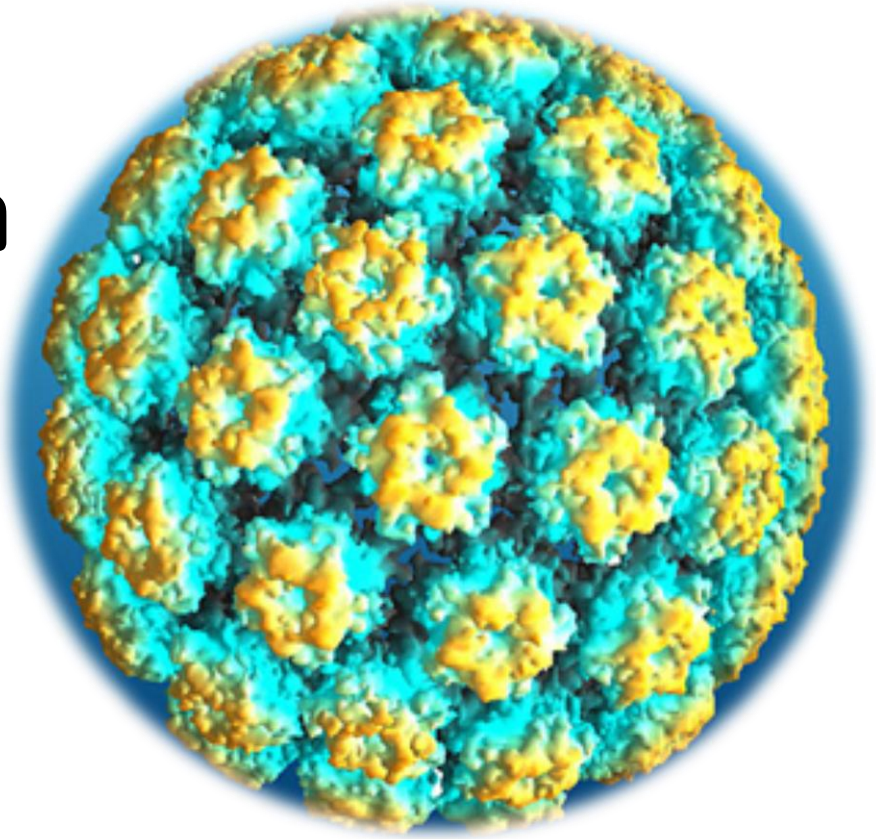
Optimizing Human Papilloma Virus immunization schedules



SAGE meeting – April 2014

Dr Sir Andrew Hall

Senior visiting Scientist

IARC

Why are we reviewing the evidence on schedules for HPV vaccines?

Emerging evidence on effect of < 3-dose schedules

Opportunities to **facilitate delivery** and increase coverage

Potential to **reduce costs** (vaccine and delivery)

Sources of DATA

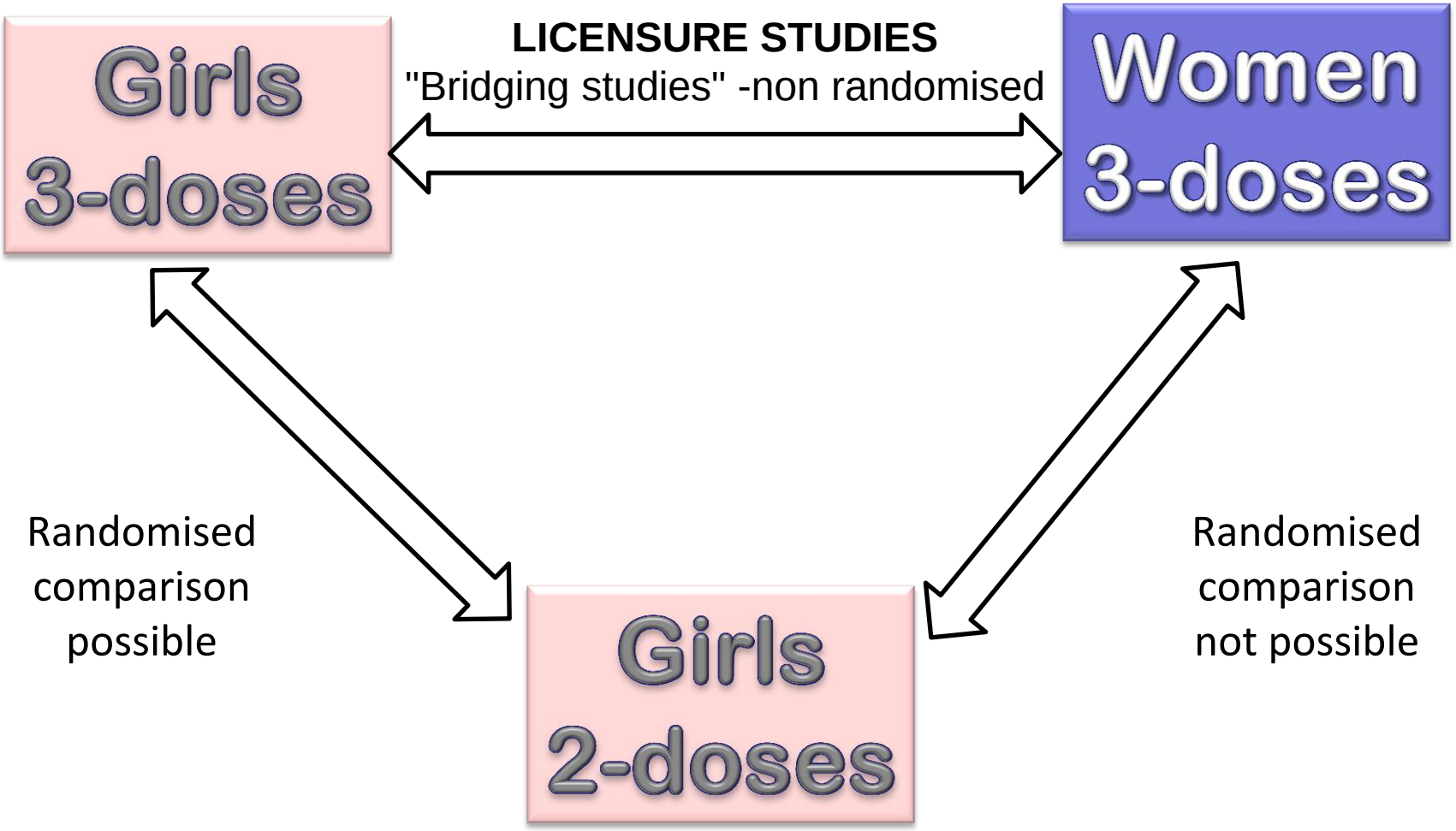
1. **Data presented during the *Ad hoc Expert Consultation on Human Papilloma Virus Vaccine schedules* organized in Geneva, November 18, 2013.**
2. **Results from a systematic review conducted by an independent team of Investigators.**

   HPV vaccines: review of alternative vaccination schedules

   (D'Addario M et al 2014)[1].
3. **Results from non-systematic review of the data from observational studies.**
4. **EMA- Report: The bivalent vaccine received approval for a pre-adolescent and adolescent indication to allow for administration of the vaccine according to an alternative 2-dose schedule (0, 6 months) in females aged 9-14 years old.**

Assessing HPV schedules in girls 9-13 yrs old

What are the possible COMPARISONS?



