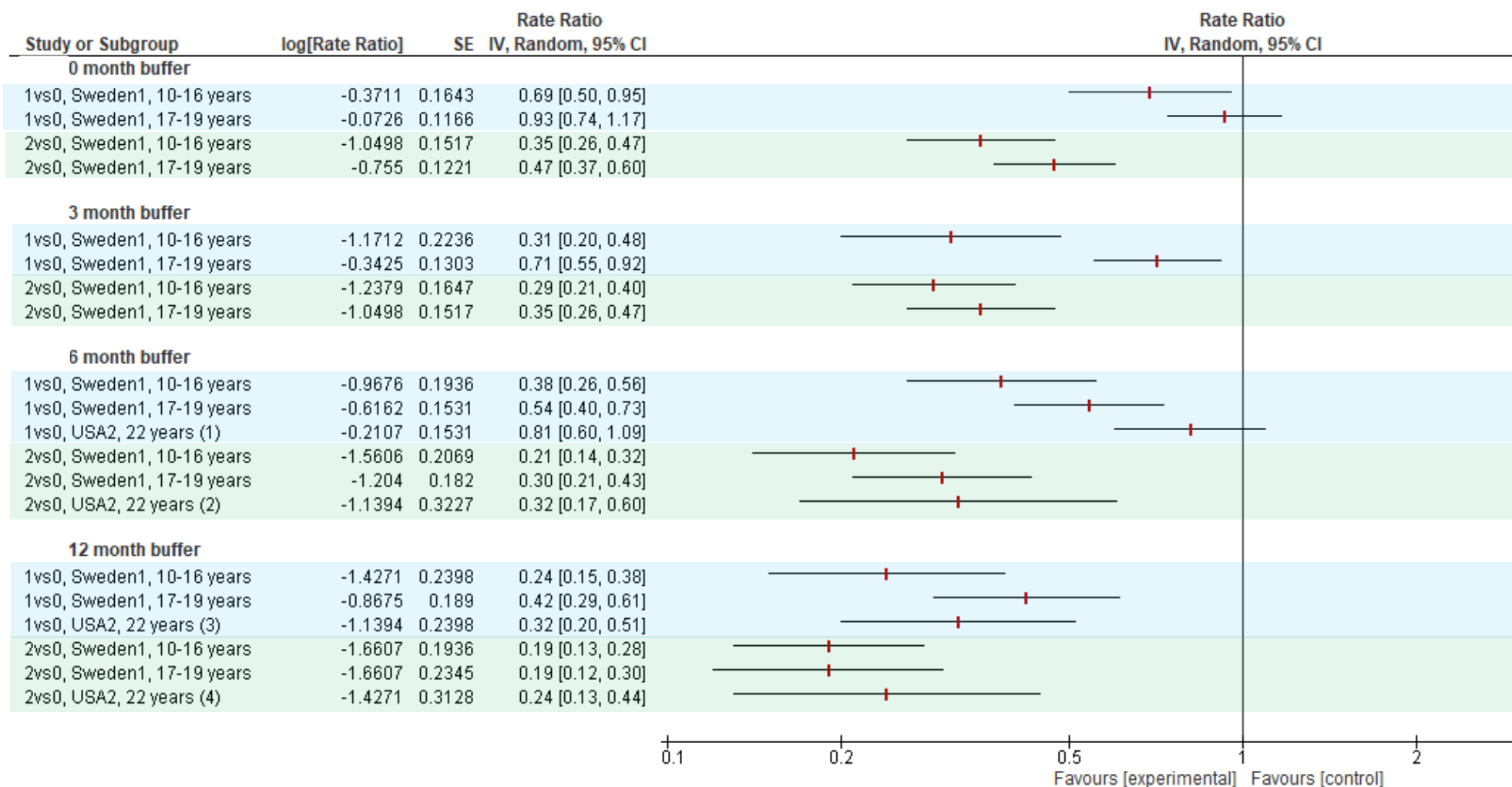
## Incident and persistent HPV infections over 7 years following one dose quadrivalent HPV vaccine versus no vaccine, two doses, or three doses; unadjusted estimates



