2-Dose Human Papillomavirus (HPV) Vaccination Schedules

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Advisory Committee on Immunization Practices
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Overview

- Background
- Recommendations/regulatory approvals
- Data on 2-dose schedules
- Countries using 2-dose schedules
- Considerations for the US
- Work Group plans

Background
HPV vaccines licensed in the United States

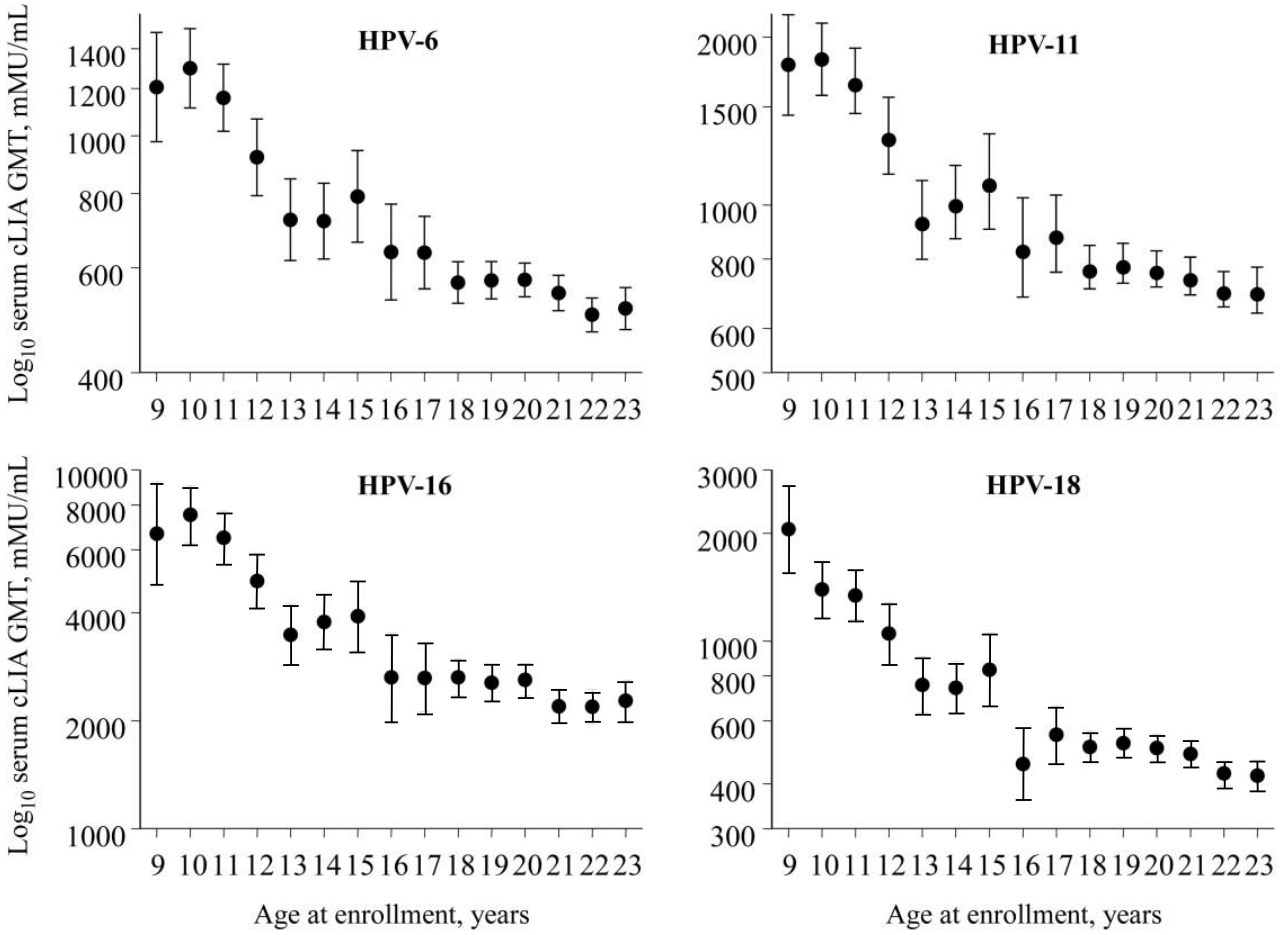
	Quadrivalent (HPV4) (Gardasil)	**Bivalent (HPV2)** (Cervarix)
HPV types	6, 11, 16, 18	16, 18
Adjuvant	AAHS	ASO4
Licensed	Females and males ages 9-26 yrs	Females ages 9-25 yrs
Schedule	3 doses (0, 2, 6 months)	3 doses (0,1, 6 months)

AAHS: 225 μg amorphous aluminum hydroxyphosphate sulfate
AS04: 500 μg aluminum hydroxide and 50 μg 3-O-desacyl-4'monophosphoryl lipid A

Background
Data required for licensure of currently available HPV vaccines

- **Efficacy trials in 15-26 year olds**
  - Endpoints – precancer lesions
- **Bridging immunogenicity trials in 9-15 year olds**
  - Licensure in this age group based on non-inferior antibody response compared with women in efficacy trials

Background
GMTs one month after 3rd dose of HPV4, by age at enrollment



Giuliano, et al. JID 2007

Background
HPV vaccines - immunogenicity

- Main basis of protection is neutralizing antibody
- The minimum protective antibody threshold not known
- Vaccination induces antibody titers higher than natural infection
- In clinical trials, some HPV4 vaccinees lost detectable HPV 18 antibody*, but no loss of protection

*by competitive Luminex immunoassay

Interest in 2-dose or alternative schedules

- Global interest in simplified schedules for HPV vaccine
- More convenient for providers, parents and vaccinees
- Facilitate implementation
  - Reduce logistical challenges
  - Decrease resource needs

Immunologic basis of HPV vaccination schedules

- 3-dose schedule (0, 1-2, 6 months) can be considered a "prime-prime-boost"
- 2-dose schedule (0, 6 months) can be considered "prime-boost"
- Memory B cells require at least 4-6 months to mature and differentiate into high-affinity B cells*
  - 6 month interval between first and last dose allows last dose to efficiently reactivate memory B cells

*Siegrist. Chapter 2. Vaccine Immunology. In Vaccines 2013

WHO's Strategic Advisory Group of Experts (SAGE) on Immunization, April 2014

- SAGE recommends a 2-dose HPV vaccination schedule for girls, if vaccination is initiated prior to 15 years of age
  - Minimal interval between 2 doses is 6 months
  - Interval may be extended to 12 months if facilitates administration
- 3-dose schedule remains necessary if immunization is initiated after the 15th birthday
- 3-dose schedule (at 0, 1-2, 6 months) remains recommended for immunocompromised individuals, including those known to be HIV-infected

http://www.who.int/immunization/sage/meetings/2014/april/report_summary_april_2014/en/
http://www.who.int/immunization/sage/meetings/2014/april/presentations_background_docs/en

Regulatory approval for 2-dose HPV vaccination schedules

- HPV2
  - Europe (EU and 5 other), Africa (18), Latin America (13), Asia (14)
- HPV4
  - Europe (EU), Africa (1), Latin America (8), Asia (1)

EU – European Union

Data provided by Merck and GSK

Consideration for 2-dose HPV vaccination schedules in the US – Regulatory issues

- **HPV2** – no submission to FDA
- **HPV4** – no plans for submission to FDA
- **9vHPV**
  - No data on 2 dose schedules included in BLA currently under consideration by FDA
  - 2 vs 3 dose trial initiated by manufacturer*

