2-dose Vaccination Schedules Bivalent and Quadrivalent HPV Vaccines

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2-dose vaccination schedules for bivalent and quadrivalent HPV vaccines

- **Useful to review as ACIP considers data on 2-doses for 9-valent HPV vaccine**
  - Trials of bivalent and quadrivalent HPV vaccines provide data to consider related to 9-valent HPV vaccine decision
    - 2- vs 3-dose trials of these vaccines have longer follow-up to date than the 9-valent HPV vaccine trial
  - Recommendations for 2-dose schedules might be considered for bivalent and quadrivalent HPV vaccines

Data on 2-dose schedules for bivalent and quadrivalent HPV vaccines

- Immunogenicity
- Efficacy (post hoc analyses)
- Post-licensure effectiveness

Bivalent HPV Vaccine

Bivalent HPV vaccine
Immunogenicity trials comparing 2 and 3 doses

Study	Country	Age (yrs) and doses		Schedule (months)	Longest follow-up
Romanowski Hum Vaccin 2011* Hum Vaccin 2014 Hum Vaccin 2016	Canada, Germany	9–14 9–14 15–25 15–25	2 doses 3 doses 2 doses 3 doses	0, 6 0, 1, 6 0, 6 0, 1, 6	24 months* 60 months**
Unpublished NCT01381575	Canada, Germany, Italy, Taiwan, Thailand	9–14 9–14 15–25	2 doses 2 doses 3 doses	0, 6 0, 12 0, 1, 6	36 months
Lazcano-Ponce Vaccine 2014	Mexico	9–10 9–10 18–24	2 doses 3 doses 3 doses	0, 6 0, 1, 6 0, 1, 6	21 months

*dose ranging study, included other groups as well

**followup study of licensed formulations

Bivalent vaccine 2 vs 3 dose immunogenicity trial (proof of concept)

- Included a dose ranging component
- Follow-up study

Study	Age (yrs) and doses		Schedule (months)	Number	Longest follow-up
Romanowski	9–14	2 doses	0, 6	78	24 months*
Hum Vaccin 2011*	9–14	3 doses	0, 1, 6	82	60 months**
Hum Vaccin 2014	15–25	2 doses	0, 6	162	
Hum Vaccin 2016	15–25	3 doses	0, 1, 6	157	

Numbers for those who received licensed formulation

*Included dose ranging results **followup of licensed formulation

Bivalent vaccine
2 vs 3 dose immunogenicity trial
(proof of concept)

- 2-dose schedule (0,6 months) in girls 9-14 yrs was non-inferior to 3-dose schedule (0,1,6 months) in young adult women 15-25 yrs
- In the same age group, GMTs lower with 2-dose schedule (0,6 months) compared with the 3-dose schedule

HPV 16 GMTs at month 7 among girls 9-14 yrs

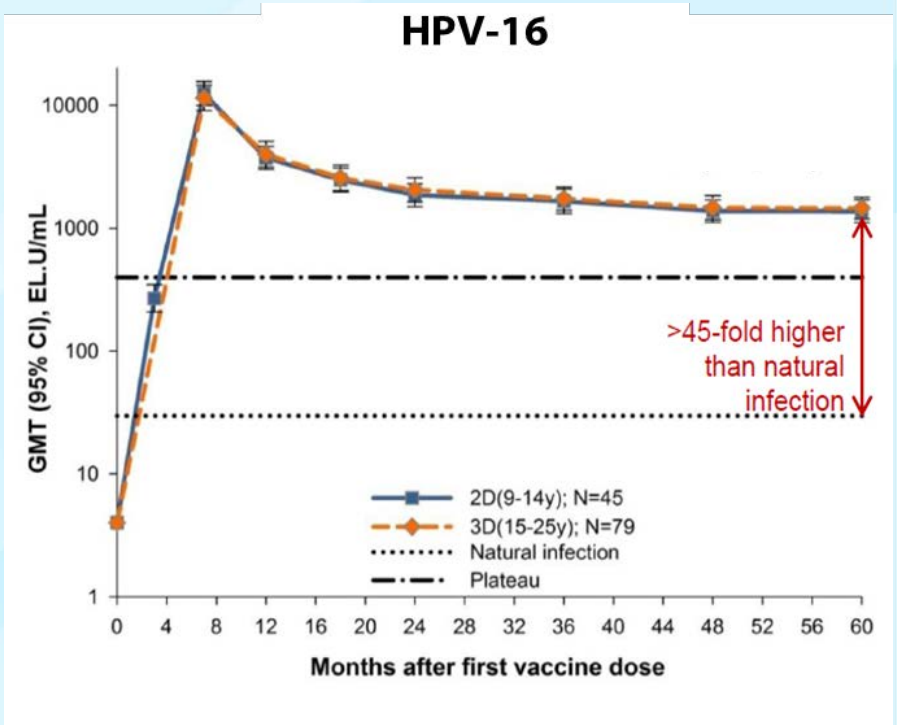
Vaccine group	HPV 16 GMTs	95% CI
2 doses	12,445	(9,930 – 15,596)
3 doses	22,813	(17,484 - 29,765)