## Genital warts following one dose of quadrivalent HPV vaccine versus two doses; adjusted and unadjusted estimates

Study	Age (years)	Number of participants or person-years (PY)	Reported estimate	Direction of effect	Risk of bias
One dose versus two doses 4-valent HPV vaccine      8 studies      LOW CERTAINTY EVIDENCE					
USA2	≤22	13,803 PY	<6m interval; 6m buffer: HR 1.13 (0.68 to 1.87)	Little or no difference	Moderate
		10,782 PY	<6m interval; 12m buffer: <b>HR 2.23 (1.09 to 4.56)</b>	One dose	
		14,039 PY	>6m interval; 6m buffer: <b>HR 0.39 (0.20 to 0.76)</b>	Two doses	
		14,224 PY	>6m interval; 12m buffer: HR 0.74 (0.35 to 1.60)	Two doses	
Sweden1	10-19	73,279 PY	3m buffer <b>IRR 0.59 (0.43 to 0.81)</b>	Two doses	Serious
			6m buffer <b>IRR 0.54 (0.38 to 0.76)</b>	Two doses	
			12m buffer <b>IRR 0.59 (0.38 to 0.91)</b>	Two doses	
Belgium2	10-23	30,402 PY	RR 0.86 (0.38 to 1.92)	Little or no difference	Serious
Canada3	19-25	2,483 PY	RR 1.39 (0.84 to 2.32)	Two doses	Serious
Denmark2	12-27	289,324 PY	<b>RR 2.28 (1.94 to 2.67)</b>	Two doses	Serious
Spain2	14	49,561 PY	RR 1.24 (0.39 to 3.90)	Little or no difference	Serious
USA6	9-25	278,576 PY	RR 1.08 (0.91 to 1.28)	Little or no difference	Serious
USA11	9-26	109,912 PY	<b>RR 0.98 (0.80 to 1.20)</b>	Little or no difference	Serious

## Effect of buffer period and age at vaccination on efficacy of one or two doses of HPV vaccine



### Footnotes

(1) hazard ratio

(2)  $\geq 6$  month interval; hazard ratio

(3) hazard ratio

(4)  $\geq 6$  month interval; hazard ratio

## Summary one dose efficacy/effectiveness

Current evidence for most outcomes was of low to very low certainty due to limitations in study design and imprecision.

Evidence suggests that one dose results in higher GMTs than no vaccine, but lower than two or three doses.

There was inconclusive evidence for one dose on CIN 1, 2, and 3 compared to no vaccine, two doses, or three doses.

One dose may result in fewer HPV 16/18 infections than no vaccine, and little to no difference to two doses.

Removing sources of bias suggest there is little to no difference between one dose and two doses for the younger age groups (<16 years) for genital warts and CIN2+.

## Results

- Efficacy and effectiveness of one dose of HPV vaccine
  - One dose vs no vaccine
  - One dose vs two doses
  - One dose vs three doses
- Different intervals between the first and second doses of HPV vaccines
- Two doses of HPV vaccine in 15-18-year-olds
  - Two doses vs no vaccine
  - Two doses vs three doses