BLA, Biologics License Application; 9vHPV, investigational 9-valent HPV vaccine

*Clinicaltrials.gov NCT01984697

Data on 2-dose schedules for HPV2 and HPV4

- Immunogenicity
- Efficacy (post hoc analyses)
- Effectiveness

Data on 2-dose schedules for HPV2 and HPV4

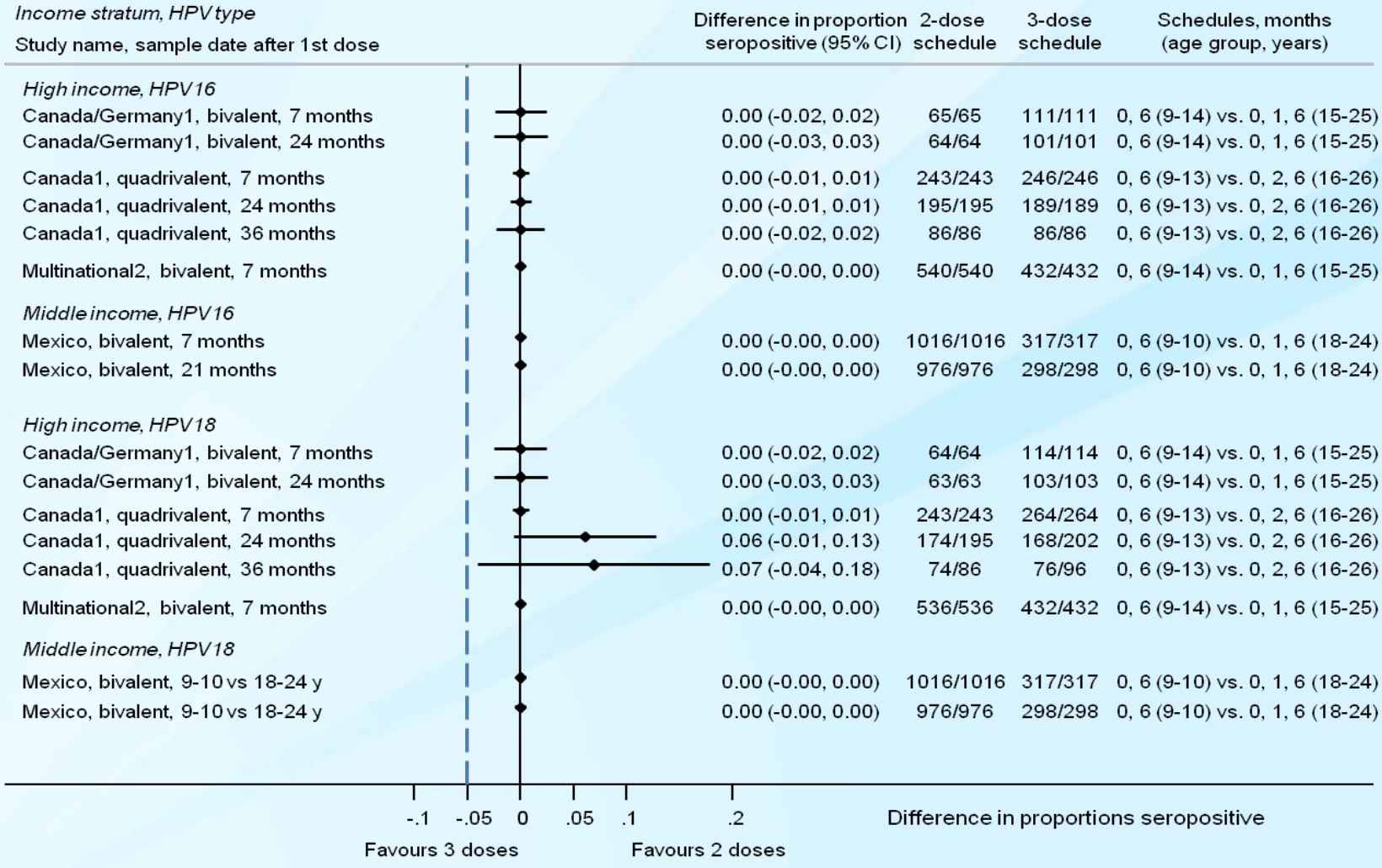
- Immunogenicity
- Efficacy (post hoc analyses)
- Effectiveness

Immunogenicity studies comparing 2 and 3 doses of HPV vaccine

Study	Country	Vaccine	Design Age and doses	Schedules	Longest followup
Romanowski (048) Hum Vaccin 2011* Hum Vaccin 2014	Canada/ Germany	HPV2	9-14 2 doses 9-14 3 doses 15-25 3 doses	0,6 0,1,6 0,1,6	24 mos 48 mos
Puthanakit (070) EUROGIN 2013 ESPID 2014	Multi-national	HPV2	9-14 2 doses 9-14 2 doses 15-25 3 doses	0,6 0,12 0,1,6	~12 mos
Lazcano-Ponce Vaccine 2014	Mexico	HPV2	9-10 2 doses 9-10 3 doses 18-24 3 doses	0,6 0,1,6 0,1,6	21 mos
Dobson JAMA 2013	Canada	HPV4	9-13 2 doses 9-13 3 doses 16-26 3 doses	0,6 0,2,6 0,2,6	36 mos
Sankaranarayanan EUROGIN 2013	India	HPV4	10-18 2 doses 10-18 3 doses	0,6 0,2,6	18 mos

*dose ranging study and included other groups as well

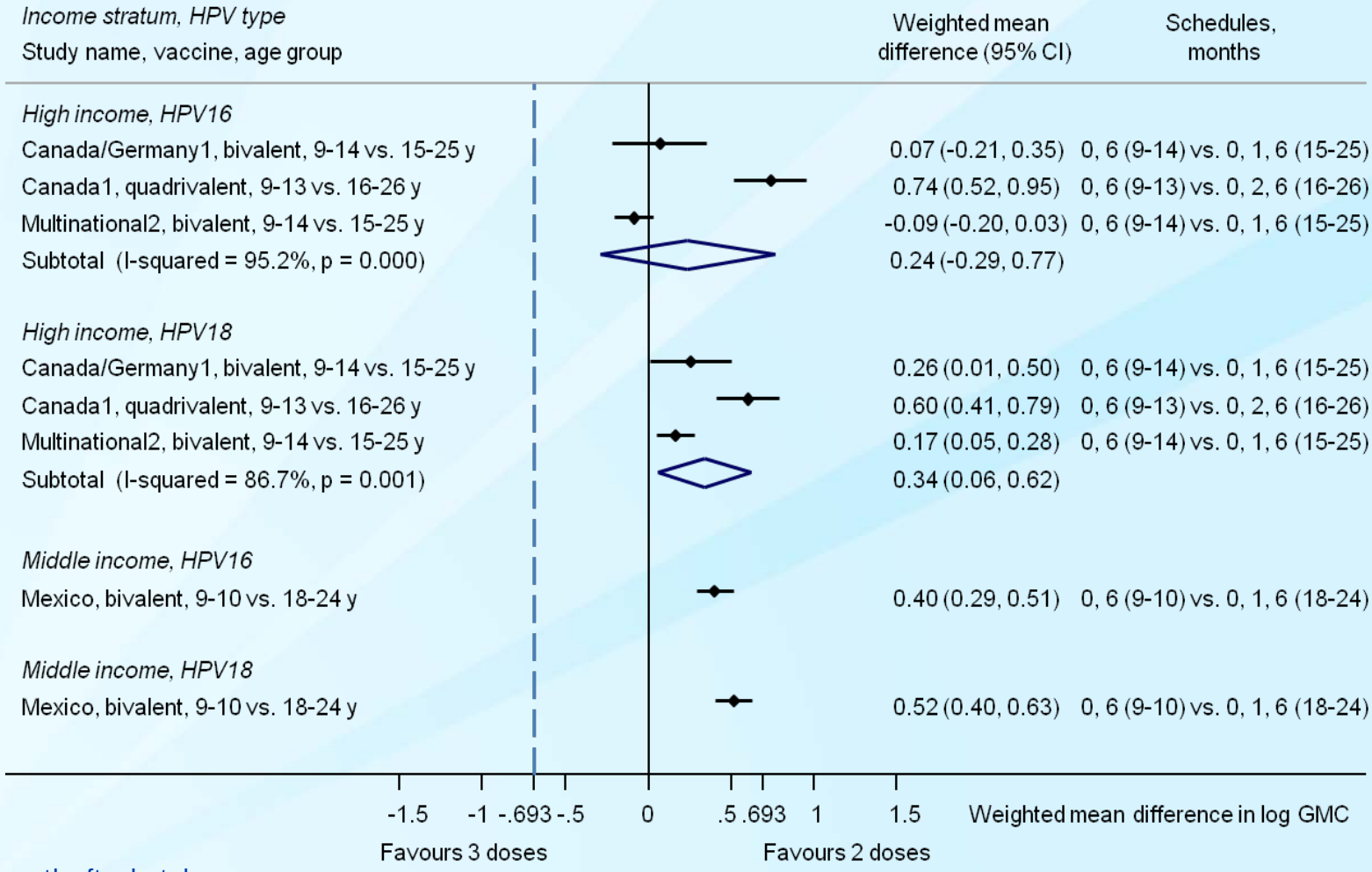
Differences in proportions seroconverting or seropositive: girls receiving 2 doses & women receiving 3 doses