Adapted from D'Addario M et al 2014

What are the OUTCOME MEASURES of interest?

Immunological

Seroconversion/seropositivity

- serum neutralizing Ab to HPV types included in vaccine
- serum neutralizing Ab to other HPV types

GMCs

Non-inferiority of immunological responses

Clinical end-points

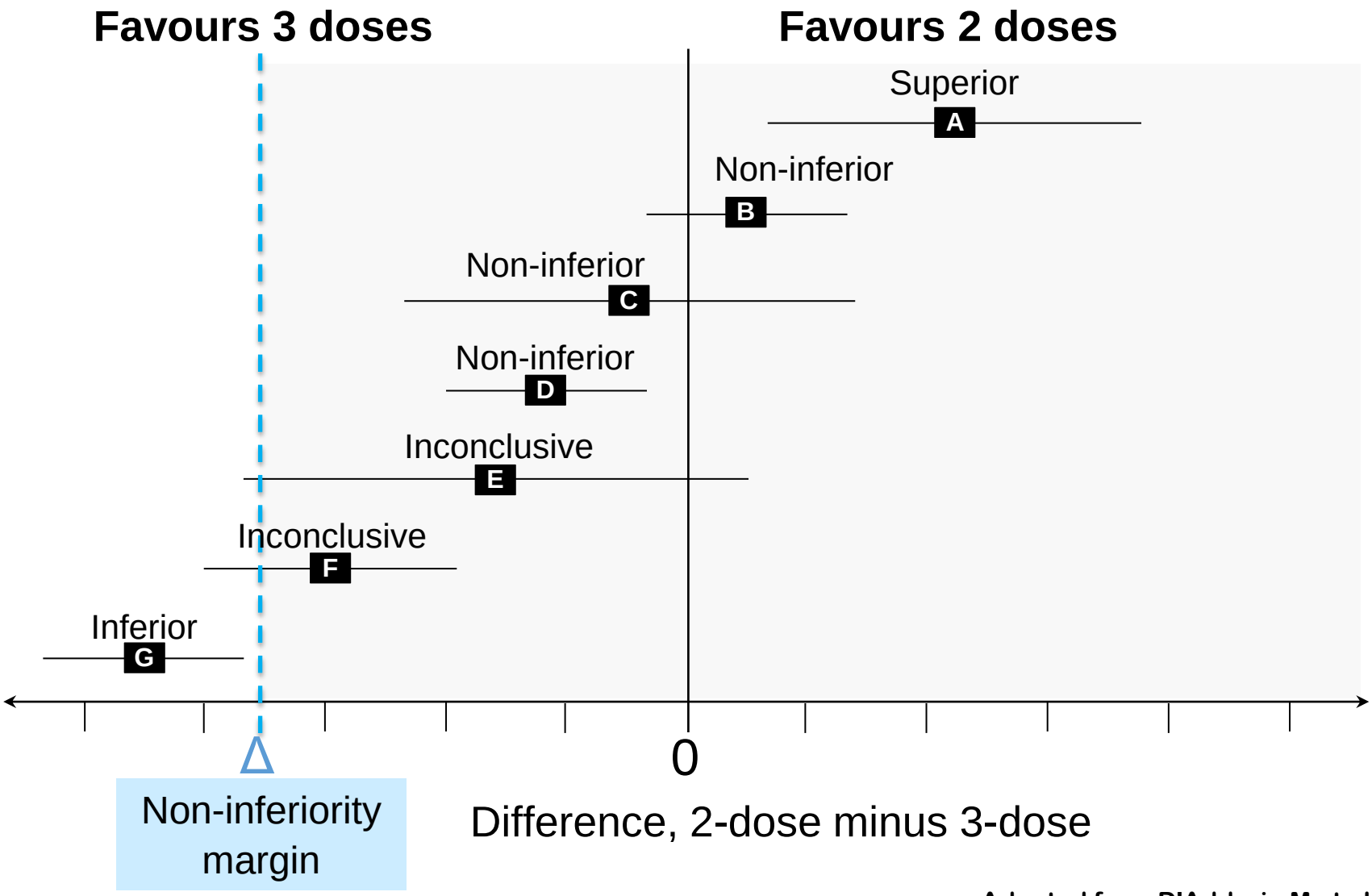
Frequency of incident and persistent vaccine type infections

Frequency of incident and persistent infection by non-targeted high risk HPV types

Vaccine type associated CIN2/3 lesions, adenocarcinoma in situ and invasive cervical cancers

CIN lesions and invasive cancer associated with other HPV types

Interpretation of differences between 2-dose and 3-dose schedules of HPV vaccines in NON-INFERIORITY trials



Adapted from D'Addario M et al 2014

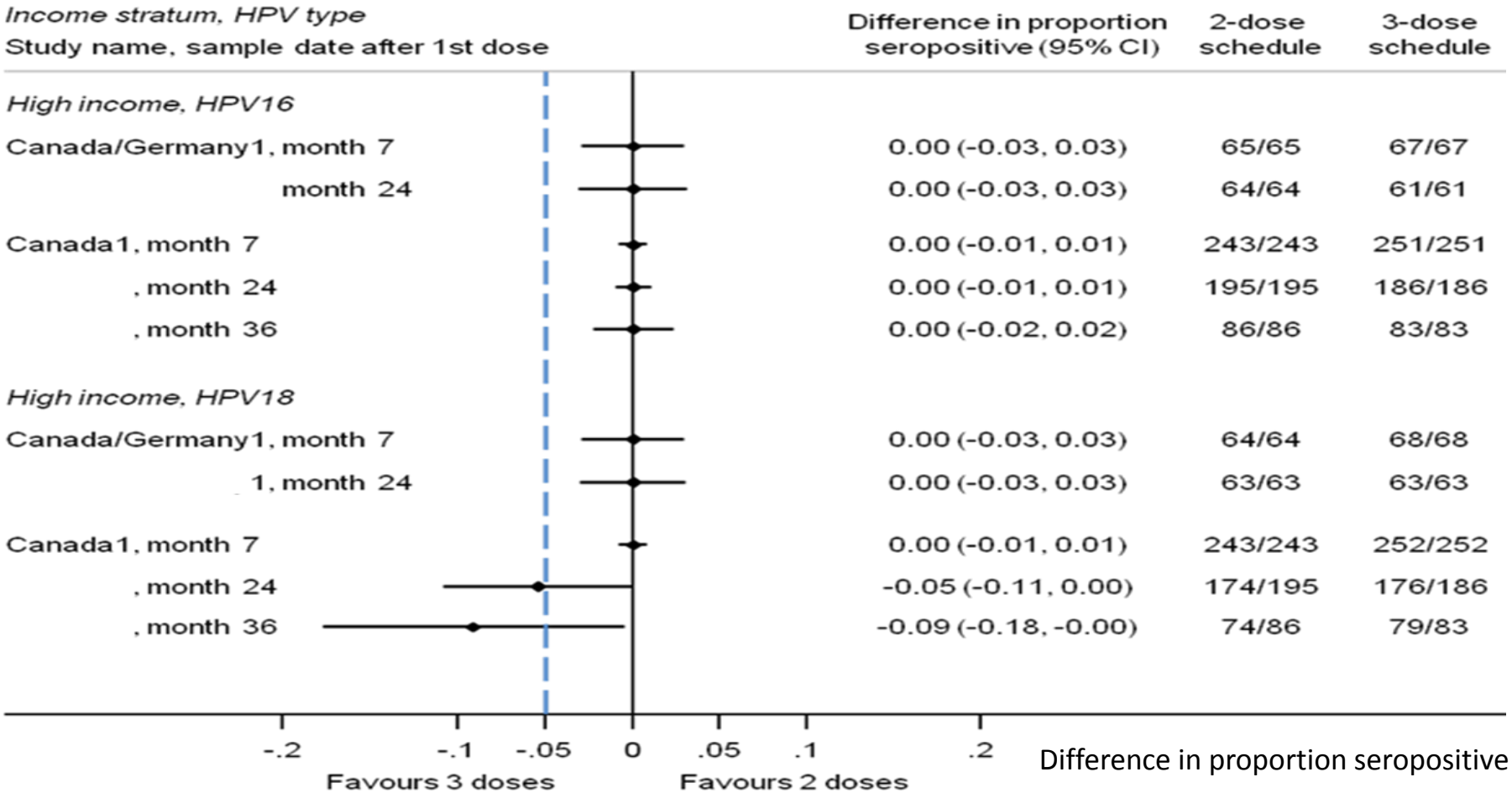
What DATA did we identify?