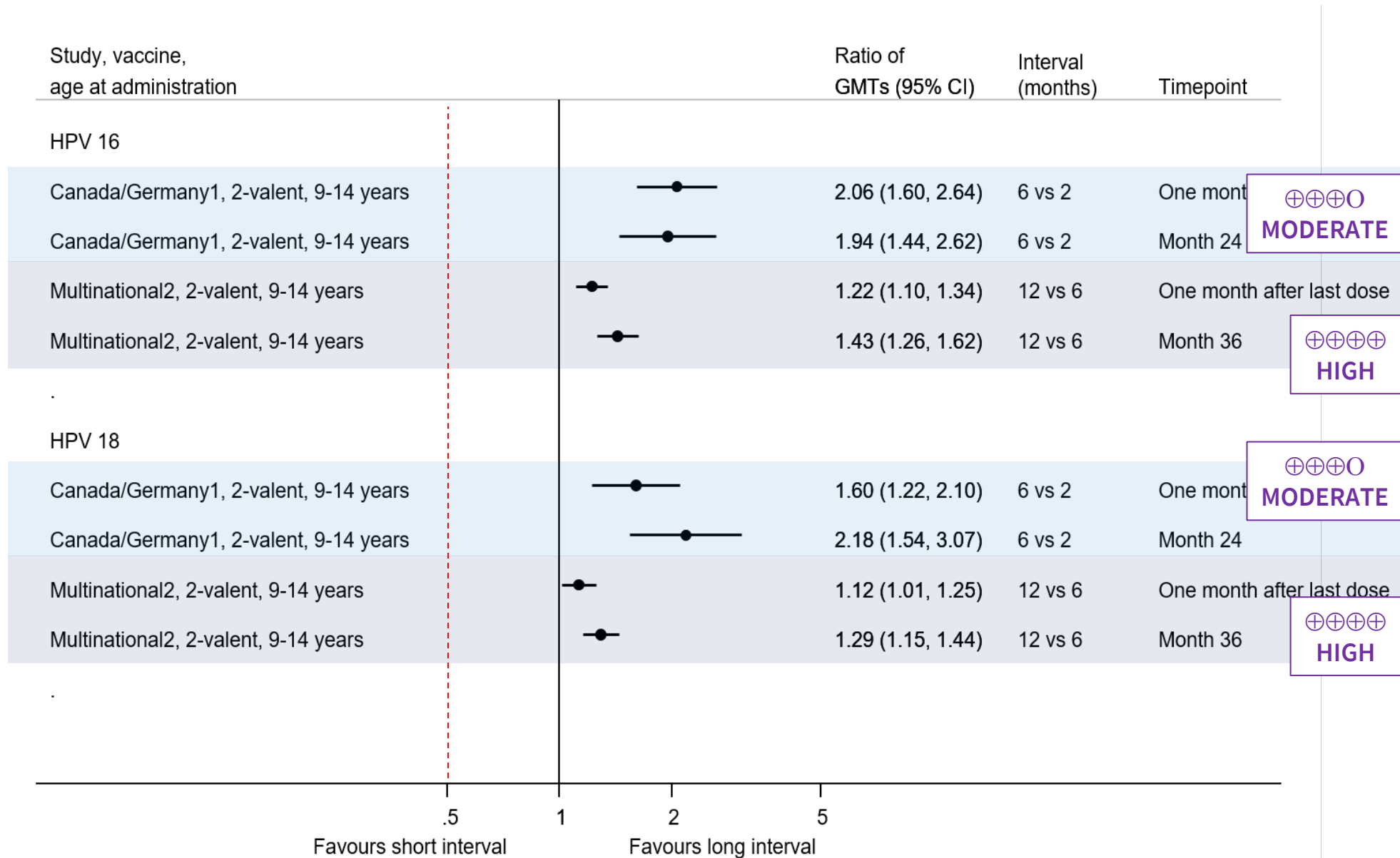


## Comparison of interval between two doses - included study characteristics

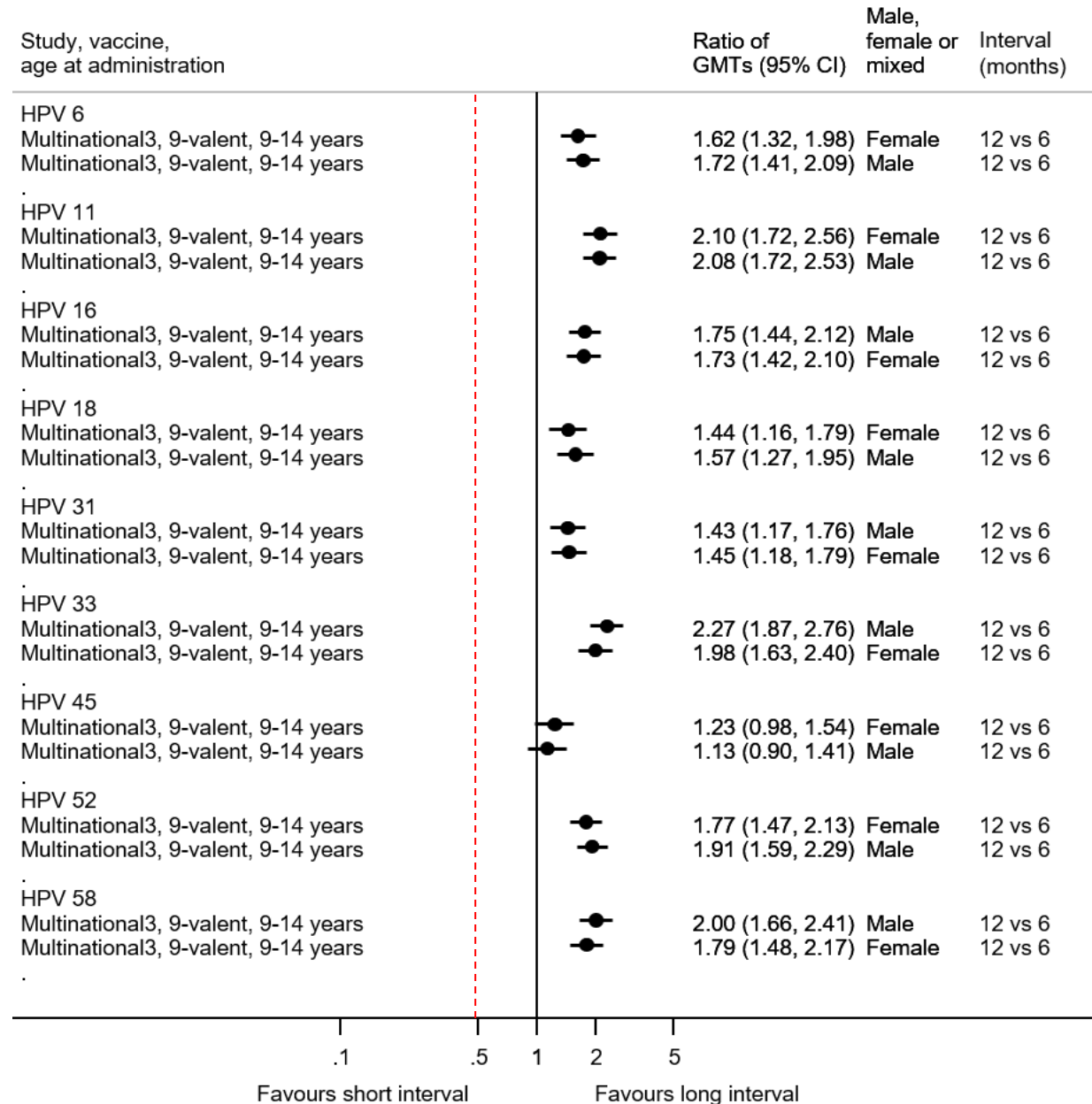
Study	Design	Vaccine	Comparison (months)	Number of participants	Outcomes
Canada/Germany1	RCT	Bivalent	6 vs 2	241 vs 240	GMT, seroconversion
Multinational2	RCT	Bivalent	12 vs 6	415 vs 550	GMT, seroconversion
Vietnam1	Cluster RCT	Quadrivalent	6 vs 3	193 vs 197	GMT
Multinational3	RCT	Nonavalent	12 vs 6	301 vs 602	GMT, seroconversion
Costa Rica1	Post-hoc analysis of RCT	Bivalent	6 vs 1	52 vs 140	GMT, HPV incidence
India1	Post-hoc analysis of RCT	Quadrivalent	6 vs 2	4,979 vs 3,452	GMT, HPV incidence
Australia1	Retrospective cohort	Quadrivalent	>6 vs <6	7,204 vs 20,297	histological (any high grade, CIN3/AIS, CIN2)
Denmark2	Retrospective cohort	Quadrivalent	3, 4, 5, 6 vs 2	Interval n values: NR 2 dose: 93,519	anogenital warts
Denmark/Sweden1	Retrospective cohort	Quadrivalent	≥5 vs 4	44,021 vs 513,507	CIN2+
Fiji1	Prospective cohort	Quadrivalent	≥6 vs <6	Interval n values: NR 2 dose: 60	GMT
Sweden2	Retrospective cohort	Quadrivalent	≥8 vs 4-7 vs 3	1,894 vs 8,095 vs 204,103	anogenital warts
Uganda1	Prospective cohort	Bivalent	>3 vs ≤3	28 vs 113	GMT
USA1	Retrospective cohort	Quadrivalent	≥6 vs <6	228 vs 376	abnormal cervical cytology
USA2	Retrospective cohort	Quadrivalent	≥6 vs <6	2,729 vs 2,730	anogenital warts
USA6	Retrospective cohort	Quadrivalent	≥5 vs <5	17,826 vs 18,757	anogenital warts
USA7	Retrospective cohort	Quadrivalent	>3 vs <3	126 vs 39	GMT
USA8	Retrospective cohort	Quadrivalent	≥8 vs 51-70 days	198 vs 192	GMT
USA11	Retrospective cohort	Quadrivalent	≥6 vs <6	16,990 vs 21,552	anogenital warts