D'Addario, et al. Systematic review prepared for SAGE 2014

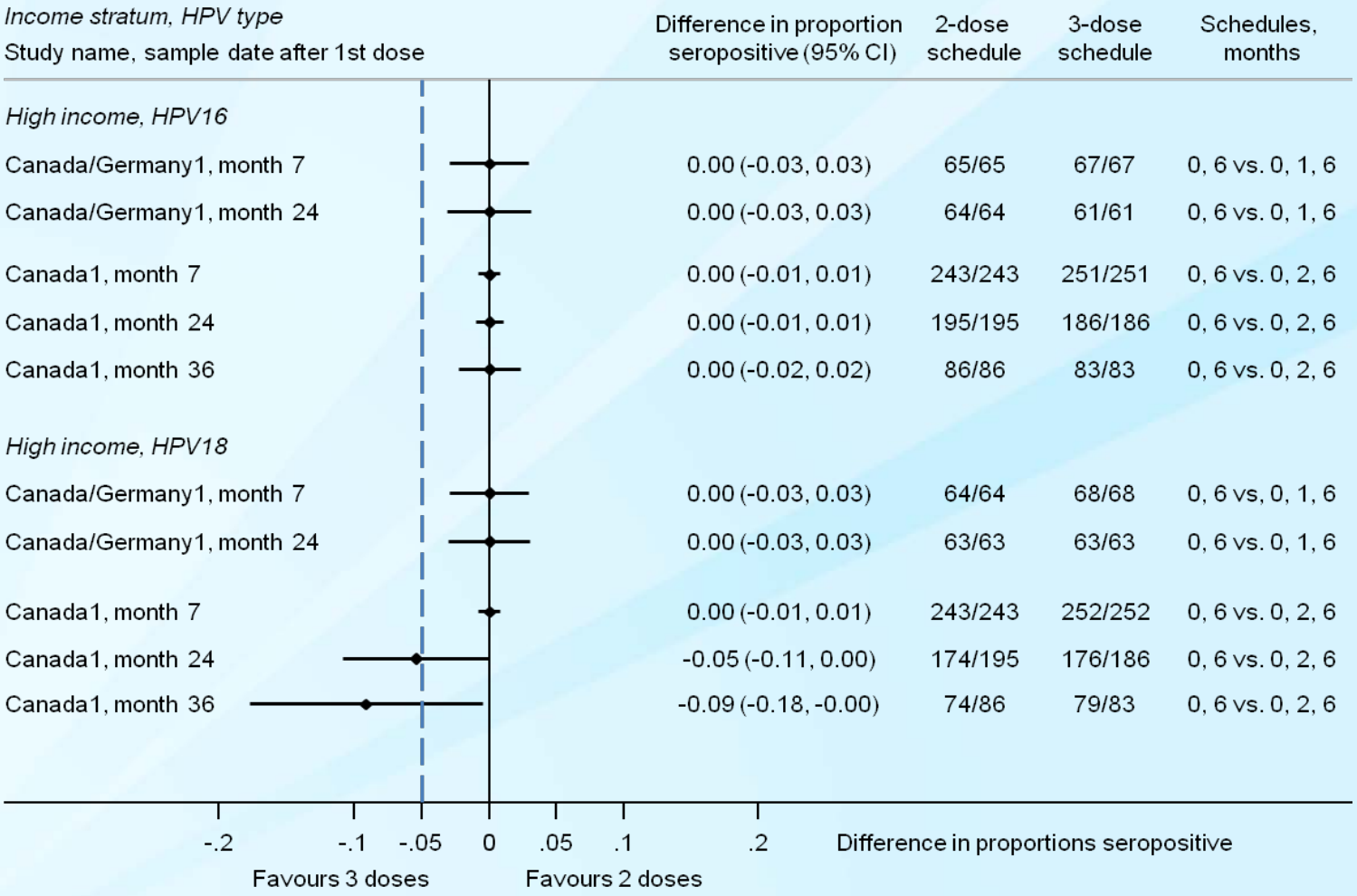
Canada1 = Dobson; Canada/Germany1 = Romanowski (Protocol 048)
Multinational 2= Protocol 070

Weighted mean differences between GMCs*: girls receiving 2 doses & women receiving 3 doses



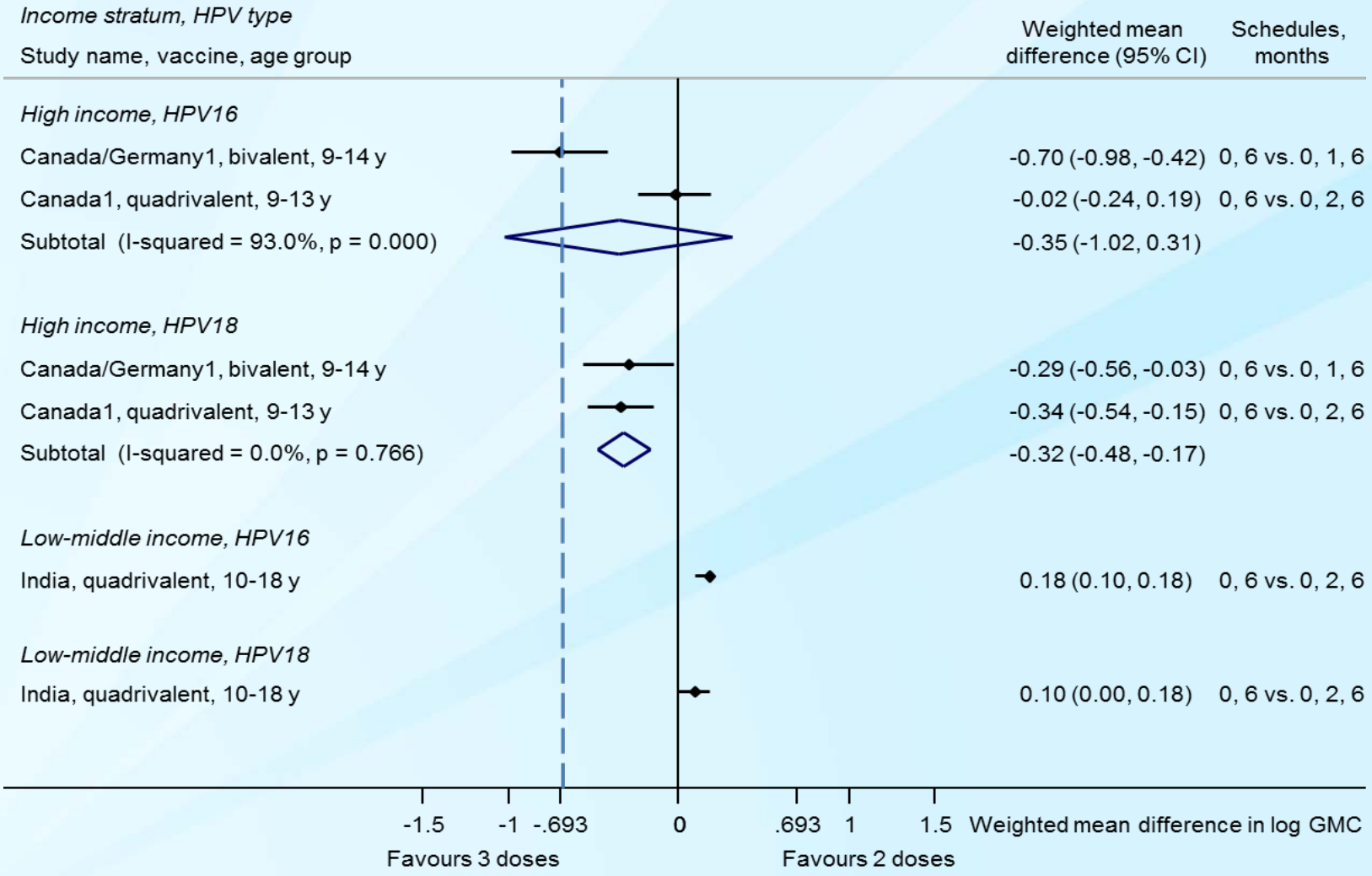
*One month after last dose

Differences in proportions seroconverting or seropositive between girls receiving 2 or 3 doses



D'Addario, et al. Systematic review prepared for SAGE 2014 Canada1 = Dobson; Canada/Germany1 = Romanowski (Protocol 048)

Weighted mean differences between GMCs: girls receiving 2 or 3 doses, 1 month after last dose