Romanowski, et al. Hum Vaccin 2016 (and supplementary tables)

Antibody measured by ELISA

Bivalent vaccine
2 vs 3 dose immunogenicity trial
(proof of concept follow-up)

- **Follow-up of 2 groups**
  - 2 doses (0,6 months) in 9-14 yrs
  - 3 doses (0,1,6 months) in 15-25 yrs
- **All subjects remained seropositive for HPV 16/18 through month 60**
- **GMTs non-inferior in 2-dose group compared with 3-dose group**



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

Romanowski, et al. Hum Vaccin 2016

Antibody measured by ELISA

Bivalent HPV vaccine
2 vs 3 dose immunogenicity trial

Study	Age (yrs) and doses		Schedule (months)	Number	Longest follow-up
Unpublished	9–14	2 doses	0, 6	550	36 months
NCT01381575	9–14	2 doses	0, 12	415	
	15–25	3 doses	0, 1, 6	482	

Clinical Study Report HPV-070 (114700) at http://www.gsk-clinicalstudyregister.com

Clinicaltrials.gov NCT01381575

Bivalent HPV vaccine
2 vs 3 dose immunogenicity trial
(1 month after last dose)

HPV Type	2 dose 9–14 yrs (0,6 mos)/ 3 dose 15–25 yrs		2 dose 9–14 yrs (0,12 mos)/ 3 dose 15–25 yrs	
	GMT ratio	(95% CI)	GMT ratio	(95% CI)
HPV 16	0.92	(0.82, 1.03)	1.12	(0.99, 1.27)
HPV 18	1.18	(1.05, 1.32)	1.33	(1.18, 1.49)

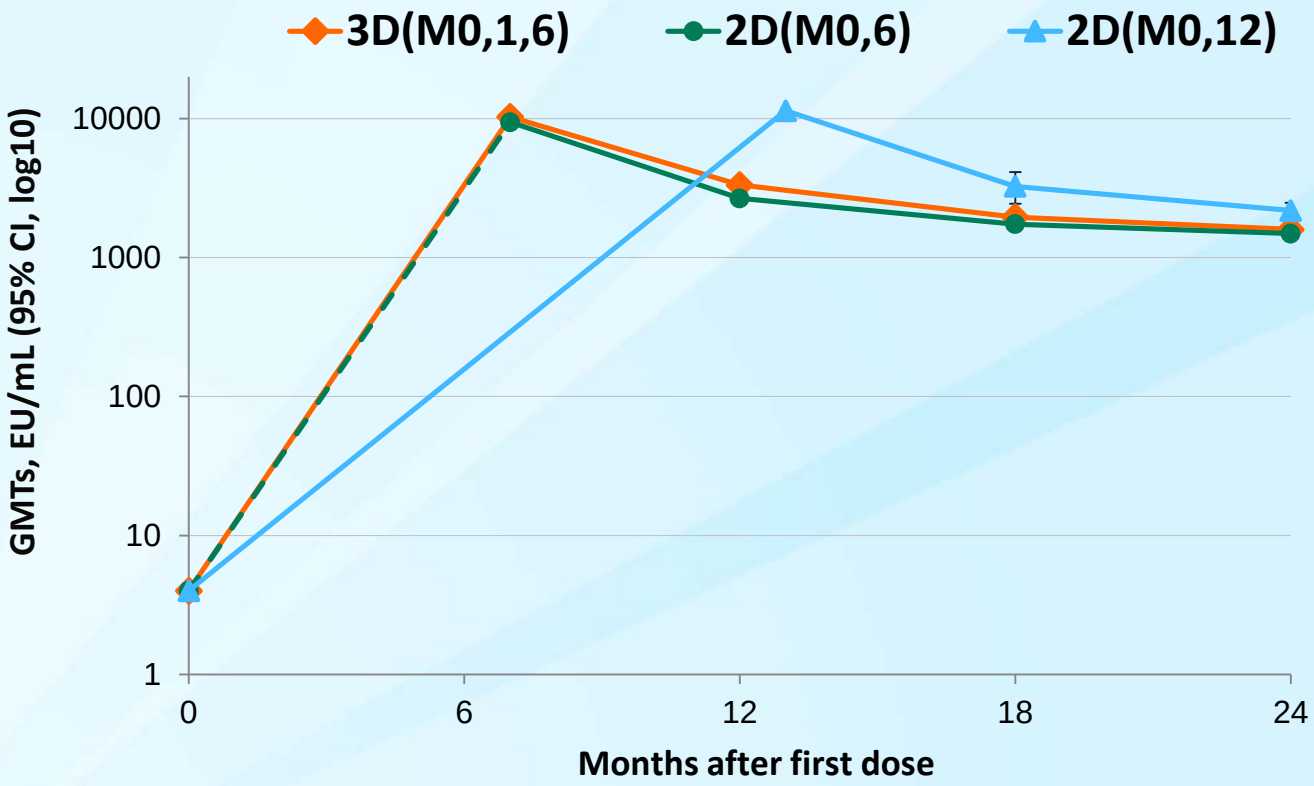
- >99% seroconversion in all groups
- One month after last dose, GMTs with 0,6 and 0,12 schedules in 9-14 yr olds were non-inferior to the 3 dose (0,1,6) schedule in 15-25 yr olds