# GMTs for HPV 16 and 18 comparing different intervals between two doses of bivalent HPV vaccine

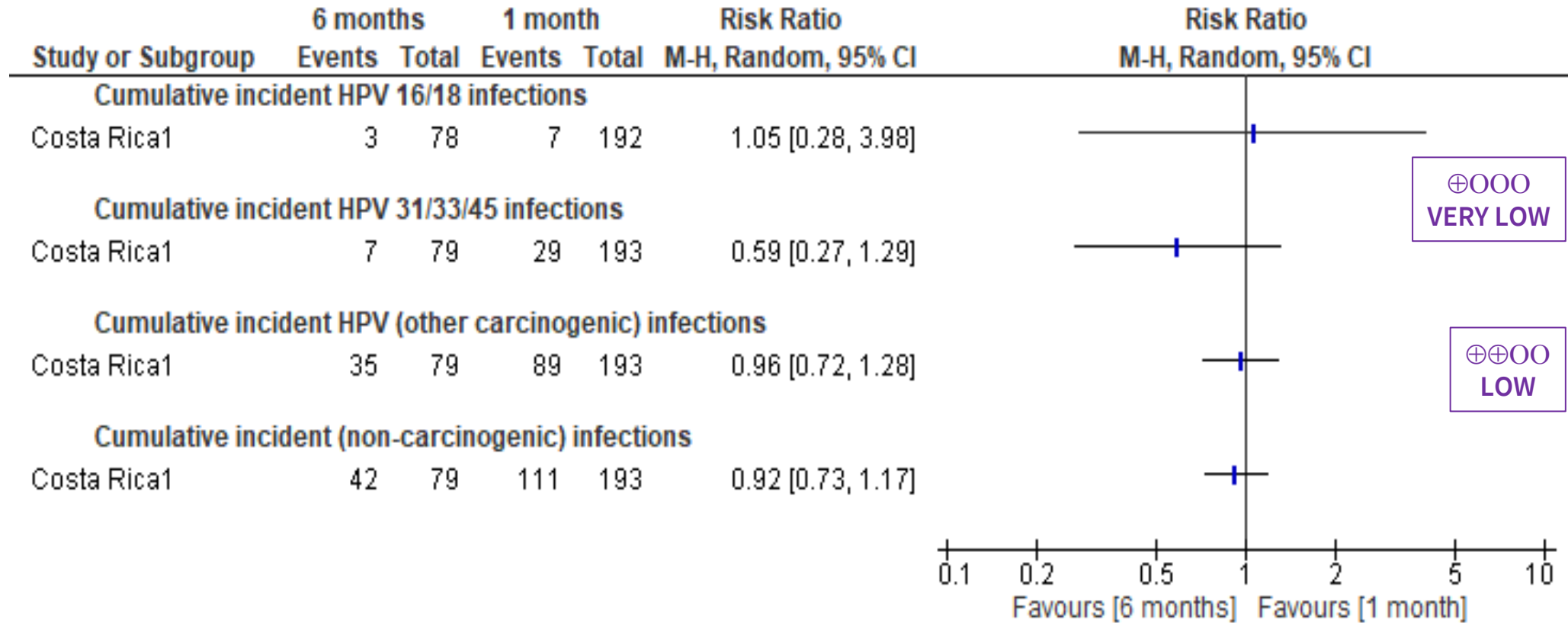


# GMTs for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 comparing 12 month to 6 month intervals between two doses of nonavalent HPV vaccine; one month after the last dose

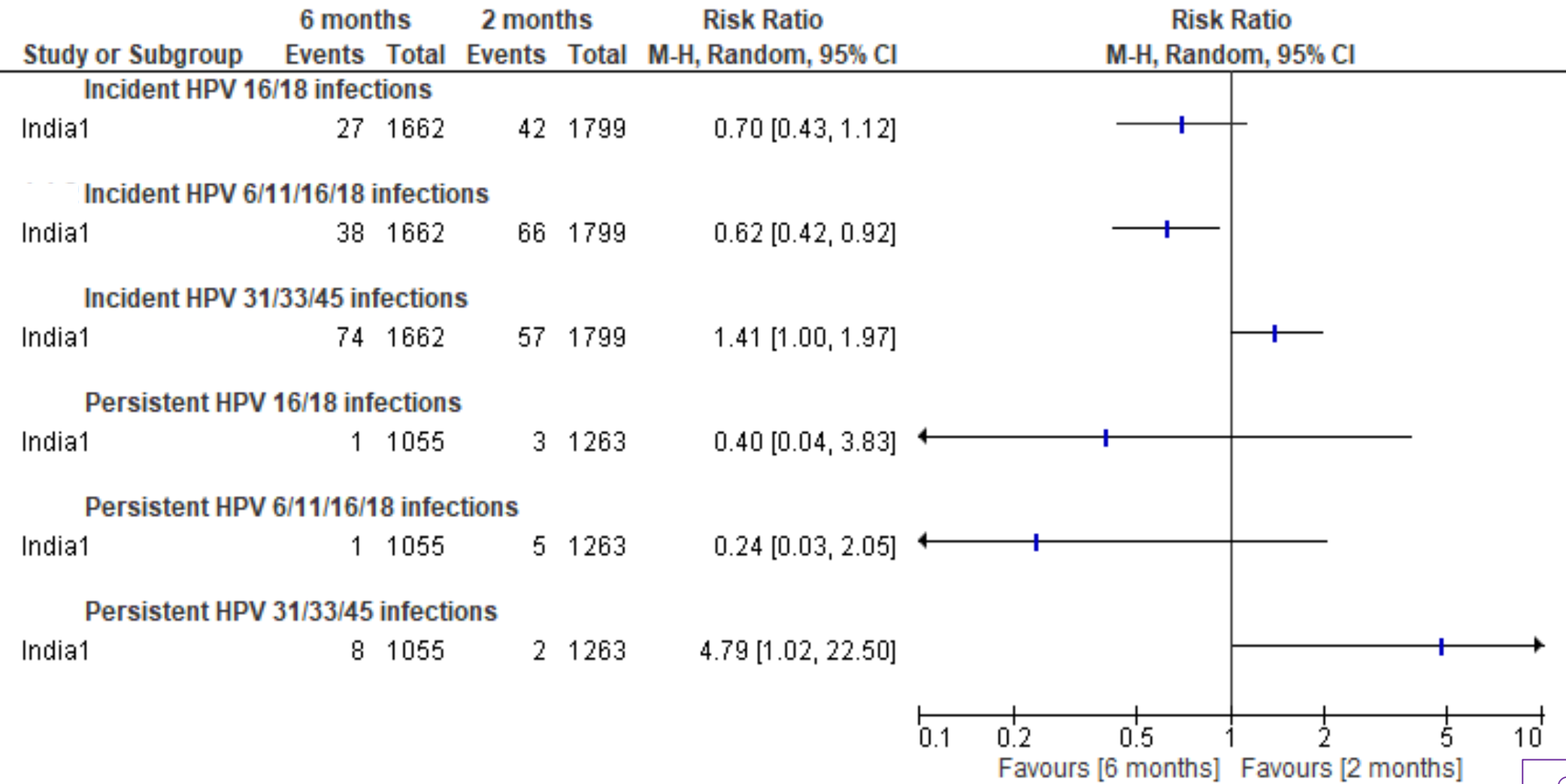


⊕⊕⊕⊕  
HIGH

## HPV infections over 7 years comparing 6 month to 1 month intervals between two doses of bivalent HPV vaccine



HPV infections comparing 6 month to 2 month intervals between two doses of quadrivalent HPV vaccine