Girls 2-doses ⟺ **Girls 3-doses**

Study name	Vaccine	Schedule	Outcomes				
			GMC		Seroconversion/ positivity		Clinical
			1 month	later	1 month	later	
Canada	Quadrivalent	0, 6m vs (0, 2, 6m)	+	+ (24, 36 m)	+	+ (24, 36 m)	
Canada/Germany	Bivalent	0, 6 m vs (0, 1-2, 6m)	+	+ (24 m)	+	+ (24m)	
India	Quadrivalent	0, 6m vs (0, 2, 6m)	+				+
Mexico	Bivalent	0, 6 (60m) (extended) vs (0, 1, 6)					
Multinational	Bivalent	0, 6 m or (0, 12m) vs (0, 1, 6m)					

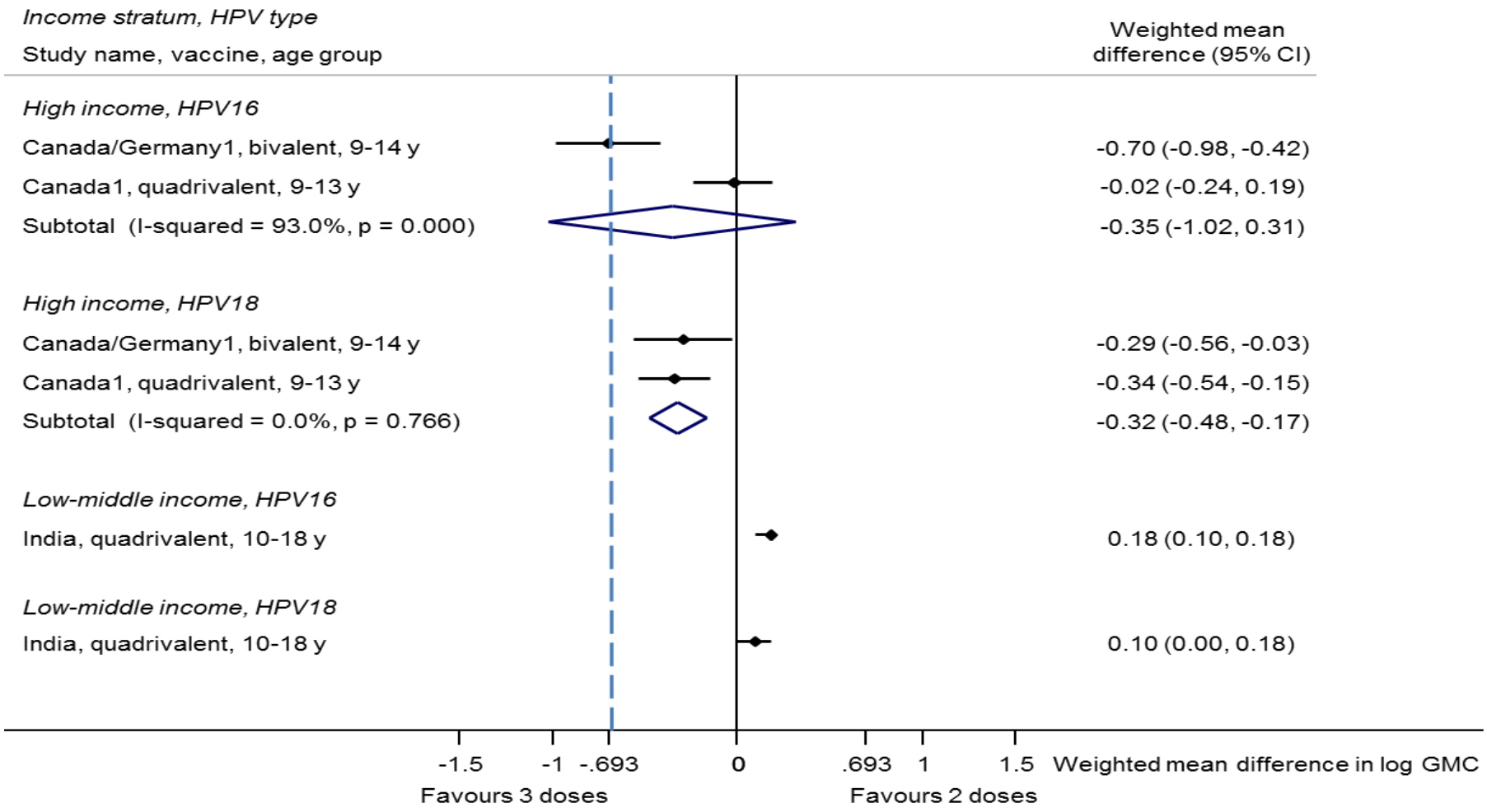
Girls 2-doses ⟷ Girls 3-doses

Differences in proportions seroconverting 7 months after the first vaccine dose and being seropositive 24 and 36 months after the first dose of HPV vaccine in girls receiving a 2-dose or 3-dose schedule