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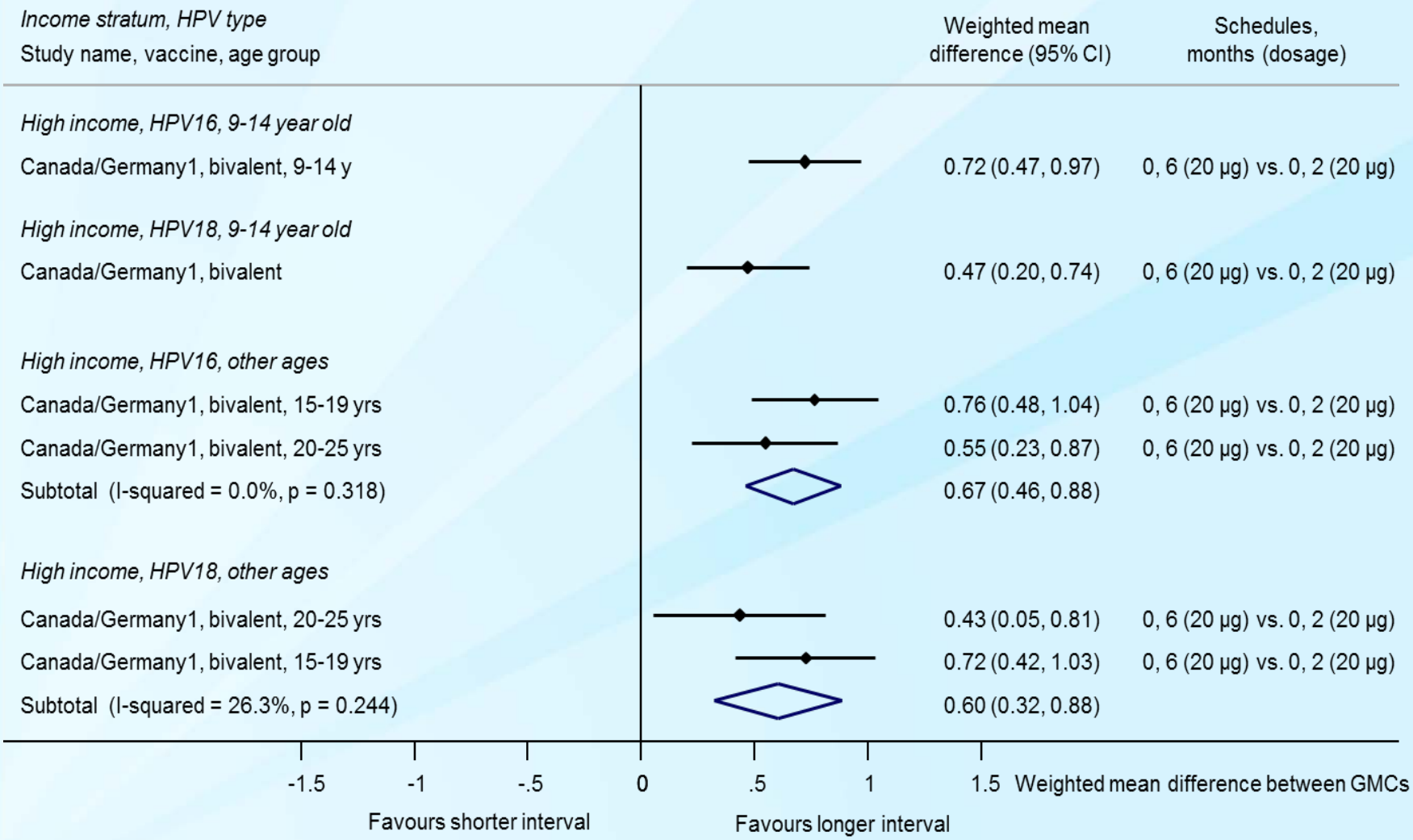
Comparison of different interval 2-dose schedules, HPV2 vaccine



D'Addario, et al. Systematic review prepared for SAGE 2014

Canada/Germany1 = Romanowski (Protocol 048)

Bivalent HPV vaccine (HPV2): data on 2-dose schedules

- **Immunogenicity data**
  - Study HPV-048[a] (Canada/Germany)
  - Study HPV-070[b] (Multinational)
- **Efficacy data**
  - Post hoc analysis of Costa Rica efficacy trial[c]
  - Post hoc analysis of GSK pivotal efficacy trial (unpublished)

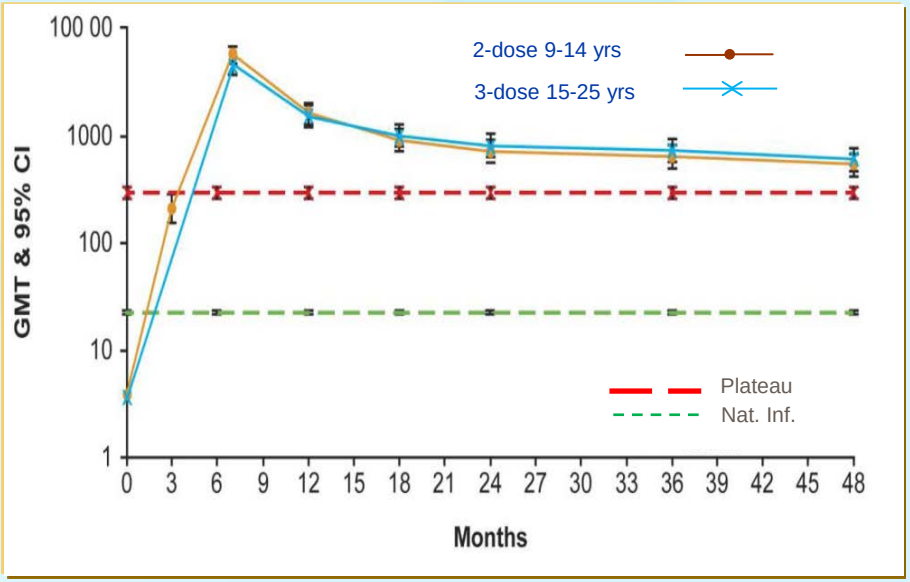
[a]Romanowski et al, Hum Vaccin 2011 and 2014
[b]Puthanakit et al, EUROGIN 2013
[c]Kreimer et al, JNCI 2011

HPV2 immunogenicity trial: 2 vs 3 doses (protocol 048)

- Dose ranging and 2 vs 3 dose trial
- 48 month follow-up: licensed formulation in 2 groups
  - 2 doses in 9-14 year olds and 3 doses in15-25 year olds

- All subjects remained seropositive for HPV16 and 18 by ELISA at month 48
- GMTs non-inferior for 2 dose group compared with 3 dose group
- Antibody kinetics similar in both groups

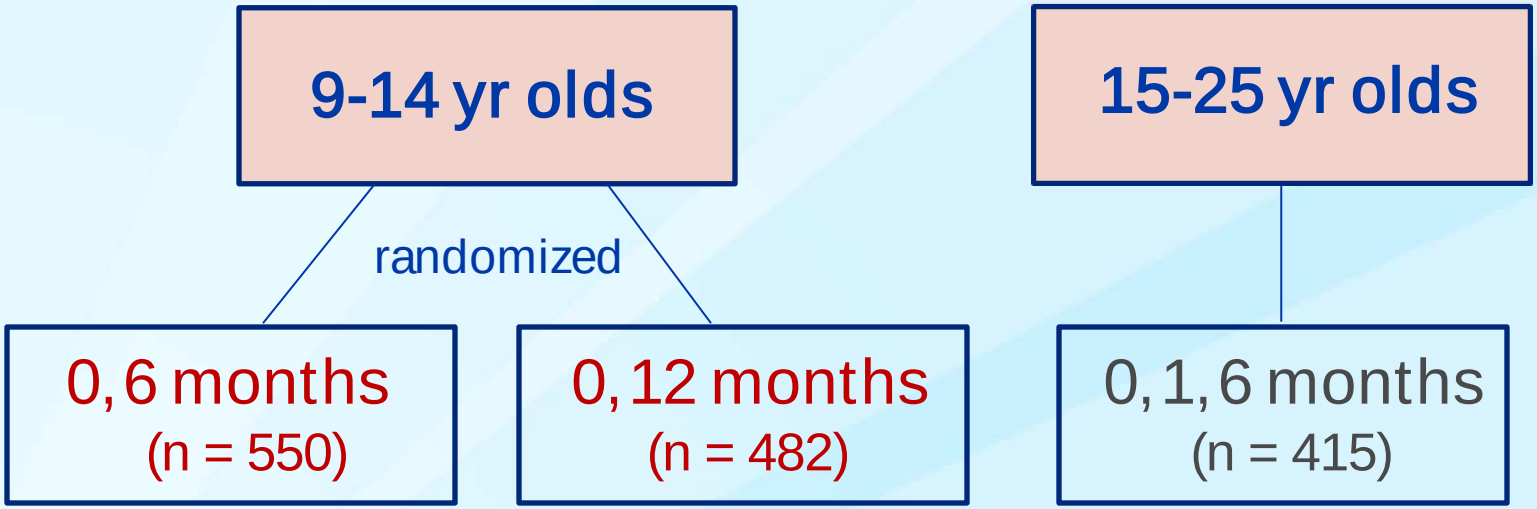
HPV 18 GMTs



Romanowski et al, Hum Vaccin 2014

Natural infection: GMT in subjects who had cleared a natural infection
Plateau: GMT at the plateau level (Month 45–50) after vaccination