⊕○○○  
VERY LOW

## Summary points

- GMTs for HPV 16 and HPV 18 were higher with a 6 month interval between doses than with 2 months for the bivalent vaccine (moderate-certainty evidence).
- GMTs for HPV 16 and HPV 18 were higher with a 12 month interval between doses than with 6 months for the bivalent vaccine (high-certainty evidence).
- GMTs for all HPV genotypes were higher with a 12 month interval between doses than with 6 months for the nonavalent vaccine (high-certainty evidence).
- Data from observational studies suggested either no difference or better outcomes following a longer interval for HPV infections and other clinical outcomes (low to very-low certainty evidence).

## Results

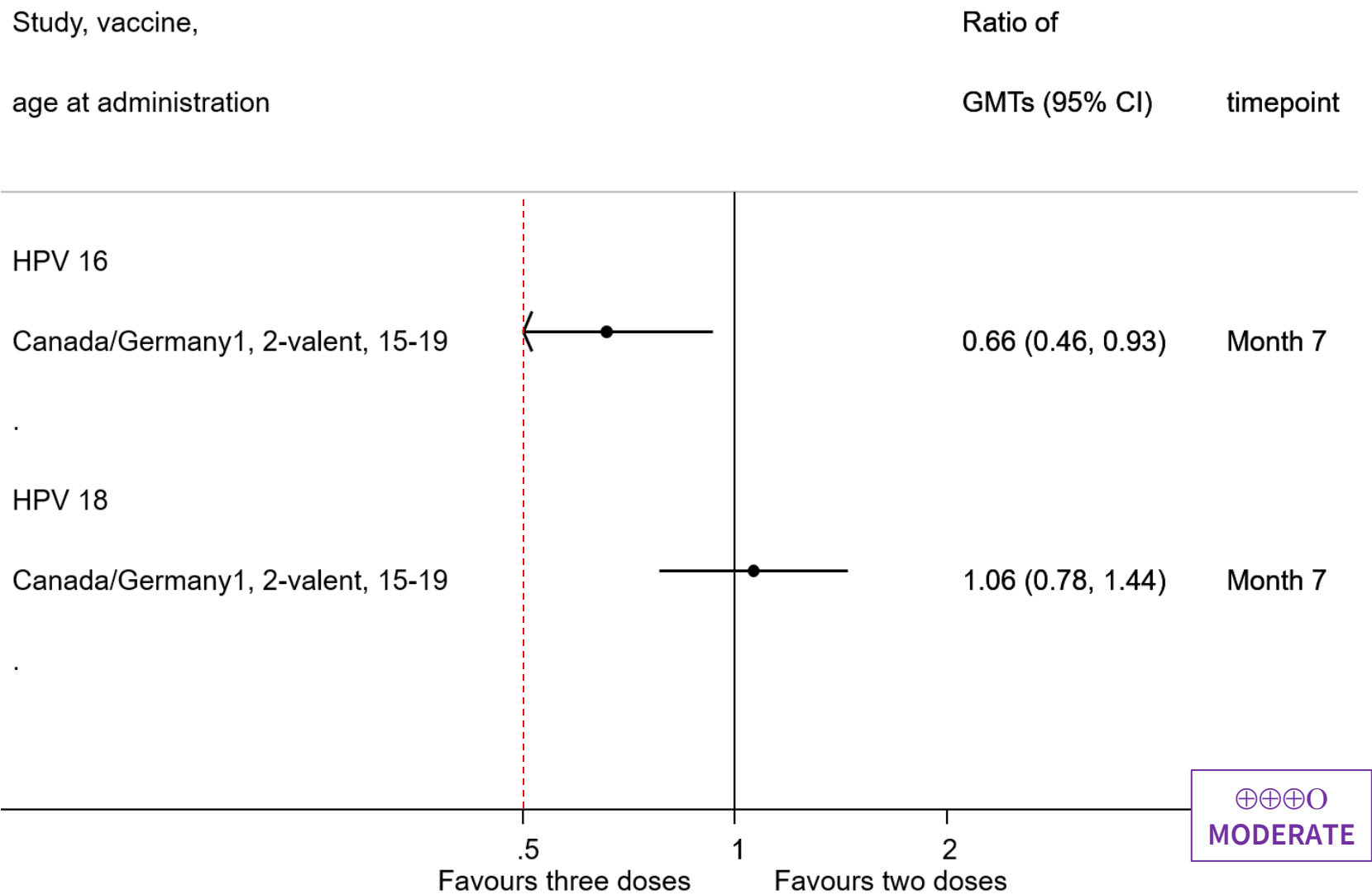
- Efficacy and effectiveness of one dose of HPV vaccine
  - One dose vs no vaccine
  - One dose vs two doses
  - One dose vs three doses
- Different intervals between the first and second doses of HPV vaccines
- Two doses in 15-18-year-olds
  - Two doses vs no vaccine
  - Two doses vs three doses