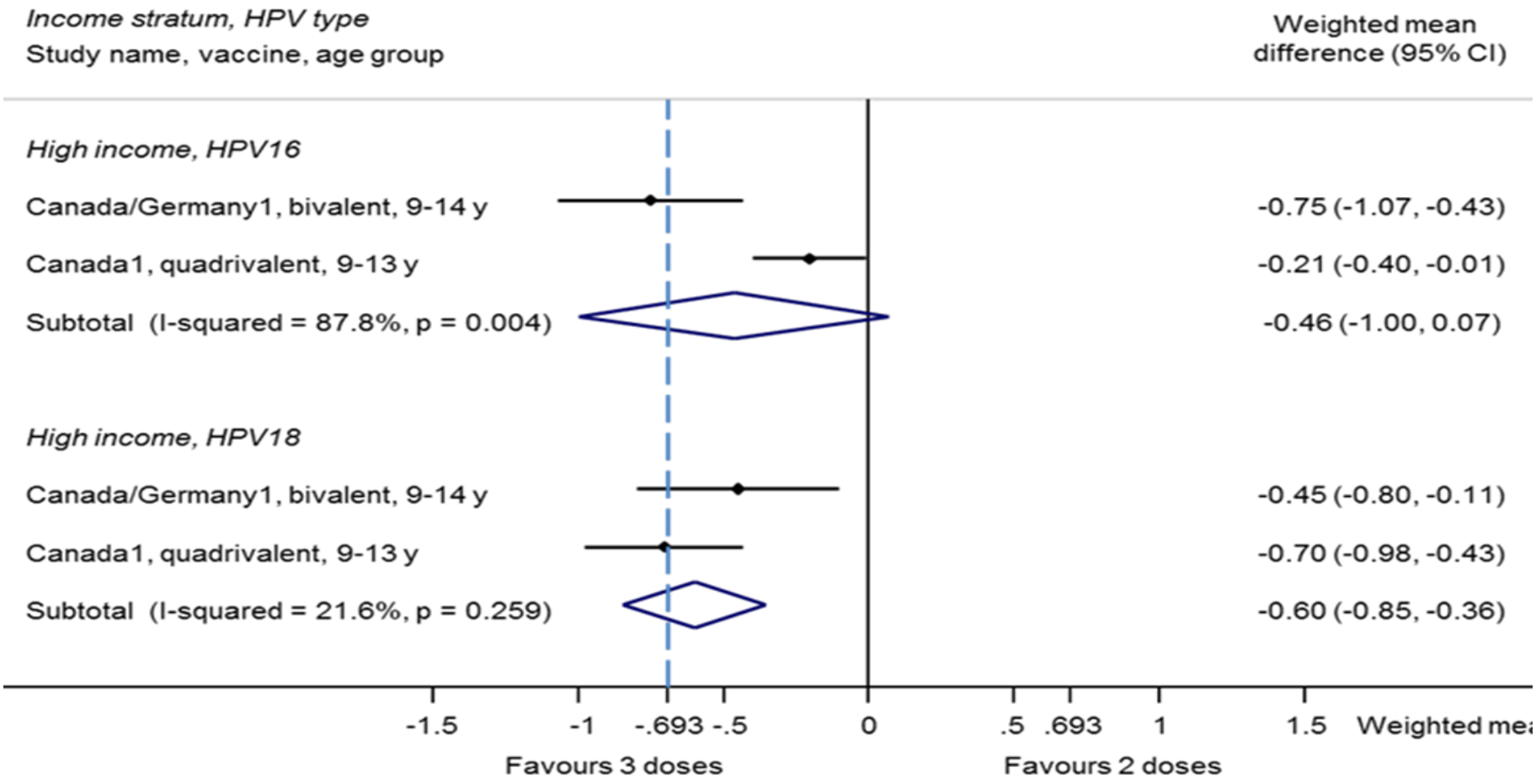
Girls 2-doses ⟷ Girls 3-doses

Weighted mean difference between GMCs in girls receiving 2 and 3 doses, one month after last dose



Girls 2-doses ⟷ Girls 3-doses

Weighted mean difference between GMCs in girls receiving 2 and 3 doses, 24 months after last dose



Girls 2-doses ⟷ Girls 3-doses

Clinical outcomes

Frequency of incident infection by vaccine included HPV types in 181 girls (18+ years old), India*

1 dose	3/56	(5%)
2 doses (1-60 d)	6/36	(17%)
2 doses (1-180+d)	4/45	(9%)
3 doses (1-60-180+d)	1/44	(2%)
Overall	14/181	(8%)

Preliminary unpublished data
from interim analysis of a non randomised subset of 600 girls

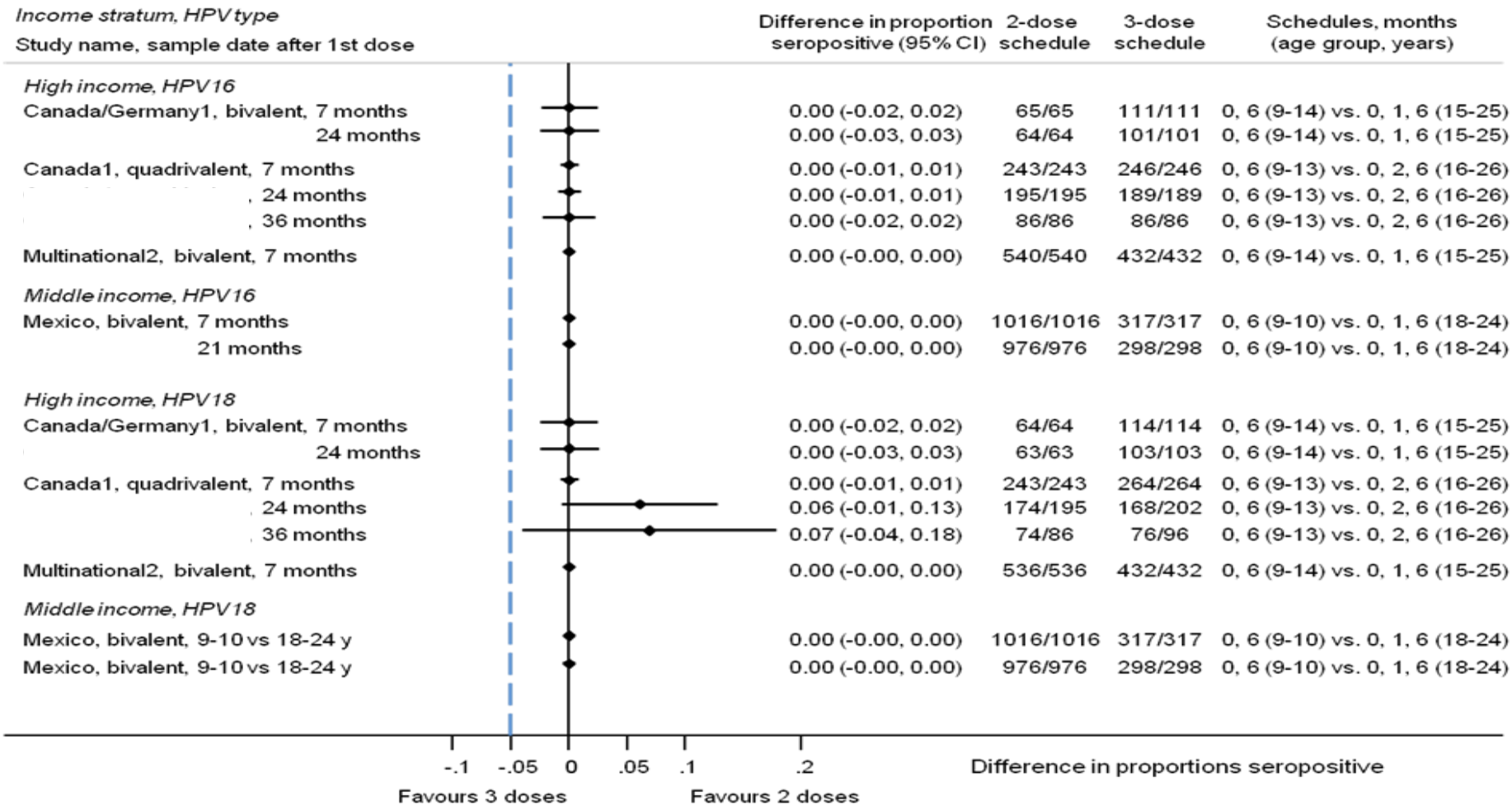
What DATA did we identify?

