GRADE process for 2-dose schedules

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GRADE PROCESS

- Develop policy questions
- Consider critical outcomes
- Review and summarize evidence of benefits and harms
- Evaluate quality of evidence
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendation and GRADE category

PICO QUESTION

- Should 2 doses of any HPV vaccine be recommended for 9–14 year-olds?

- Population: Girls and boys aged 9–14 years
- Intervention: 2 doses of HPV vaccine, separated by 6–12 months
- Comparison: 3 doses of HPV vaccine, at 0, 1–2, and 6 months, among women in the age group in which efficacy has been demonstrated*
- Outcome: Immunogenicity

* Immunobridging studies; analyses with comparison groups age 9–14 years were considered supplemental

IMMUNOBRIDGING STUDIES

- The minimum threshold level of HPV antibodies required for protection has not been established, and might vary depending on the assay
- Data from clinical trials suggest minimum level of antibody needed for protection is below that detected by current assays
- Immunobridging studies are used to compare immunogenicity in the group of interest (e.g., age 9–14) with a comparison group in which efficacy has been demonstrated in clinical trials (e.g., age 16–26)
  - Non-inferiority criteria met when the lower bound of the 95% CI for the ratio comparing the groups is not less than a preset value (e.g., 0.5)
  - Basis on which HPV vaccines were originally licensed for age 9–15

CRITICAL OUTCOMES

Benefits	Importance	Include in evidence profile
Immunogenicity (seroconversion/GMTs/avidity)	**Important**	**Yes**
HPV infections	Important	No†
Genital warts/condyloma	Important	No†
Cervical precancer*	Critical	No‡
Cervical cancer	Critical	No‡
Oropharyngeal cancer	Critical	No‡
Anal cancer	Critical	No‡
Vaginal/vulvar cancer	Critical	No‡
Penile cancer	Critical	No‡

* Cervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma in situ (AIS) 2/3
† No data available for interval or age range specified in PICO question
‡ No data available on these HPV-associated outcomes

EVIDENCE RETRIEVAL

- Systematic review of studies from PubMed and clinicaltrials.gov published between 2006, when HPV vaccine was first licensed, and June 17, 2016
  - Efforts made to obtain unpublished or other relevant data
  - Initial search terms included both:
    - "HPV" and "vaccine," or "HPV vaccine," or "papillomavirus" and "vaccine," or "papillomavirus vaccine," AND
    - "2-dose" or "2 doses" or "two-dose" or "two doses"
  - Relevant studies included:
    - Human subjects, primary data, and data relevant to the outcomes shown above for 9vHPV, 4vHPV, or 2vHPV

EVIDENCE RETRIEVAL

- Search identified 117 publications listed in PubMed:
  - 9 relevant publications reviewed in detail:
    - 6 non-redundant publications included in evidence tables
  - 108 excluded:
    - 31 not primary data (reviews, editorials)
    - 57 other outcomes (coverage, knowledge/preferences, cost-effectiveness)
    - 19 assessed relevant outcomes but did not report results by timing of doses administered or number of doses in the age group of interest
- Also identified 14 studies on clinicaltrials.gov:
  - 1 additional relevant non-redundant study included in evidence tables
- Relevant studies and additional data were previously presented to ACIP

EVIDENCE TYPES

Initial evidence type	Study design
1	Randomized controlled trials (RCTs) or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

GRADE for 2-dose schedules of 9vHPV

Should 2 doses of 9vHPV be recommended routinely for 9–14 year-olds?

CHARACTERISTICS OF INCLUDED STUDIES

Author, year	Methods	Participants	Intervention	Main outcomes	Funding source	Notes
Unpublished (Protocol 010)	Immuno-bridging study	Girls, age 9-14 Boys, age 9-14 Women, age 16-26	9vHPV 2 doses (M0, 6) 2 doses (M0, 12) 3 doses (M0, 2, 6) ±4 weeks	Immunogenicity (seroconversion and GMTs)	Merck	NCT 1984697; presented at ACIP in February 2016