HPV2 immunogenicity trial: 2 vs 3 doses (protocol 070)

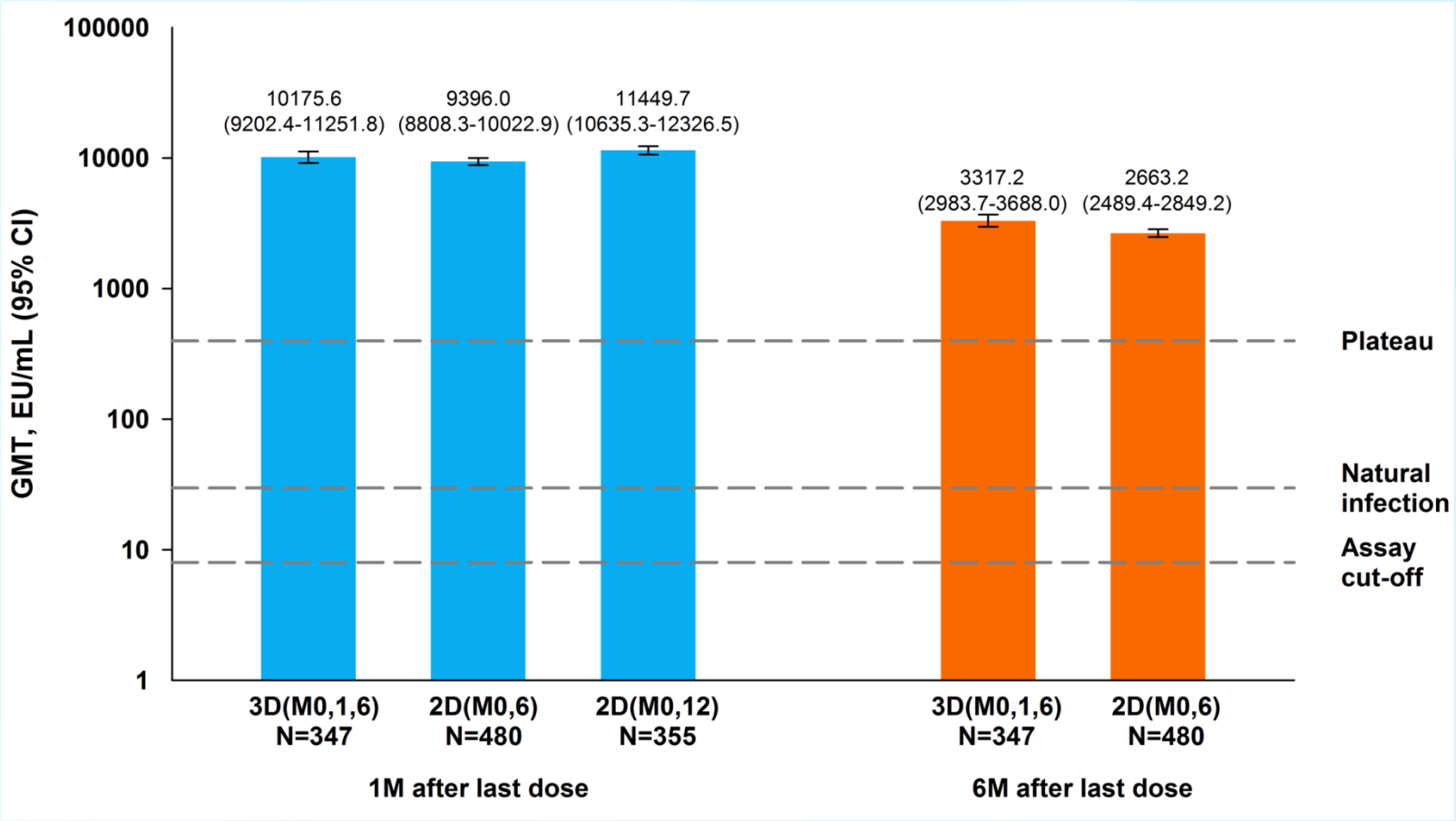


*referred to as "multinational" in SAGE review

http://www.gsk-clinicalstudyregister.com

HPV2 immunogenicity trial: 2 vs 3 doses (protocol 070)

HPV 16 GMTs at 1 month and 6 months after last dose



ELISA, initially seronegative participants

Post-hoc evaluation of efficacy against persistent infection, HPV2 trial, Costa Rica

- RCT in women aged 18-25 yrs; 20% received less than 3 doses
- Endpoint was incident infection that lasted at least 10 months*

Doses	Arm	N	Events	%	VE	(95% CI)
3 doses	HPV	2957	25	0.8%	**80.9%**	(71.1, 87.7)
	Control	3010	133	4.4%		
2 doses	HPV	422	3	0.7%	**84.1%**	(50.2, 96.3)
	Control	380	17	4.5%		
1 dose	HPV	196	0	0.0%	**100.0%**	(66.5, 100)
	Control	188	10	5.3%		

*Excludes women DNA positive to HPV 16/18 and those with no follow-up; Median time of follow-up post first dose, 4.2 yrs

Kreimer A, et al. JNCI 2011

Post-hoc evaluation of efficacy against 6 month persistent infection, HPV2 trial (protocol 008)

- Pivotal RCT in 15-25 yr old females (N=18,729)
- 997(5%) received 2 doses

Doses	Arm	N	Events	VE	(95% CI)
3 doses	HPV	5427	35	**93.7%**	(91.1,95.6)
	Control	5339	521		
2 doses	HPV	117	0	**100%**	(33.1, 100)
	Control	118	7		

*HPV-naïve at enrollment, with follow-up information

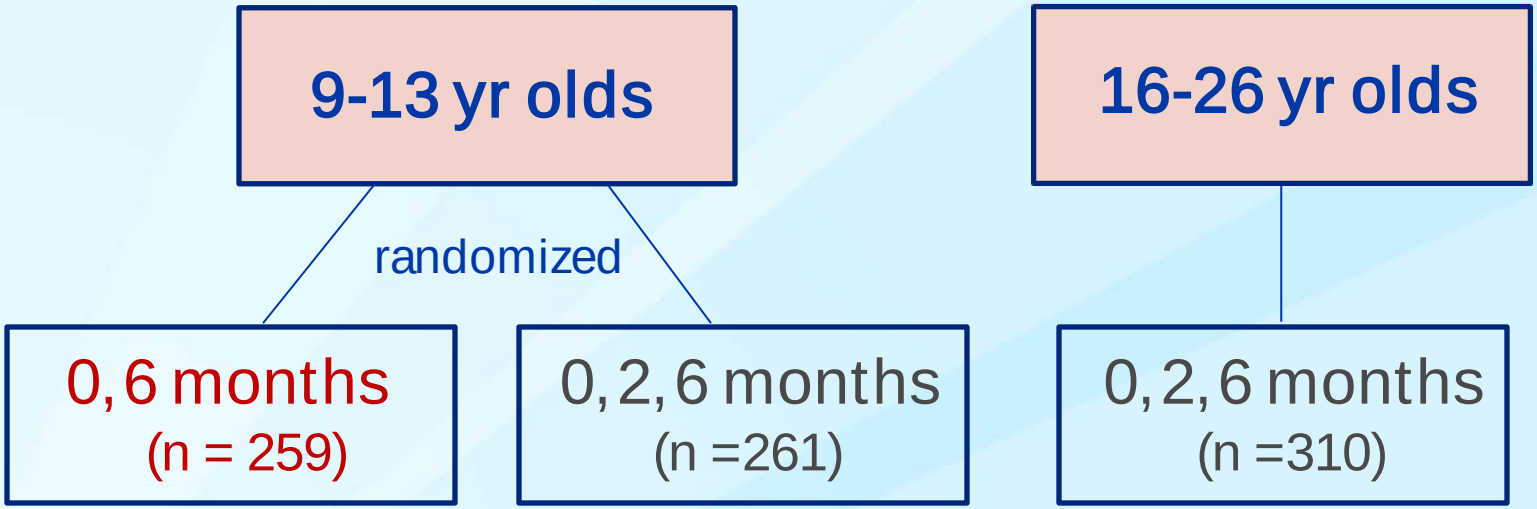
GlaxoSmithKline. *GSKBio_WWMA_DoF068_1_2011*, Data on file. 2011; Assessment report, EMA/789820/2013