Girls 2-doses ⟺ **Women 3-doses**

Study name	Vaccine	Schedule	Outcomes				
			GMC		Seroconversion/ positivity		Clinical
			1 month	later	1 month	later	
Canada1	Quadrivalent	0,6 m vs (0, 2, 6m)	+	+ (24, 36)	+	+ (24, 36)	
Canada/Germany1	Bivalent	0, 6m vs (0, 1, 6m)	+	+ (24)	+	+ (24)	
India	Quadrivalent	0, 6m vs (0, 2, 6m)	-				
Mexico	Bivalent	0, 6 (60m) (extended) vs (0, 1, 6)	+	+ (21)	+	+ (21)	
Multinational2	Bivalent	0, 6 m or (0, 12m) vs (0, 1, 6m)	+		+		

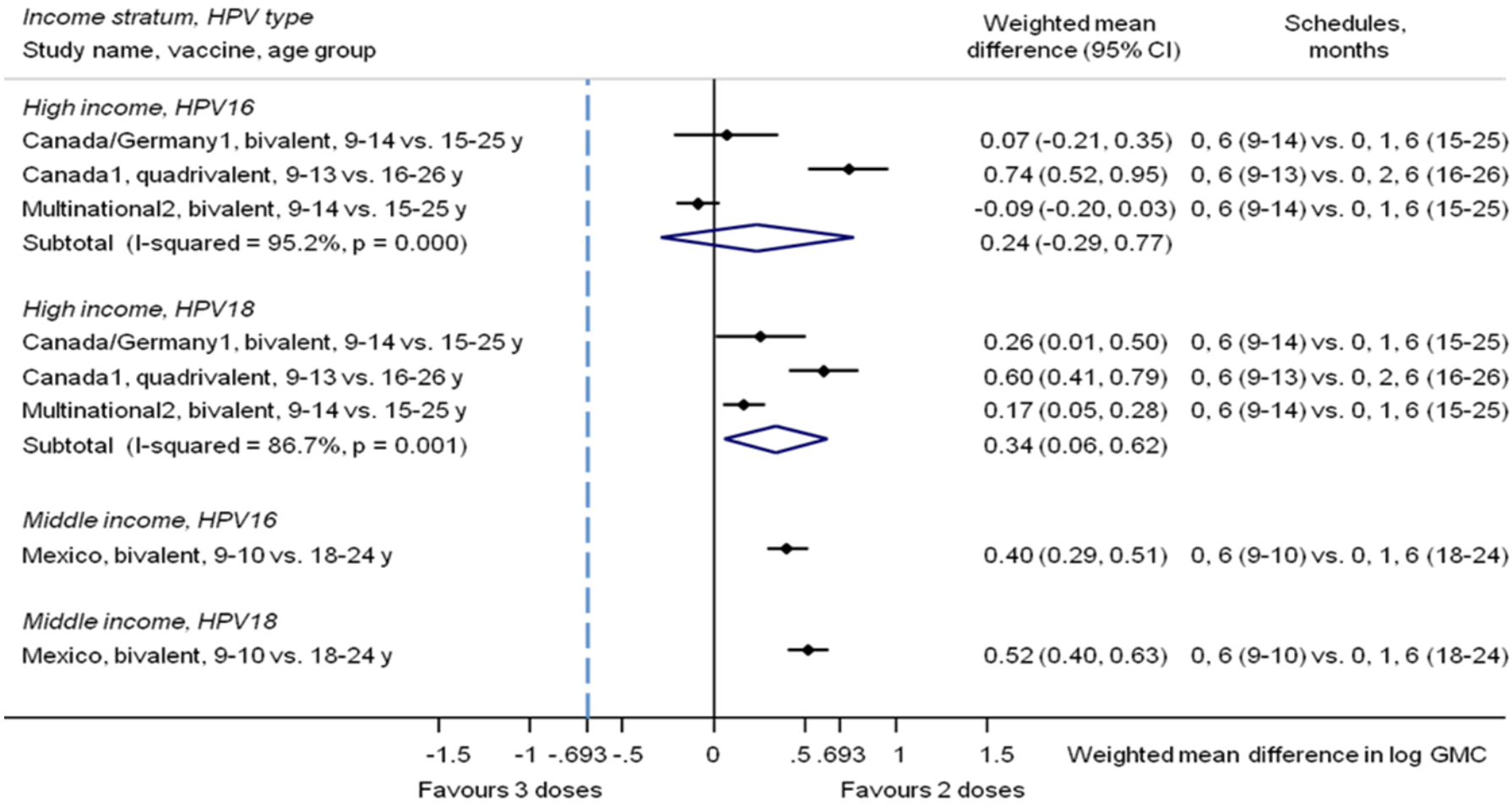
Girls 2-doses ⟷ Women 3-doses

Differences in proportions seroconverting 7 months after the first vaccine dose and being seropositive 24 and 36 months after the first dose of HPV vaccine in girls receiving a 2-dose schedule and women receiving a 3-dose schedule