INCLUDED DATA, IMMUNOGENICITY

Outcome	N subjects (studies)	Analysis	Benefits	P-value
Immunogenicity (seroconversion to 9vHPV types)	1516 (1)	Girls/boys (M0,6) and Girls/boys (M0,12) and Women (0,2,6)	**≥97.9% seroconverted at 4 weeks post last dose -**	
Immunogenicity (GMTs for 9vHPV types)	1516 (1)	Girls (M0,6) versus Women (M0,2,6)	**Non-inferiority criteria met for all 9vHPV types**	All p<0.001
		Boys (M0,6) versus Women (M0,2,6)	**Non-inferiority criteria met for all 9vHPV types**	All p<0.001
		Girls/boys (M0,12) versus Women (M0,2,6)	**Non-inferiority criteria met for all 9vHPV types**	All p<0.001

TYPE OF EVIDENCE

Finding	Design (number of studies)	Initial evidence level	Risk of bias	Inconsis-tency	Indirect-ness	Imprecision	Other consider-ations*	Evidence type
Non-inferior immuno-genicity, 9vHPV types	Obs (1)	3	No serious	No serious	No serious†	No serious	None	**3**

* Strength of association, dose-response, plausible residual confounding, publication bias

† Not downgraded for indirectness since immunobridging studies use comparison group in which efficacy has been established

SUPPLEMENTAL DATA, IMMUNOGENICITY

Outcome	N subjects (studies)	Analysis	Benefit to 2-dose group	P-value
Immunogenicity (seroconversion to 9vHPV types)	1516 (1)	Girls/boys 2-dose (M0,6 or 12) versus 3-dose (M0,2,6)	≥99.2% seroconverted at 4 weeks post last dose	-
Immunogenicity (GMTs for 9vHPV types)	1516 (1)	Girls 2-dose (0,6) versus 3-dose (0,2,6)	Lower GMTs in 2-dose group for 4/9 types	-
		Girls 2-dose (0,12) versus 3-dose (0,2,6)	Lower GMTs in 2-dose group for 1/9 types	-

GRADE for 2-dose schedules of 4vHPV

Should 2 doses of 4vHPV be considered adequate vaccination for 9–14 year-olds?

CHARACTERISTICS OF INCLUDED STUDIES, IMMUNOGENICITY

Author, year	Methods	Participants	Intervention	Main outcomes	Funding source	Notes
Dobson, 2013	Immuno-bridging study, Canada	Girls age 9-13, Women age 16-26	4vHPV Girls (M0,6) Women (M0,2,6)	Immunogenicity (seroconversion and GMTs)	Ministries of Health in British Columbia, Nova Scotia, and Quebec (Labs: Provincial Health Services Authority; Merck)	NCT 00501 137
Hernández-Ávila, 2016	Immuno-bridging study, Mexico	Girls age 9-10, Women age 18-24	4vHPV Girls (M0,6) Women (M0,2,6)	Immunogenicity (seroconversion and GMTs)	Ministry of Health in Mexico; National Institute of Public Health in Mexico (Labs: Merck)	NCT 01717 118

INCLUDED DATA, IMMUNOGENICITY

Outcome	N subjects (studies)	Analysis	Benefit	P-value
Immunogenicity (seroconversion to 4vHPV types)	970 (2, Dobson, Hernández-Ávila)	Girls (M0,6) and Women (M0,2,6)	**≥97.1% seropositive at 7 months in all groups**	-
Immunogenicity (GMTs for 4vHPV types)	970 (2, Dobson, Hernández-Ávila)	Girls (M0,6) versus Women (M0,2,6)	**Non-inferiority criteria met for all 4vHPV types** at M7/18/21/24/36	-

TYPE OF EVIDENCE

Finding	Design (number of studies)	Initial evidence level	Risk of bias	Inconsis-tency	Indirect-ness	Imprecision	Other consider-ations*	Evidence type
Non-inferior immuno-genicity, 4vHPV types	Obs (2)	3	No serious	No serious	No serious†	No serious	None	3

* Strength of association, dose-response, plausible residual confounding, publication bias
† Not downgraded for indirectness since immunobridging studies use comparison group in which efficacy has been established

SUPPLEMENTAL DATA, IMMUNOGENICITY

Outcome (not in GRADE)	N subjects (studies)	Analysis	Benefit to 2-dose group
Immunogenicity (seroconversion to 4vHPV types)	970 (2, Dobson, Hernández-Ávila)	Girls 2-doses (M0,6) and 3-doses (M0,2,6)	At M 7, ≥97.2% seropositive to 4/4 types in all groups
Immunogenicity (GMTs for 4vHPV types)	520 (1, Dobson)	Girls 2-doses (M0,6) versus 3-doses (M0,2,6)	By M18, non-inferiority met for 3/4 types but not HPV 18 By M36, non-inferiority met for 2/4 types but not HPV 6 or 18
	450 (1, Hernández-Ávila)	Girls 2-doses (M0,6) versus 3-doses (M0,2,6)	At M7, non-inferiority met for 2/4 types but not HPV 6 or 18 At M21, non-inferiority met for 4/4 types

GRADE for 2-dose schedules of 2vHPV

Should 2 doses of 2vHPV be considered adequate vaccination for 9–14 year-olds?