Quadrivalent HPV vaccine (HPV4): data for 2-dose schedules

- **Immunogenicity data**
  - 2 doses in younger adolescents vs 3 doses in young women[a]
  - Alternative 3-dose schedules in girls 11 to 13 years[b]

[a]Dobson, et al. JAMA 2013
[b]Neuzil, et al. JAMA 2011 and LaMontagne, et al. JID 2014

HPV4: 2-dose vs 3-dose immunogenicity trial, Canada



Dobson, et al. JAMA 2013

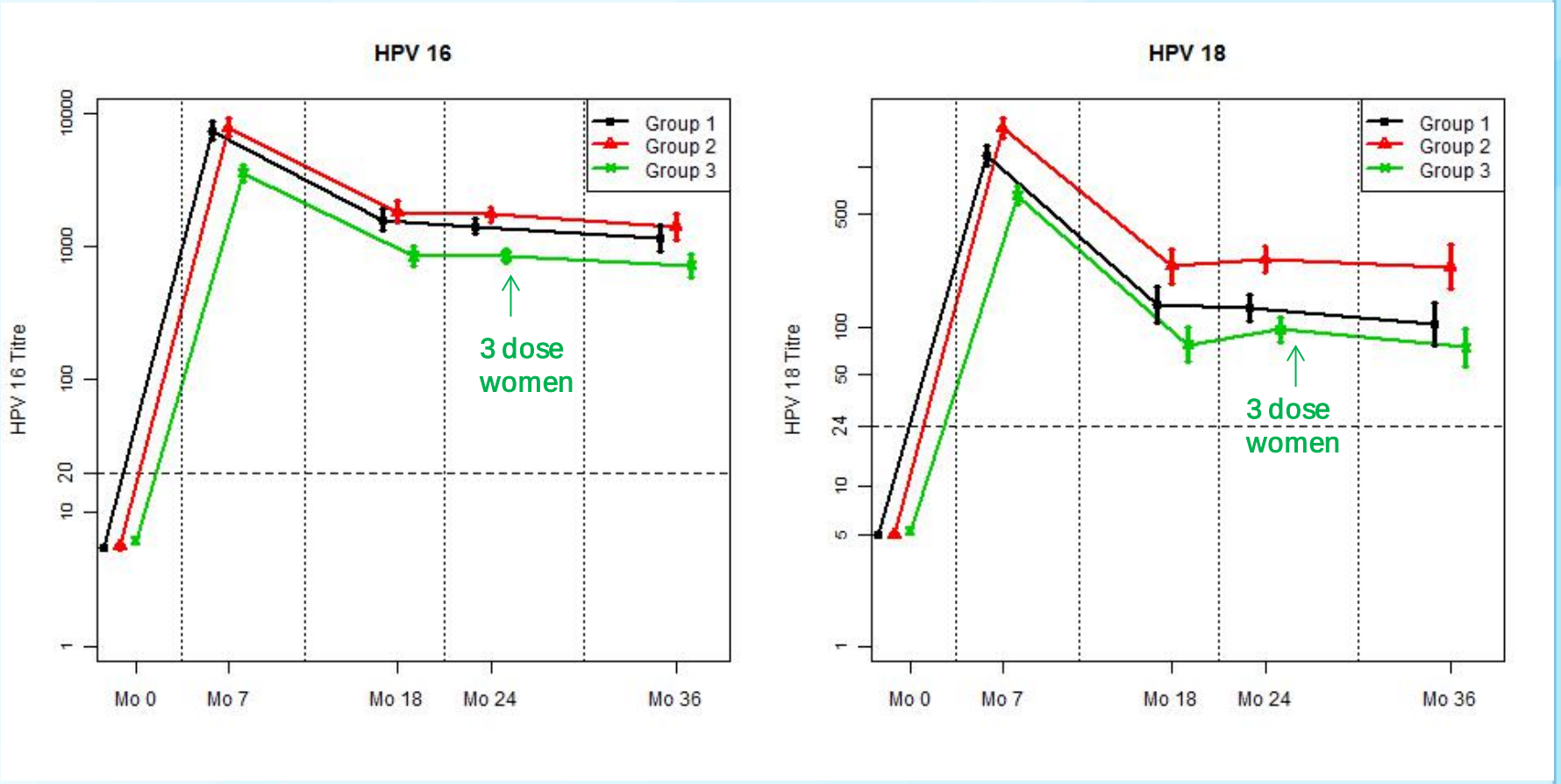
HPV4: 2-dose vs 3-dose immunogenicity trial
(36 month results)

HPV Type	2 dose 9-13 yrs/3 dose 16-26 yrs		2 dose 9-13 yrs/3 dose 9-13 yrs	
	GMT ratio	(95% CI)	GMT ratio	(95% CI)
HPV 6	1.36	(0.97, 1.90)	0.64	(0.46, 0.90)
HPV 11	1.43	(1.03, 1.99)	0.73	(0.52, 1.02)
HPV 16	1.70	(1.16, 2.49)	0.81	(0.55, 1.20)
HPV 18	1.46	(0.88, 2.41)	0.43	(0.26, 0.73)

- **Main analysis comparing 2-dose 9-13 yrs with 3-dose 16-26 yrs**
  - Non-inferiority criteria met
  - Antibody response generally higher in the 9-13 yr olds
- **Analysis comparing 2-dose and 3-dose 9-13 yrs**
  - Non-inferiority lost for HPV 18 by 24 months and HPV 6 by 36 months

Dobson, et al, JAMA 2013

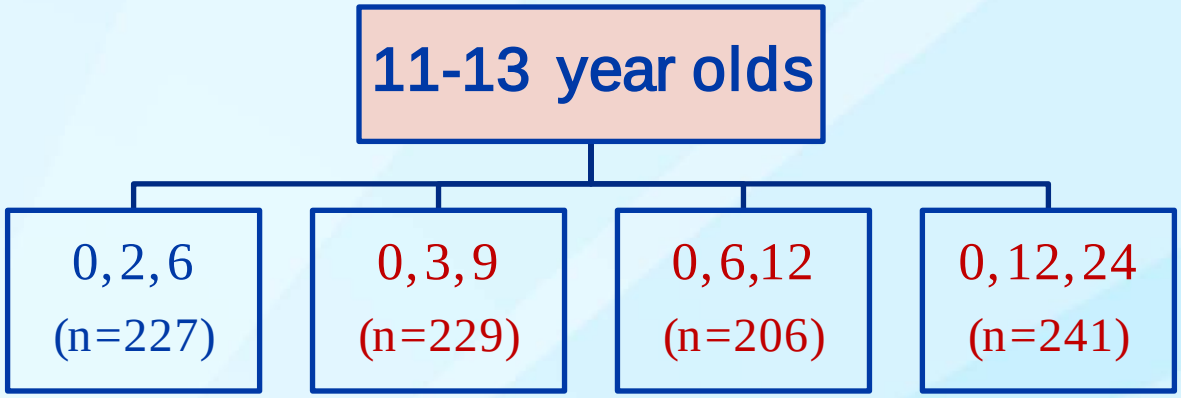
HPV4: 2-dose vs 3-dose immunogenicity trial
HPV 16 and 18 GMTs



Green = 3 dose women; **Black** = 2 dose girls, **Red** = 3 dose girls

From: Dobson, et al, JAMA 2013

HPV4: Randomized trial of alternative 3-dose schedules, Vietnam



- **Results**
  - GMTs1 month post dose 3
    - 0,3,9 and 0,6,12 schedules: non-inferiority criteria met for all types
  - GMTs 29-32 months post dose 3
    - All schedules: non-inferiority criteria met for all types

Neuzil, et al. JAMA 2011; LaMontagne, et al. JID 2013

HPV4: Randomized trial of alternative 3-dose schedules, post dose 2 GMTs

- Serology sample drawn pre and post dose 3
- Trend for higher antibody levels pre dose 3 with increasing intervals between dose 1 and dose 2