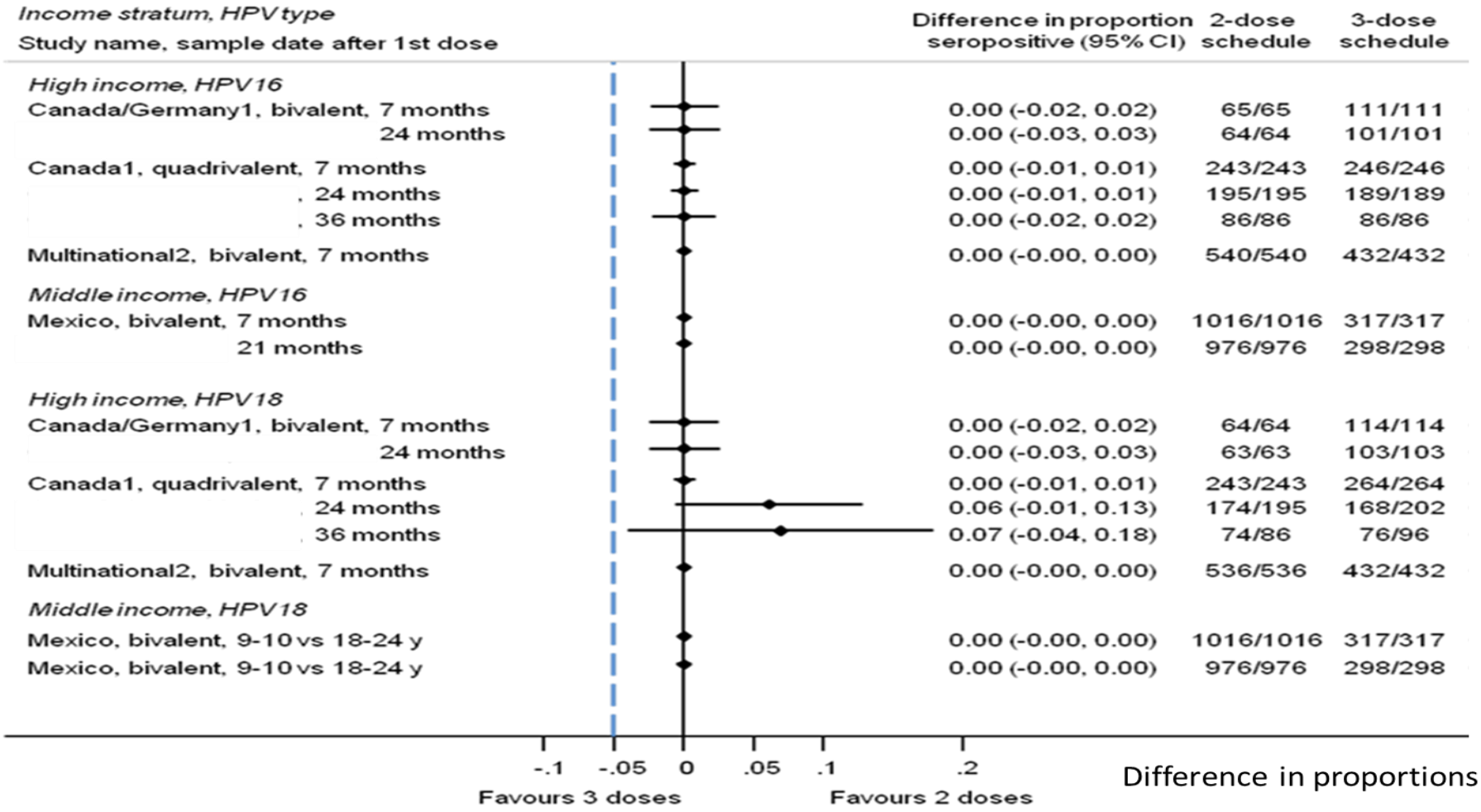
Girls 2-doses ⟷ Women 3-doses

Weighted mean difference between GMCs in girls receiving a 2-dose schedule and women receiving a 3-dose schedule, one month after last dose



Girls 2-doses ⟷ Women 3-doses

Weighted mean difference between GMCs in girls receiving a 2-dose schedule and women receiving 3-dose schedule, 21 or 24 months after last dose



Observational Studies

Observational studies providing information on effect of fewer than 3 doses of HPV vaccines

Study	Vaccine	Type of study	Outcome measured
Australia, Gertig et al 2013	Quadrivalent	Cohort study	Risk of cervical abnormalities
Victoria, Australia. Garland et al 2013	Quadrivalent	Cross sectional study	Vaccine related infection and disease (CIN3)
Queensland, Australia. Crowe et al 2013	Quadrivalent	Case control	Vaccine effectiveness against cervical abnormalities
Sweden, Levál et al 2013	Quadrivalent	Population based study	Genital warts incidence
Sweden, Herweijer et al 2014	Quadrivalent	Cohort study	First occurrence of condyloma
Denmark, Bloomberg et al 2013	Quadrivalent	Population based study	Genital warts
Uganda, Safaeian et al 2013	Bivalent		GMTs

Observational Studies

Australia, Gertig et al 2013

- Retrospective cohort
- Females aged 17 or younger in 2007
- Pap test recorded from 1 April 2007 to 31 December 2011
- Average follow up: 4.8 years
- Censoring: date of outcome, death, hysterectomy, end of study
- Lower risk of any histologically confirmed cervical abnormality for vaccinated women (any dose) vs unvaccinated women

Histological abnormalities	Number of doses	Hazard Ratio (95%CI)
Any high grade	Vaccinated (adjusted)	0.72 (0.58 to 0.91)
	1 dose	1.47 (0.97 to 2.23)
	2 dose	1.02 (0.68 to 1.53)
	3 dose	0.61 (0.48 to 0.78)

Adapted from Gertig et al 2013

Vaccinated (any dose) vs unvaccinated:
HR 0.72 (95%CI 0.58 to 0.91)

Observational Studies

Victoria, Australia, Garland et al 2013

- Cross sectional study

Sub study A

- Women 18-25 years (81% fully vaccinated)
- Questionnaire and Self collected vaginal swab
- HPV vaccine-related infection and disease (CIN3)
- Prevalence (interim analysis)
  - **HPV 16 was 1.6% (95 CI 0.6 to 3.5)**
  - **Any high risk type 14.4% (95 CI 11 to 18.4)**
  - **No HPV 18 detected**

Observational Studies

Queensland, Australia, Crowe et al 2014

- Case control study
- Females aged 12-26 years in 2007
- First cervical smear test between April 2007 and March 2011
- 3 doses vs no vaccination

- **VE 3 doses High grade cases 46% (33-67) Other 34% (30-38)**
- **VE 2 doses High grade cases 21% (2-36) Other 21% (5-26)**

Observational Studies

Sweden. Levál et al 2013

- Cohort study
- Females aged 10 to 44 years
- Incidence of genital warts
- 124 000 females vaccinated between 2006 - 2010
- 3 doses (first dose < 20 years) vs no vaccination

Age at vaccination	Estimated IRR (95%CI)	Estimated effectiveness (95%CI)
< 14 y	0.07 (0.02 to 0.27)	93% (73 to 98)
14 to 16 y	0.20 (0.17 to 0.25)	80% (75 to 83)
17 to 19 y	0.29 (0.24 to 0.35)	71% (65 to 76)
20 to 22 y	0.52 (0.35 to 0.78)	48% (22 to 65)