Note: GMTs presented as 3 doses/2 doses in abstract
Antibody measured by ELISA; non-inferiority defined as lower 95% CI of GMT ratio >.5

Tang R-B. Asia-Pacific Conference on Medical Virology, 2015, and GSK Study Register HPV-070 (ID # 114700)
Clinicaltrials.gov NCT01381575

Bivalent vaccine
2 vs 3 dose immunogenicity trial

HPV 16 GMTs through 24 months



Tang R-B. Asia-Pacific Conference on Medical Virology, 2015, and GSK Study Register HPV-070 (ID # 114700)
Clinicaltrials.gov NCT01381575

Bivalent vaccine immunogenicity trial, Mexico

Study	Age (yrs) and doses		Schedule (months)	Number	Longest follow-up
Lazcano-Ponce Vaccine 2014	9–10	2 doses	0, 6	1026	21 months
	9–10	3 doses	0, 1, 6	474	
	18–24	3 doses	0, 1, 6	400	

- Open label, non-randomized

Note: Group providing data on 2 doses was on a 0, 6, 60 month schedule, with planned interim analysis at month 21 (before dose 3 at 60 months)

Bivalent HPV vaccine immunogenicity trial, Mexico
(21 month GMT data)

HPV Type	2 dose 9–10 yrs/ 3 dose 18–24 yrs		2 dose 9–10 yrs/ 3 dose 9–10 yrs	
	GMT ratio	(95% CI)	GMT ratio	(95% CI)
HPV 16	1.4	(1.3, 1.4)	0.6	(0.6, 0.7)
HPV 18	1.4	(1.3, 1.7)	0.6	(0.5, 0.7)

- **All vaccinees seropositive at 7 months and 21 months**
- **2 doses in 9–10 yrs compared with 3 doses in 18–24 yrs**
  - Antibody response generally higher in 9–10 yrs
  - Non-inferiority criterion met
- **2 doses compared with 3 doses in 9–10 yrs**
  - GMTs lower in 2 dose group, but study non-inferiority criterion met

Lazcano-Ponce, et al. Vaccine 2014 *non-inferiority defined as the lower 95% CI of GMT ratio >0.5
Note: GMTs presented as 3 doses/2 doses in publication

Quadrivalent HPV vaccine

Quadrivalent HPV vaccine immunogenicity trials comparing 2 and 3 doses

Study	Country	Age (yrs) and doses		Schedule (months)	Longest follow-up
Dobson JAMA 2013	Canada	9–13 9–13 16–26	2 doses 3 doses 3 doses	0, 6 0, 2, 6 0, 2, 6	36 months
Hernandez-Avila Hum Vaccin & Immunother 2015	Mexico	9–10 9–10 18–24	2 doses 3 doses 3 doses	0, 6 0, 2, 6 0, 2, 6	21 months
Sankaranarayanan Lancet Oncol 2016	India	10–18 10–18	2 doses 3 doses	0, 6 0, 2, 6	48 months