Schedule (months)	Pre dose 3 HPV 16 GMT (95% CI)	Months between dose 2 & blood draw
0, 2, 6	657 (573, 752)	4
0, 3, 9	881 (776, 999)	6
0, 6, 12	921 (748, 1133)	6
0, 12, 24	1581 (1373,1821)	12

Neuzil, et al. JAMA 2011

Data on 2-dose schedules for HPV2 and HPV4

- Immunogenicity
- Efficacy (post hoc analyses)
- Effectiveness

Post-licensure monitoring of HPV vaccine impact

- Population level impact on some early outcomes* has been demonstrated in countries with high as well as those with low or moderate vaccine coverage
  - Australia
  - Denmark
  - Germany
  - New Zealand
  - Scotland
  - Sweden
  - United Kingdom
  - United States

*HPV vaccine type prevalence, genital warts, cervical lesions

Studies that examined HPV vaccine effectiveness by number of doses

Study	Country /vaccine	Design	Outcome
Gertig BMC Med 2013	Australia **HPV4**	Retrospective cohort study using linked registry data	Cytological and histological cervical abnormalities
Crowe BMJ 2014	Australia **HPV4**	Case-control study using linked registry data	Histologically confirmed high grade cervical lesions
Herweijer JAMA 2014	Sweden **HPV4**	Open cohort using nationwide health data registers	Condyloma
Kavanagh BJC 2014	Scotland **HPV2**	Cross section of women screened for cervical cancer	HPV prevalence

Challenges and Limitations:

- Outcomes in 'catch-up' population
- Differences between 2 and 3 dose recipients
- Evaluations do not examine 0,6 month 2-dose schedule

HPV4: Effectiveness for prevention of cervical abnormalities, Australia

Outcome/doses	No. woman doses	No. of abnormalities	Rate	Hazard Ratio
CIN3/AIS				
unvaccinated	15,192	61	2.8	1.0
1 dose	2,568	12	4.3	1.40 (.75, 2.61)
2 doses	3,412	11	2.7	0.87 (.46, 1.67)
3 doses	21,199	47	1.5	0.53 (.36, .77)
CIN2				
unvaccinated	15,192	87	4.0	1.0
1 dose	2,568	16	5.7	1.29 (.76, 2.20)
2 doses	3,412	18	4.4	0.99 (.59, 1.64)
3 doses	21,199	88	2.9	0.70 (.52, .94)

Gertig, et al. BMC 2013

HPV4: Effectiveness study in Australia (cont.)

- Compared with women who received 3 doses:
  - Women who received 1 or 2 doses
    - Younger age at first screening (earlier sexual debut)
    - Older at vaccination
    - Lower SES

Gertig, et al. BMC 2013

HPV4: Effectiveness study for prevention of cervical abnormalities, Australia (case - control study)

	Controls	High grade cases	Adjusted OR
11-27 yrs			
unvaccinated	53,032	729	Ref
1 dose	9,535	114	0.95 (.77, 1.16)
2 doses	10,850	100	0.79 (.64, .98)
3 doses	22,987	119	0.54 (.43, .67)
15-18 yrs			
unvaccinated	9,918	101	Ref
1 dose	2,564	22	0.86 (.54, 1.37)
2 doses	4,195	31	0.77 (.51, 1.16)
3 doses	15,367	59	0.43 (.31, .62)

Crowe, et al. BMJ 2014

HPV4: Effectiveness for prevention of condyloma, Sweden

- Open cohort of all females aged 10 – 24 yrs living in Sweden
- Followed 2006 – 2010 using population-based health registers
- >1 million females; 20,383 genital wart cases

Girls vaccinated at 10-16 years

Number of doses	Incidence ratio	(95% CI)
Unvaccinated	Ref	-
1 dose	0.31	(.20, .49)
2 doses	0.29	(.21, 40)
3 doses	0.18	(.15, .22)

- Main analysis used 3 months between vaccination and case counting
  - With a time ≥5 months, no statistically significant difference in the risk of condyloma between 2 and 3 doses recipients

Herweijer, et al. JAMA 2014

HPV2: Effectiveness for prevention of HPV vaccine type prevalence, Scotland

- Cross sectional study, women aged 20 – 21 yrs presenting for cervical cancer screening
- 4729 samples tested from 2009 – 2012
- Data linked to immunization registries

Number of doses	Adjusted OR	(95% CI)
Unvaccinated	Ref	-
1 dose	0.95	(.51, 1.76)
2 doses	0.68	(.42, 1.12)
3 doses	0.43	(.34, .55)

Kavanagh, et al. BJC 2014

Summary: 2-dose schedules

- **Immunogenicity**
  - HPV2 and HPV 4: GMTs non-inferior after 2 doses given 6 mos apart in young adolescent girls compared with 3 doses (0,1-2 , 6 mos) in 15-26 yr olds
  - HPV2 and HPV4: GMTs lower but non-inferior after 2 doses (0,6 mos) compared with 3 doses (0,1-2, 6 mos) in young adolescents; HPV4: non-inferiority lost for HPV 6 and 18 at later time points
  - HPV2 and HPV4: GMTs higher with longer interval between doses for 2-dose schedules

Summary: 2-dose schedules

- **Efficacy**
  - HPV2: 2 small post-hoc efficacy analyses found high efficacy with 2 doses
  - HPV4: More data available in future from study in India?
- **Effectiveness**
  - 4 post-licensure effectiveness evaluations evaluated number of doses: HPV4 (3 studies) and HPV2 (1 study)
  - Lower effectiveness found for 2 vs 3 doses
  - However, there are limitations and challenges with post licensure effectiveness evaluations:
    - 2-dose recipients did not receive 0,6 month schedule
    - Differences between 2-dose and 3-dose recipients
    - Outcomes in 'catch-up' population

Remaining questions

- Differences in duration of protection for 2- and 3-dose schedules?
  - Longer follow-up will be available from some studies
  - Modeling studies suggest*
    - If 2-dose schedules protect for 20 years, then the benefits of the 3rd dose are small
    - If 2 doses protect for 10 years, then the 3rd dose may prevent as many cancers as the first 2 doses

*Jit et al. Vaccine 2014:32

Examples of national/provincial programs with 2-dose or "extended 3-dose" (0, 6, 60 months) schedules

- **Quebec, Canada**
  - Implemented extended HPV4 3-dose schedule in 2008
  - Changed to HPV4 2-dose schedule in 2013
- **British Columbia, Canada**
  - Changed from HPV4 3-dose schedule to extended HPV4 3-dose schedule in 2010
- **Mexico**
  - Using extended 3-dose schedule (since national program 2012)
- **Switzerland**
  - Changed from 3-dose to 2-dose schedule for 11-14 yr olds in 2012
- **England**
  - Will change from HPV4 3-dose to HPV4 2-dose schedule in fall of 2014*

*https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310958/HPV_Joint_Letter_14_May.pdf

Regulatory consideration of 2-dose HPV vaccination schedules in the US

- **HPV2** – no submission to FDA
- **HPV4** – no plans for submission to FDA
- **9vHPV**
  - No data on 2 doses included in BLA currently under consideration by FDA
  - 2 vs 3 dose trial initiated by manufacturer