## Included studies (15-18-year-olds)

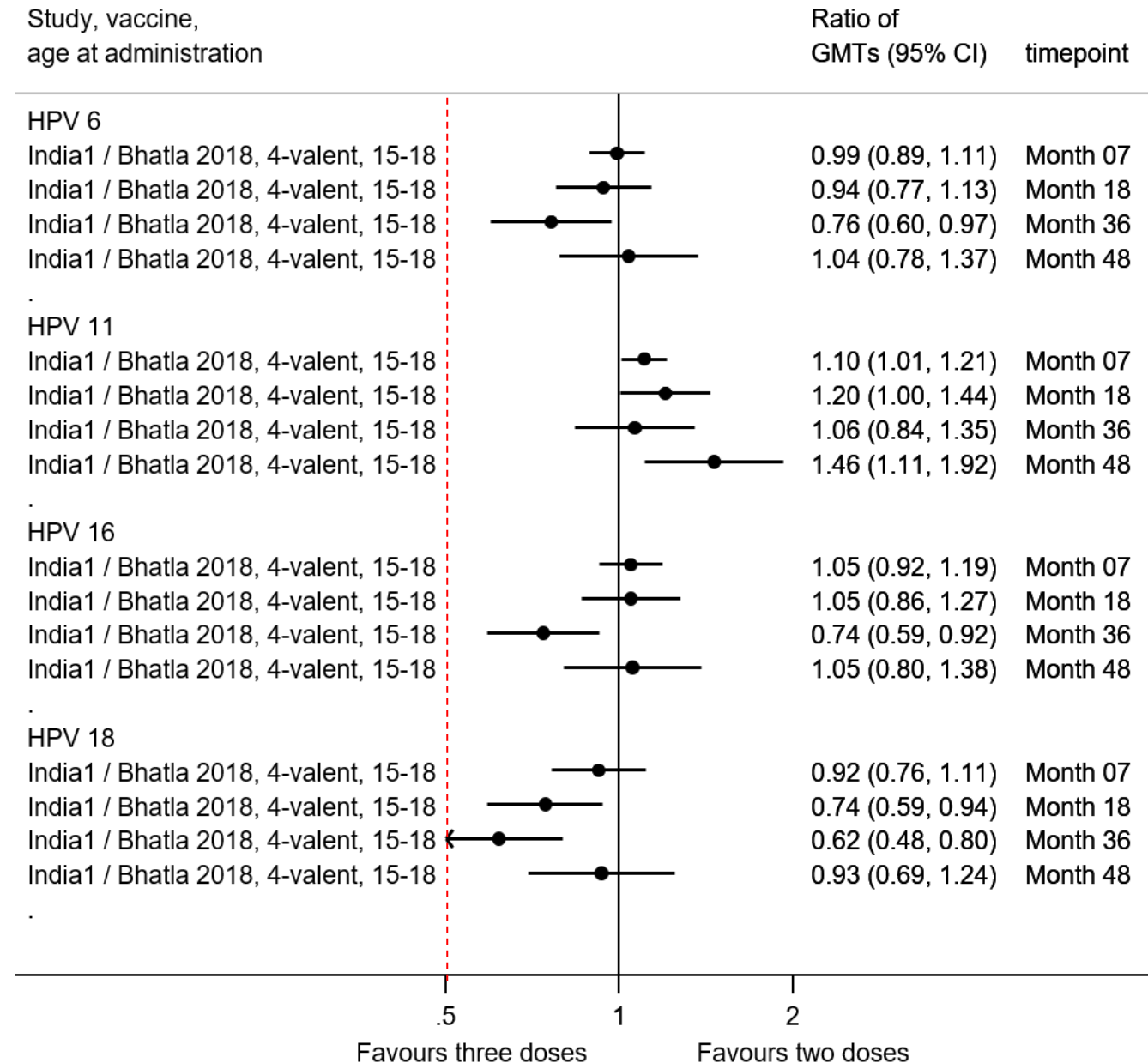
- Two doses vs no vaccine
  - One post-hoc analysis of an RCT (India1)
  - Two retrospective cohort studies (USA1, USA10)
- Two doses vs three doses
  - One RCT evaluating the bivalent vaccine in 15-19-year-old females (Canada/Germany1)
  - One post-hoc analysis of an RCT (India1)
  - Two retrospective cohort studies (Denmark2, USA1)
- No studies in males or on the nonavalent vaccine were identified.