Quadrivalent HPV vaccine
2 vs 3 dose immunogenicity trial, Canada

Study	Age (yrs) and doses		Schedule (months)	Number	Longest follow-up
Dobson	9–13	2 doses	0, 6	259	36 months
JAMA 2013	9–13	3 doses	0, 2, 6	261	
	16–26	3 doses	0, 2, 6	310	

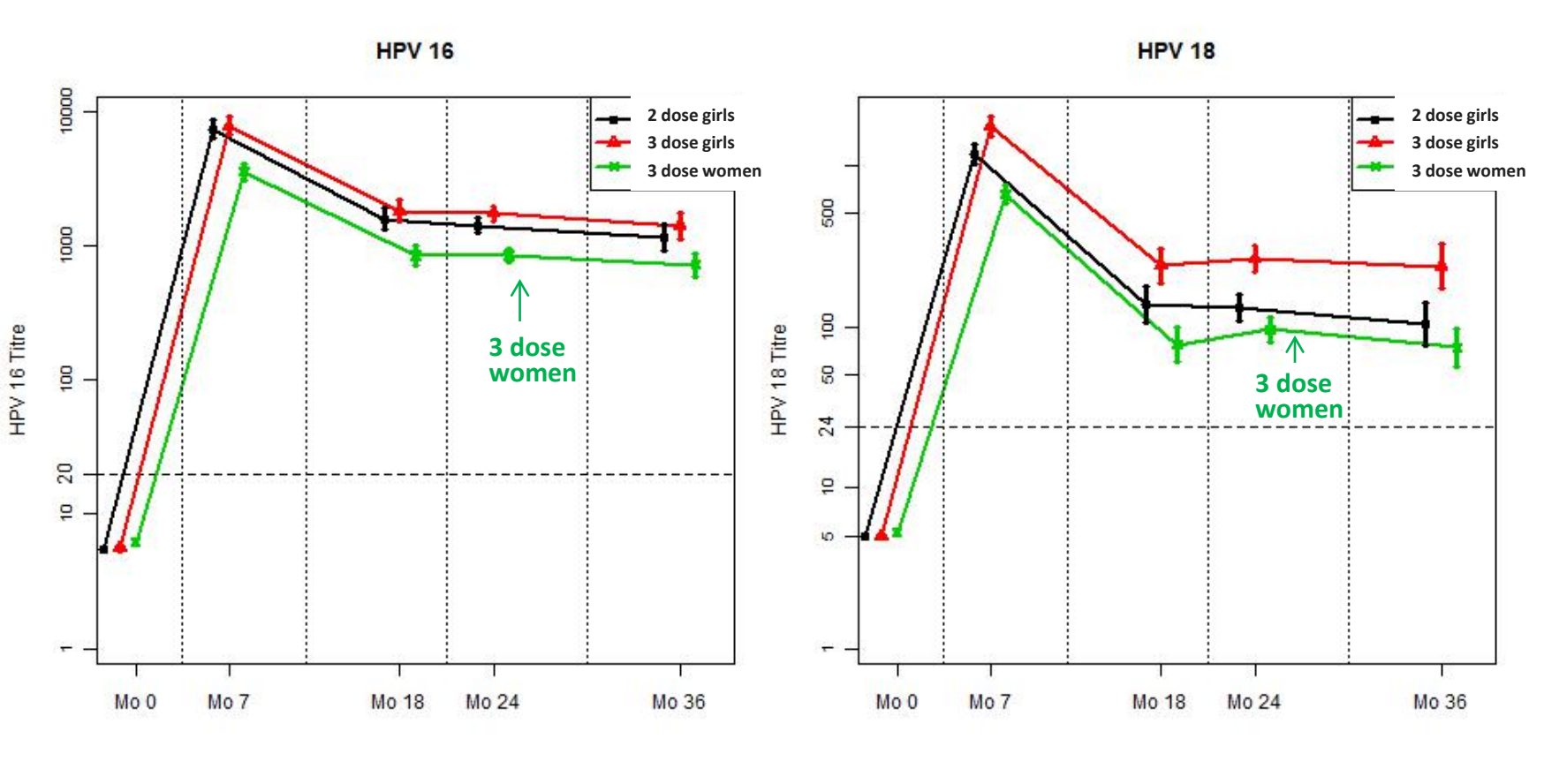
Quadrivalent HPV vaccine
2 vs 3 dose immunogenicity trial, Canada
(36 month data)