BLA, Biologics License Application

9vHPV - 2 vs 3 dose trial

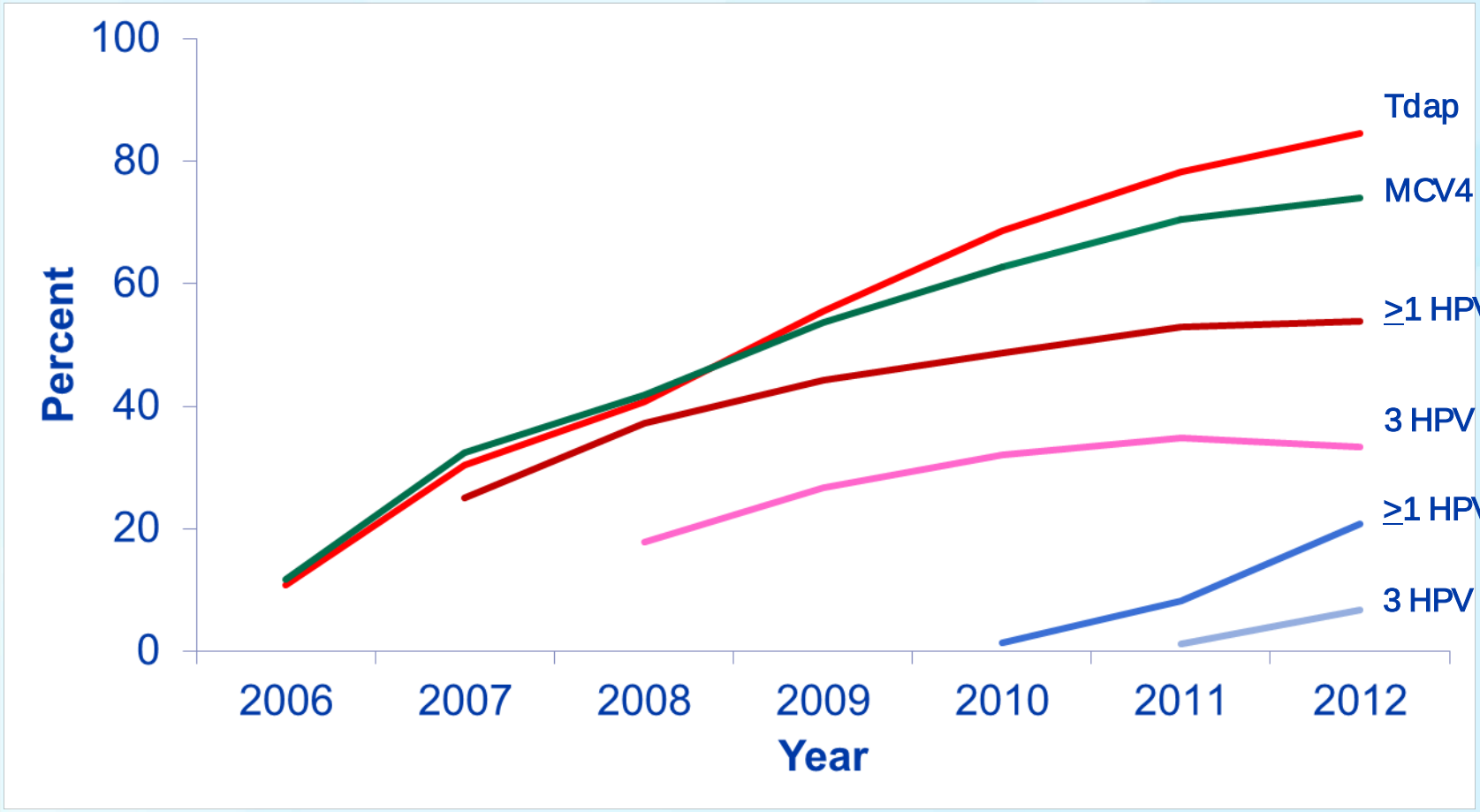
- Immunogenicity trial
- Start date: 12/2013; last visit: 7/2015
- 5 arms (N=1500)
  - 2 doses 0,6 months: 9-14 yr old girls
  - 2 doses 0,6 months: 9-14 yr old boys
  - 2 doses 0,12 months: 9-14 yr old girls and boys
  - 3 doses 0,2,6 months: 9-14 yr old girls and boys
  - 3 doses 0,2,6 months: 15-26 yr old women

Clinicaltrials.gov identifier NCT01984697

Summary HPV vaccine WG plans

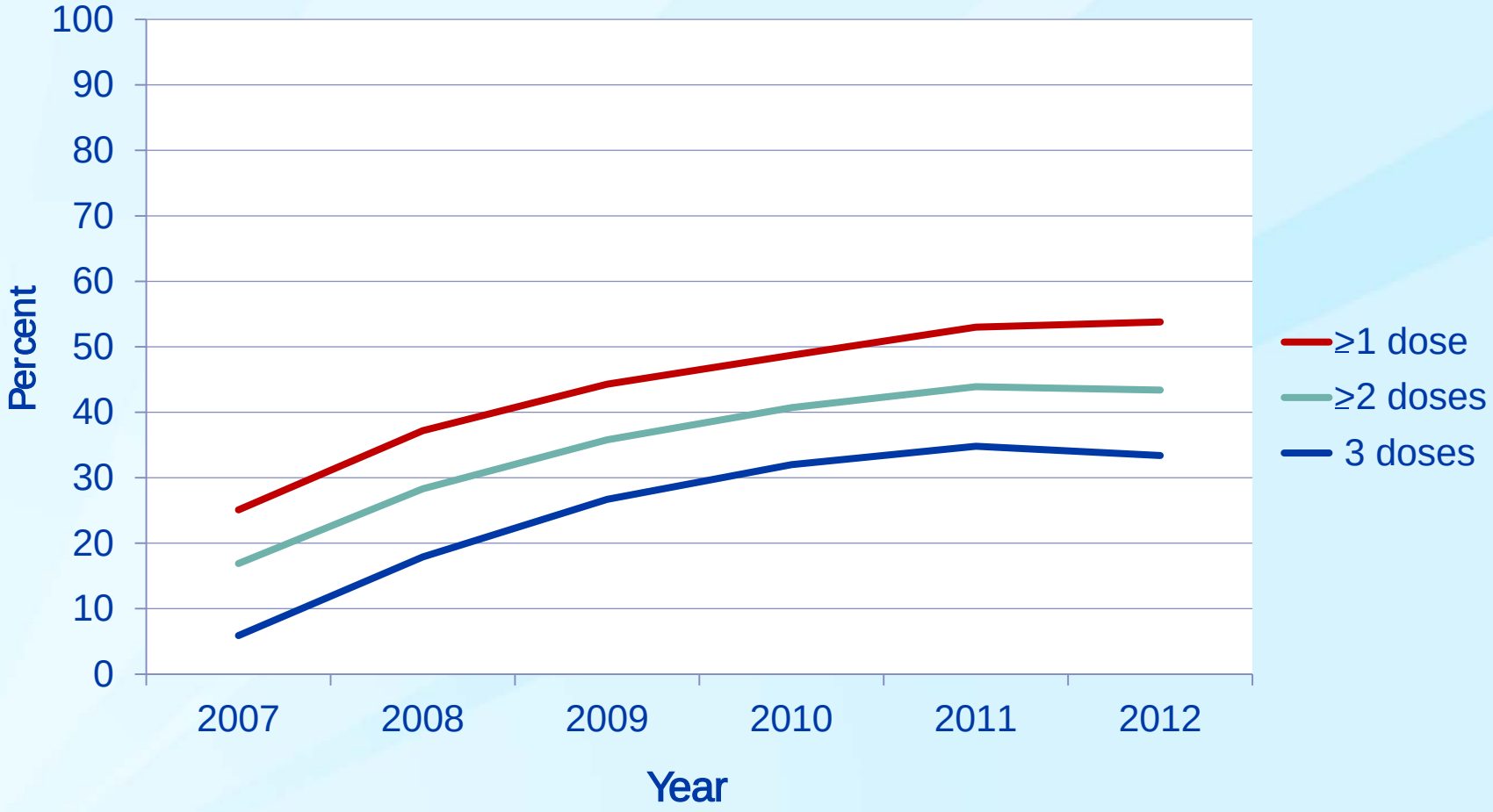
- **Review and consider 9vHPV as 3-dose schedule**
  - Consider 2-dose schedules when data from 2 vs 3 dose trial of 9vHPV available
- **Other options discussed:**
  - Consider a 2-dose schedule now for HPV2 and HPV4 in 9-14 year-olds
  - If a 2-dose schedule is recommended, options when 9vHPV licensed?
    - Wait until there are data for a 2-dose schedule before considering recommendations for 9vHPV
    - Recommend 9vHPV as 3-dose schedule
    - Recommend 9vHPV as 2-dose schedule, with no data

National estimated vaccination coverage levels among adolescents 13-17 years, NIS-Teen 2006-2012



Source: MMWR 2013;62;685-93

National estimated HPV vaccination coverage, by number of doses among females 13-17 years, NIS-Teen 2007-2012



Source: MMWR 2013;62;685-93

Estimated ACIP timeline

ACIP Date	Topic
Feb 2014	Attribution of types in HPV-associated disease 9vHPV clinical trial data
June 2014	9vHPV clinical trial data Policy questions to be addressed
Oct 2014	GRADE 9vHPV Economic analyses 9vHPV clinical trial data (Immunogenicity: males 16-26 years) Recommendation options
Feb 2015	Estimated earliest possible vote on 9vHPV
Oct 2015	Potential data from 9vHPV 2-dose trial

Acknowledgements

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Shannon Stokley
Elizabeth Unger

ACIP HPV Vaccine WG

Thank you

For more information please contact Centers for Disease Control and Prevention

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