GMTs for HPV 16 and 18 at one month after last dose comparing two doses to three doses of bivalent HPV vaccine



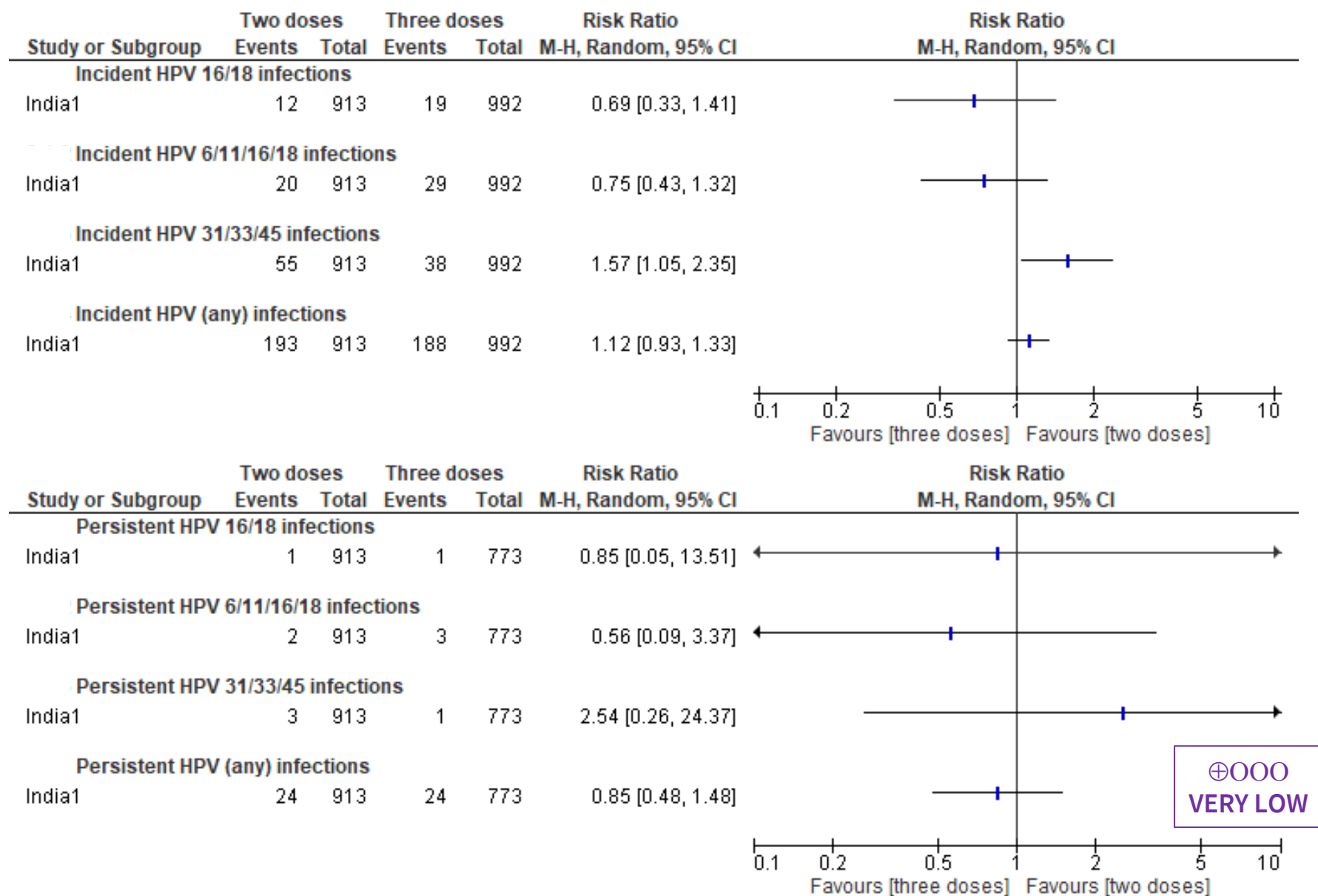


# GMTs for HPV 6, 11, 16 and 18 up to 48 months following two doses or three doses of quadrivalent HPV vaccine



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LOW

# HPV infections comparing two doses to three doses of quadrivalent HPV vaccine in 15-18-year-olds



## Summary points (females aged 15-18 years)

- Two doses may result in fewer incident HPV infections compared to no vaccine (low certainty evidence)
- Two doses of bivalent vaccine were non-inferior to three doses for GMT of HPV 18; non-inferiority was inconclusive for HPV 16 (moderate certainty evidence)
- Two doses of quadrivalent vaccine were non-inferior to three doses for GMTs of HPV 6, 11, 16, and 18 over 48 months (low certainty evidence)
- The evidence for clinical outcomes (HPV infection, anogenital warts) was of low to very low certainty

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## **Conflict of interest statement**

No financial or non-financial conflicts of interest declared