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)

Dobson, et al, JAMA 2013

Antibody measured by competitive Luminex immunoassay; *non-inferiority defined as the lower 95% CI of GMT ratio >0.5

Quadrivalent HPV vaccine
2 vs 3 dose immunogenicity trial, Canada
HPV 16 and 18 GMTs through 36 months



Adapted from: Dobson, et al. JAMA 2013

Dashed line is serostatus cut-off

Quadrivalent HPV vaccine immunogenicity trial, Mexico

Study	Age (yrs) and doses		Schedule (months)	Number	Longest follow-up
Hernandez-Avila Hum Vaccin & Immunother 2015	9-10	2 doses	0, 6	148	21 months
	9-10	3 doses	0, 2, 6	150	
	18-24	3 doses	0, 2, 6	143	

- Open label, non-randomized

Quadrivalent HPV vaccine 2 vs 3 dose immunogenicity trial, Mexico seropositivity at month 7 and 21

Month	HPV Type	9-10 years 2-dose group	9-10 years 3-dose group	18-24 years 3-dose group
7	HPV 6	97.2	98.7	97.1
	HPV 11	99.3	100	100
	HPV 16	100	100	100
	HPV 18	100	100	100
21	HPV 6	95.7	95.9	89.0
	HPV 11	97.2	100	97.1
	HPV 16	99.3	99.3	98.5
	HPV 18	70.2	86.3	56.6

- Consistent with findings in pre-liensure efficacy trials: loss of detection of HPV 18 antibody by the cLIA but no loss of protection observed

Hernandez-Avila, et al. Hum Vaccin & Immunothera 2015

Antibody measured by competitive Luminex immunoassay (cLIA)

Quadrivalent HPV vaccine 2 vs 3 dose immunogenicity trial, Mexico (21 month data)

HPV Type	2 dose 9–10 yrs/ 3 dose 18–24 yrs		2 dose 9–10 yrs/ 3 dose 9–10 yrs	
	GMT ratio	(95% CI)	GMT ratio	(95% CI)
HPV 6	1.29	(1.02 – 1.62)	1.21	(0.96 – 1.52)
HPV 11	1.52	(1.21 – 1.91)	0.87	(0.69 – 1.10)
HPV 16	1.49	(1.12 – 1.98)	1.16	(0.88 – 1.55)
HPV 18	1.27	(0.96 – 1.67)	0.74	(0.57– 0.98)

- **2 doses in 9–10 yrs compared with 3 doses in 18–24 yrs**
  - Non-inferiority criterion met
  - Antibody response generally higher in 9–10 yrs
- **2 doses compared with 3 doses in 9–10 yrs**
  - At 21 months, GMTs lower, but non-inferiority criterion met

Hernandez-Avila, et al. Hum Vaccin & Immunothera 2015 *non inferiority defined as lower limit of GMT ratio 95% CI >.05
Antibody measured by competitive Luminex immunoassay (cLIA)

Immunogenicity and efficacy RCT of 2 vs 3 doses of quadrivalent HPV vaccine, India