Adapted from Levál et al 2013

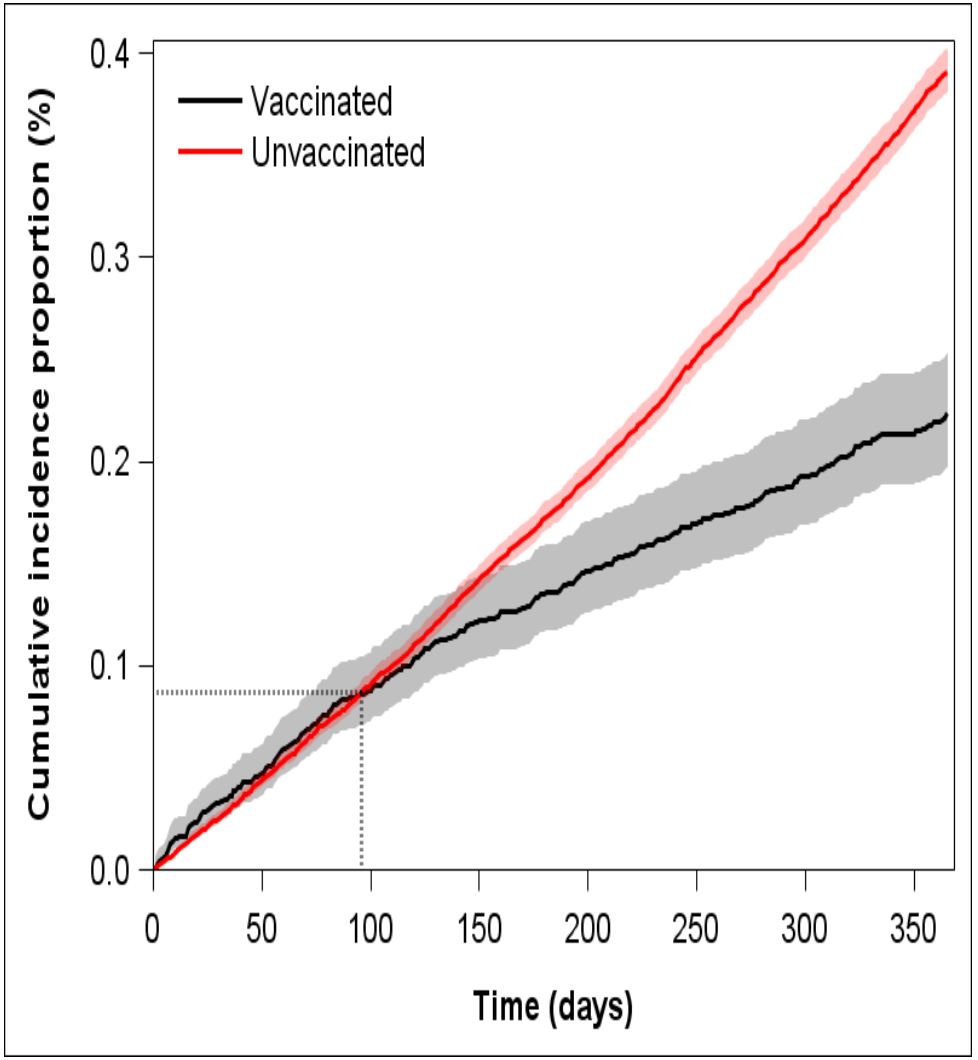
Observational Studies

Sweden, Herweijer et al 2014

- Population based study
- Nationwide registers
- Females 10 to 24 y
- Follow up 2006 – 2010
- First occurrence of condyloma
- Censorings:
  - First occurrence of condyloma
  - Vaccinated with bivalent vaccine
  - 25th birthday
  - Death

IRR in 10 to 16 years at 1st vaccination

- **3 doses 0.18 (95%CI 0.15 to 0.22)**
- **2 doses 0.29 (95%CI 0.21 to 0.40)**
- **1 dose 0.31 (95%CI 0.20 to 0.49)**



Herweijer et al 2014

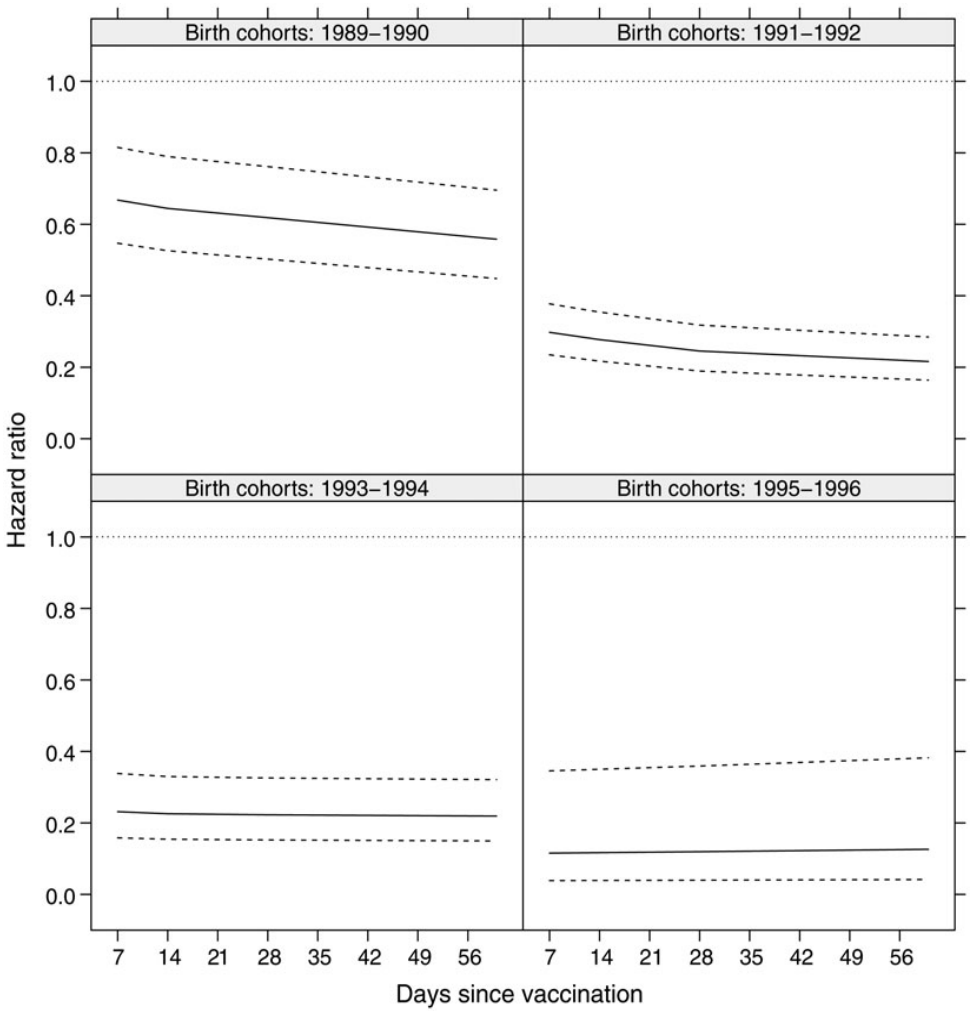
Observational Studies

Denmark, Blomberg et al 2013

- Cohort study
- Risk of genital warts (GW)
- Population-based registries
- Girls born 1989 to 1999 in Denmark

RR of GW at least 1 dose

Birth Cohort	HR (95%CI)
1995-1996	0.12 (0.04 to 0.36)
1993-1994	0.22 (0.15 to 0.33)
1991-1992	0.25 (0.19 to 0.32)
1989-1990	0.62 (0.50 to 0.76)