CHARACTERISTICS OF INCLUDED STUDIES

Author, year	Methods	Participants	Intervention	Main outcomes	Funding source	Notes
Romanowski 2016	Immunobridging study in Canada and Germany	Girls age 9-14, Women age 15-25	2vHPV 2 doses (M0,6) 3 doses (M0,1,6)	Immunogenicity (seroconversion and GMTs)	Glaxo Smith Kline	NCT 00541970
Puthanakit 2016	Immunobridging study in Canada, Germany, Italy, Taiwan, Thailand	Girls age 9-14, Women age 15-25	2vHPV 2 doses (M0,6) 2 doses (M0,12) 3 doses (M0,1,6)	Immunogenicity (seroconversion and GMTs)	Glaxo Smith Kline	NCT 01381575
Lazcano-Ponce 2014	Immunobridging study in Mexico	Girls age 9-10 Women age 18-24	2vHPV 2 doses (M0, 6) 3 doses (0,1,6)	Immunogenicity (seroconversion and GMTs)	Ministry of Health in Mexico	NCT 01717118
Boxus, 2014	Observational	Girls age 10-14 Women age 15+	2vHPV 2-dose (M0,6) 3-dose (M0,1,6)	Immunogenicity (avidity)	Glaxo Smith Kline	Specimens from NCTs 00541970, 00196924 00196937

INCLUDED DATA, IMMUNOGENICITY

Outcome	N subjects (studies)	Analysis	Benefit	P-value
Immunogenicity (seroconversion to 2vHPV types)	4407 (3, Romanowski, Puthanakit, Lazcano-Ponce)	Girls (M0,6) and Women (M0,1,6)	**100% seroconverted to both 2vHPV types** at M1/7/ 21/60	-
Immunogenicity (GMTs for 2vHPV types)	4407 (3, Romanowski, Puthanakit, Lazcano-Ponce)	Girls (M0,6) versus Women (M0,1,6)	**Non-inferiority criteria met for both 2vHPV types** at M1/7/ 21/60	p<0.05
Immunogenicity (antibody avidity for 2vHPV types)	203 (1, Boxus)	Girls (M0,6) and Women (M0,1,6)	**No differences in avidity index, suggesting similar quality of antibody response** at M7/24/48 in 2-dose versus 3-dose recipients	p≥0.31

TYPE OF EVIDENCE

Finding	Design (number of studies)	Initial evidence level	Risk of bias	Inconsis-tency	Indirect-ness	Imprecision	Other consider-ations*	Evidence type
Non-inferior immuno-genicity, 2vHPV types	Obs (4)	3	No serious	No serious	No serious†	No serious	None	3

* Strength of association, dose-response, plausible residual confounding, publication bias
† Not downgraded for indirectness since immunobridging studies use comparison group in which efficacy has been established

SUPPLEMENTAL DATA, IMMUNOGENICITY

Outcome	N subjects (studies)	Analysis	Benefit to 2-dose group
Immunogenicity (seroconversion to 2vHPV types)	2960 (2, Romanowski, Lazcano-Ponce)	Girls 2-doses (M0,6) and 3-doses (M0,1,6)	At M7/21/60, 100% seroconverted to 2/2 types
Immunogenicity (GMTs for 2vHPV types)	2000 (1, Lazcano-Ponce)	Girls 2-doses (M0,6) versus 3-doses (M0,1,6)	At M21, GMT ratios lower but non-inferiority met for 2/2 types

HARMS

Adverse events

- Safety profile has been well-established for HPV vaccines
  - Serious adverse events extremely rare
- In the 9vHPV trial:
  - No serious vaccine-related adverse events in participants in 2-dose cohorts (n=0/883) or 3-dose controls (n=0/616)
- Any potential adverse events following a dose of vaccine (e.g., injection site reactions) can be expected to be reduced when fewer doses are given
  - No data suggest that adverse events increase with fewer doses