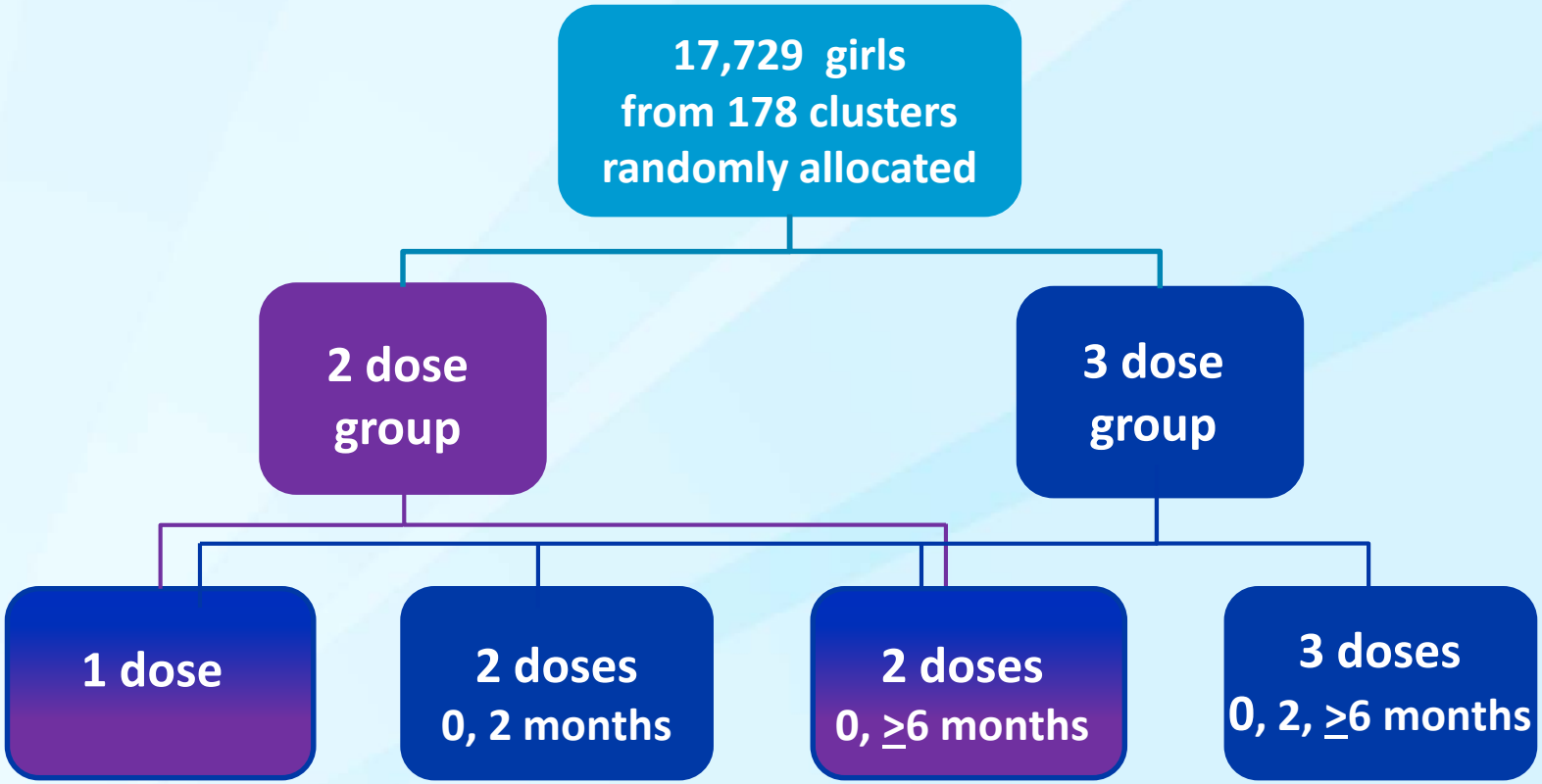
Girls age 10-18 years enrolled

Recruitment and vaccination suspended for reasons unrelated to the study

Sankaranarayanan, et al. Lancet Oncol 2016

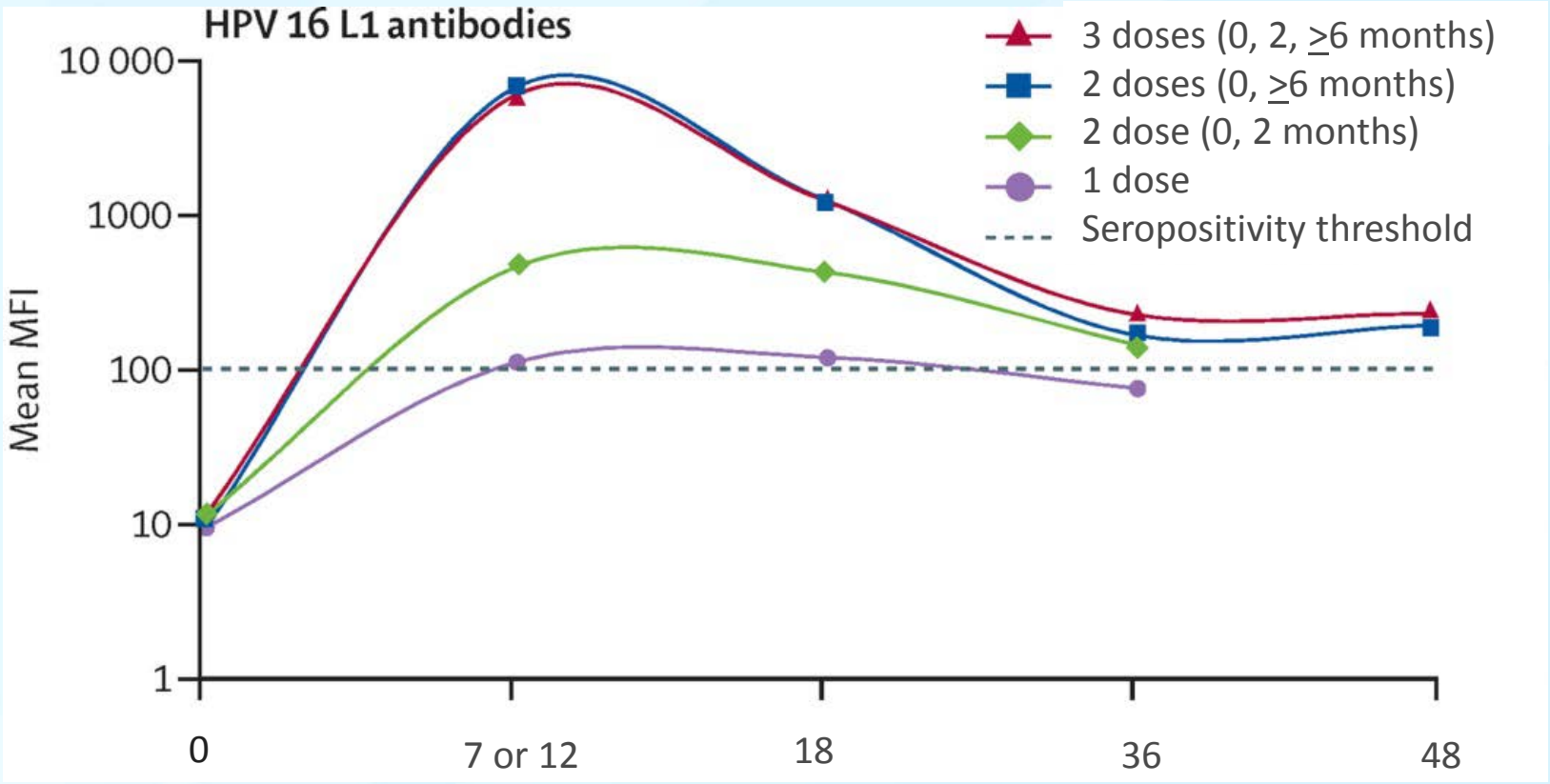
Immunogenicity and HPV infection of 1, 2 and 3 doses of quadrivalent HPV vaccine, India

Randomized trial design lost and analyzed as observational cohort



Sankaranarayanan, et al. Lancet Oncol 2016

Immunogenicity of 1, 2 and 3 doses of quadrivalent HPV vaccine, girls 10-18 years, India



Antibody measured by Luminex based multiplex serology assay and expressed as mean median fluorescence intensity (MFI)

Sankaranarayanan, et al. Lancet Oncol 2016

Summary
Immunogenicity of 2-dose schedules
Bivalent and quadrivalent HPV vaccines

- **2 doses (0,6 months or 0,12 months) in girls vs standard 3 doses in young adult women**
  - Antibody response non-inferior in 2-dose groups (and generally higher) for both vaccines
  - Antibody kinetics similar
  - Consistent in all trials (5 evaluated 0,6 months; 1 evaluated 0,12 months)
- **2 doses (0,6 months) vs 3 doses in girls the same age**
  - 2vHPV: GMTs generally lower in 2-dose group in 2/2 studies
  - 4vHPV: GMTs lower for some types in 2/3 studies

Data on 2-dose schedules for bivalent and quadrivalent HPV vaccines

- Immunogenicity
- Efficacy (post hoc analyses)
- Post-licensure effectiveness

Bivalent Vaccine
Post-hoc analysis of efficacy against incident HPV 16/18 infection, by number of doses

Costa Rica Vaccine Trial and PATRICIA

- Combined data from 2 RCTs, women age 15-25 years
- Participants randomized to 3 doses (0,1,6 months) of HPV vaccine or control; not all completed schedule