Adapted from Blomberg 2013

Observational Studies

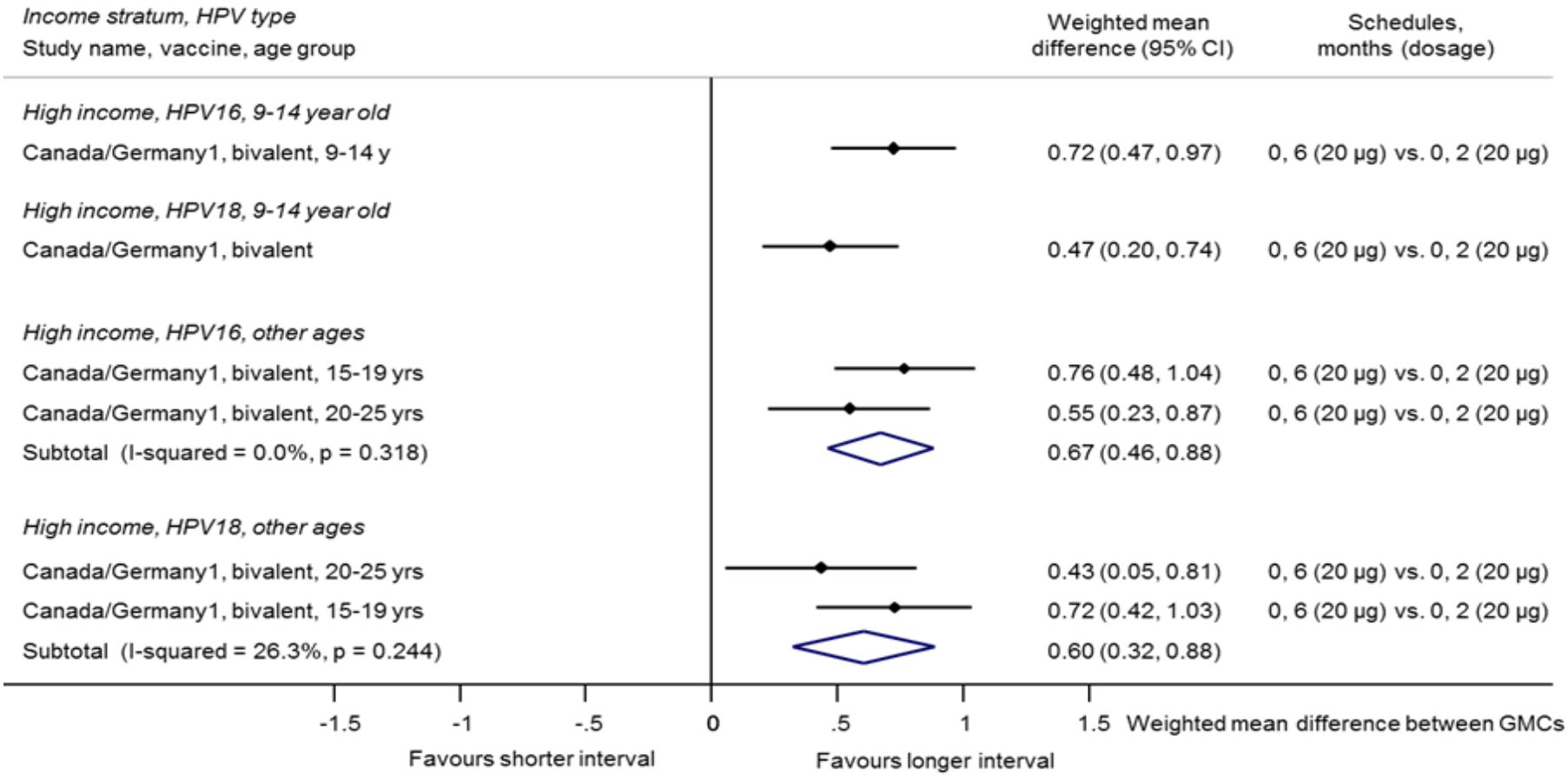
Uganda, Safaeian et al 2013

- HPV demonstration project in Uganda (2008-2009)
- Girls who received 1, 2 or 3 doses
- In addition: 24 months since vaccination
- ELISA: HPV-16 and HPV-18 specific antibody levels
- 2 vs 3 doses
- **GMT ratios**

HPV-16	**0.51 (97.5%CI 0.37 to 0.69)**
HPV-18	**0.69 (97.5%CI 0.50 to 0.96)**

Two doses administered at different intervals between doses

Weighted mean difference between GMCs one month after the last vaccine dose in girls and women receiving two doses at 0, 6 months or 2 doses at 0, 2 months



Special populations
HIV infected individuals

Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV-infected females, the potential benefit of vaccination in this group is particularly great owing to their increased risk of HPV-related disease, including cervical cancer.

There are limited data from HIV-infected individuals receiving a 3-dose schedule and, no data from HIV-infected individuals receiving a 2-dose schedule.

Summary of Findings

2-dose schedule versus 3-dose schedules

In randomised comparisons,

Seroconversion and seropositivity were non-inferior or inconclusive at all time points.

Geometric mean concentrations (GMCs), 1 month after the last dose, in the 2-dose group were lower but non-inferior or inconclusive compared with the 3-dose group.

Summary of Findings

2-dose schedule versus 3-dose schedules

In non-randomised comparisons,

All available data for seroconversion and seropositivity showed non-inferiority of the 2-dose compared with the 3-dose schedule.

GMCs were non-inferior or superior in girls receiving the 2-dose schedule compared with women receiving the 3-dose schedule at all time points assessed, up to 36 months after vaccination.

Summary of Findings

2-dose schedule versus 3-dose schedules

Limited data about clinical outcomes.

The efficacy against virological endpoints in initially HPV-naïve subjects who received 2 doses of bivalent vaccine at month 48 indicates that the two-dose schedule prevents HPV-16/18 infection in subjects who did not receive a complete 3-dose vaccination course.

In the randomized comparisons, in one study, incident infections with any of the vaccine types in the quadrivalent vaccine were more common in the 2-dose than the 3-dose group.

Summary of Findings

2-dose schedule versus 3-dose schedules

Observational data overall support the findings from the trials.

However it should be noted that

girls or women receiving 2 doses probably differ from those receiving 3, in particular they may have different exposure to infection, adjustment for confounding is unlikely to remove all of this difference

Summary of Findings

2-dose schedule versus 3-dose schedules

Interval between doses

Two RCTs compared two 2-dose schedules with different intervals (0, 6 and 0, 12 months).

Data from one of them reported that the 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years).

Mathematical models

UK and Canadian models:

under the hypothetical assumption that a female-only two dose schedule has a duration of protection of at least 20 years, then there will be few additional cases prevented by adding a third dose

EMEA assessment

…as the immune responses are comparable between the reduced dose schedule in the target population (9-14 years old girls) and the standard schedule in the population where clinical protection was demonstrated…..

CHMP endorsed the introduction of a two dose (0,6 months) schedule in girls aged 9-14 years

Research Priorities 1

- Follow up of the cohorts under study in India and duplicate similar studies especially in LMICs.

- Definition of end points for second generation vaccines to provide additional guidance for the evaluation of alternative schedules, different intervals between doses in different epidemiological settings.

- Head to head comparisons of the two licensed vaccines of various alternative schedules.

- Longer-term clinical effectiveness studies to define the duration of protection after a 3-dose or 2-dose schedules, and whether a booster may be needed.

Research Priorities 2

- Studies in regions where high rates of vaccination have not yet occurred because of high herd protection conferred by the 3-dose regimen.

- Multicenter studies in LICs in healthy adolescent girls and special populations to provide additional evidence.

- Systematically review and assess the available (and limited) data on the impact of various schedules among HIV-infected individuals.

- Explore the impact of cost-effectiveness of 2-dose vs. 3-dose in LMICs.

- The US National Cancer Institute (NCI) is considering an RCT to assess the effect on persistence of DNA and immunogenicity of HPV vaccines after 1 or 2 doses in an area with low to moderate vaccine uptake.

Support?