SUMMARY

GRADE SUMMARY

Comparison	Outcome	Study design (number of studies*)	Findings	Evidence type	Overall evidence type
2 doses of HPV vaccine (age 9–14) versus 3 doses of HPV vaccine (age 15–26)	Immunogenicity to 9vHPV types	Observational (1)	Non-inferior immunogenicity	3	3
	Immunogenicity to 4vHPV types	Observational (2)	Non-inferior immunogenicity	3	
	Immunogenicity to 2vHPV types	Observational (4)	Non-inferior immunogenicity	3	

* Supplemental data reviewed for additional available analyses from each study

CONSIDERATIONS FOR FORMULATING RECOMMENDATIONS: 2 DOSES OF HPV VACCINE

Key Factors	Comments
Balances between benefits and harms	Benefits are non-inferior and harms are reduced compared to 3 doses If benefits are expected to be similar and the potential adverse events are lower, then the balance of benefits over harms is greater
Evidence type for benefits	Evidence type 3
Values	High value on programmatic considerations as well as prevention of outcomes due to HPV vaccine types
Cost-effectiveness	Likely cost-effective compared to 3 doses

REFERENCES

9vHPV

- Unpublished (Merck)

4vHPV

- Dobson SR, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *JAMA*. 2013 May 1;309(17):1793-802.
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2vHPV

- Boxus M, et al. Antibody avidity measurements in recipients of Cervarix vaccine following a two-dose schedule or a three-dose schedule. *Vaccine*. 2014 May 30;32(26):3232-6. doi: 10.1016/j.vaccine.2014.04.005. Epub 2014 Apr 13.
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Safety

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CHARACTERISTICS OF 4vHPV SUPPLEMENTAL STUDIES, OTHER OUTCOMES (HPV INFECTIONS/WARTS)

Author, year	Methods	Participants	Intervention	Main outcomes	Funding source	Notes
Sankara-narayanan, 2016	Immuno-bridging study in India, 2009-2010	Girls age 10–18	4vHPV 3 doses (M0,2,6) 2 doses (M0,6) 2 doses (M0,2) 1 dose only Cervical cell samples	HPV infections (supplemental)	Gates Foundation	NCT 00923 702
Blomberg, 2015	Observa-tional study in Denmark	Girls age 15-27	4vHPV any schedule	Genital warts (supplemental)	Aragon Foundation; Danielsens Foundation; Mermaid II Project	NCT 01456 715

SUPPLEMENTAL 4vHPV DATA, OTHER OUTCOMES (HPV INFECTIONS/WARTS)

Outcome	N subjects (studies)	Analysis	Benefit	P-value
Persistent cervical HPV infection with 4vHPV types	2649 (1, Sankaranarayanan)	HPV 16 or 18 or 6 or 11 incident and persistent infections	Frequency of incident HPV 16/18/6/11 was similar irrespective of the number of vaccine doses received. No persistent infections (>12 months) at a median follow-up of 4.7 years	-
Genital warts	361734 (1, Blomberg)	Incidence rate ratio of genital warts after 2 doses versus 3 doses (M0,2,6) adjusted for age, education, income, and calendar time	Effect of 2 doses approached that of 3 doses when given at 5–6 month intervals: IRR 1.08 (95% CI: 0.52-2.24) for age <16 years	<.05

CHARACTERISTICS OF 2vHPV SUPPLEMENTAL STUDIES, OTHER OUTCOMES (HPV INFECTIONS)

Author, year	Methods	Participants	Intervention	Main outcomes	Funding source	Notes
Kreimer 2015	Post-hoc analysis of Costa Rica study data	Women age 18-25	2vHPV 2-dose (M0,6) 3-dose (M0,1,6)	HPV infections (supplemental)	NCI, NIH	Data from NCT 00128661

SUPPLEMENTAL 2vHPV DATA, HPV INFECTIONS

Outcome	N subjects (studies)	Analysis	Benefit	P-value
Incidence of cervical HPV infection with 2vHPV types	748 person-years (1, Kreimer)	Women (M0,6) Women (M0,1) Women (M0,1,6)	Vaccine efficacy against incident HPV type 16/18 was higher but not statistically superior for 2 doses (M0,6) compared with either 3 doses or 2 doses (M0,1)	-