Doses	Group	N	Events	Vaccine efficacy (95% CI)
3 doses	HPV Vaccine	11,110	529	**77.0%** (74.7, 79.1)
	Control	11,217	2,172	
2 doses	HPV Vaccine	611	22	**76.0%** (62.0, 85.3)
	Control	574	82	
1 dose	HPV Vaccine	292	8	**85.7%** (70.7, 93.7)
	Control	251	45	

Mean follow-up time, 47.6 months; most 2-dose recipients received vaccine at 0,1 months

Kreimer, et al. Lancet Oncol 2015

HPV 6/11/16/18 infection after 1, 2 and 3 doses of quadrivalent HPV vaccine, India

- Girls age 10-18 years randomized to receive 2 or 3 doses
- Randomized trial design lost and analyzed as observational cohort
- Median time between first vaccination and cervical sample 3.9 yrs

Doses (month intervals)	N tested	Incident Infections	Incidence % (95% CI)
3 (0, 2, 6)	536	3	0.6 (0.1, 1.6)
2 (0, 6)	526	5	1.0 (0.3, 2.2)
2 (0, 2)	717	14	2.0 (1.1,3.3)
1	870	14	1.6 (0.9,2.7)

Sankaranarayanan, et al. Lancet Oncol 2016

Data on 2-dose schedules for bivalent and quadrivalent HPV vaccines

- Immunogenicity
- Efficacy (post hoc analyses)
- Post-licensure effectiveness

Post-licensure HPV vaccine effectiveness studies with evaluation by number of doses

Vaccine	Country	Design/study population	Outcome
4vHPV	Australia[1]	Retrospective cohort study using linked registry data	Cytological and histological cervical abnormalities
	Australia[2]	Case-control study using linked registry data	Histological cervical lesions
	Sweden[3]	Open cohort using nationwide health registers	Condyloma
	Denmark[4]	Cohort using nationwide health registries	Condyloma
	Belgium[5]	Retrospective cohort using reimbursement database	Condyloma
2vHPV	Scotland[6]	Women screened for cervical cancer	HPV prevalence

Challenges and Limitations:

- Differences between 2 and 3 dose recipients
- Most 2-dose recipients did not receive 0,6 month 2-dose schedule
- Other methodologic challenges

[1]Gertig BMC Med 2013, [2]Crowe BMJ 2014, [3]Herwijer JAMA 2014, [4] Blomberg CID 2015, [5]Dominiak-Felden PloS One 2015, [6]Kavanagh BJC 2014

Summary: 2-dose schedules bivalent and quadrivalent HPV vaccines

Immunogenicity

- Main analyses (and those used by regulatory agencies) are comparisons of antibody response of 2 doses in ~9-14 yr olds with 3 doses in young adult women, age group in which efficacy demonstrated
  - No established minimum antibody threshold for protection
  - 2 doses (0,6 months or 0,12 months) in ~9-14 yr olds were non-inferior to 3 doses in young adult women
  - Follow up through 36 months for bivalent and quadrivalent HPV vaccines
- Antibody titers lower after 2 doses (0,6 months) compared with 3 doses in same age group for some types (in some trials)

Summary: 2-dose schedules bivalent and quadrivalent HPV vaccines

Efficacy and incidence data – limited to date

- Bivalent HPV vaccine: Post hoc analysis of 3-dose RCTs in 15-25 yr olds
- Quadrivalent HPV vaccine: Interrupted RCT of 2 vs 3 doses in 10-18 yr olds (analyzed as observational study)
- Data suggest efficacy with less than 3 doses; ~4 years of follow-up
  - Evaluated older age group than the focus of immunobridging studies and different dose interval
- Additional data in the future from study in India and others

Post-licensure effectiveness

- To be reviewed with ACIP at next meeting

Conclusions

- **2-dose data for bivalent and quadrivalent HPV vaccines**
  - Provide supplementary evidence for consideration of 2-dose schedules for 9-valent HPV vaccine
    - However, there are some differences between vaccines
  - Provide evidence for consideration of 2-dose recommendations for bivalent and quadrivalent HPV vaccines
- **These data will be further reviewed by the HPV Vaccines WG and evaluated, along with other data, using GRADE**
  - Presented at future ACIP meeting

GRADE: Grading of Recommendations Assessment, Development and Evaluation

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