Grading of Recommendations Assessment, Development and Evaluation (GRADE) of a 2-dose schedule for human papillomavirus (HPV) vaccination

Introduction

Three HPV vaccines are licensed for use in the United States as a 3-dose series: quadrivalent and 9-valent HPV vaccines (4vHPV and 9vHPV, Gardasil and Gardasil 9, Merck and Co, Inc., Whitehouse Station, NJ)(1, 2) and bivalent HPV vaccine (2vHPV, Cervarix, GlaxoSmithKline, Rixensart, Belgium).(3) In October 2016, 9vHPV was approved for use in a 2-dose series for girls and boys initiating the vaccination series at ages 9 through 14 years. Grading of Recommendations Assessment, Development and Evaluation (GRADE) was adopted by the Advisory Committee on Immunization Practices (ACIP) in 2011,(4) and a 2-dose schedule for HPV vaccine was considered using GRADE. The main policy question was, "Should 2 doses of any HPV vaccine given 6–12 months apart be recommended routinely for 9 through 14 year-olds?" Factors considered in determining the recommendation included benefits and harm, GRADE evidence type, values and preferences, and health economic analyses.

Methods for GRADE

Scientific literature was searched from January 2006 through June 2016 using the PubMed database and ClinicalTrials.gov. The medical subject headings (MeSH) searched were Papillomavirus Vaccines, including all subheadings, with no limitations except human subjects. Text word searches were performed on additional terms, including HPV vaccine, impact, effective, dose, and doses. Studies were included if the population was adolescents (any gender) aged 9–14 years; intervention was administration of 2 doses of any HPV vaccine separated by 6 or more months (±4 weeks); comparison was 3 doses of HPV vaccine among young adults within the age group (15–26 years) in which efficacy was demonstrated in clinical trials; and outcomes were primary data on HPV-associated health outcomes.

The draft policy note based on the ACIP recommendation was shared with ACIP voting members and revisions were made based in part on their feedback. The CDC Director approved a decision memo outlining the recommendation prior to publication of the policy note. The opinions of individual members of ACIP might not be fully reflected in this document, as the guideline represents the position of CDC based on the ACIP recommendation to the CDC director and is not a consensus document. The Work Group continues to review data as they become available, and considers any needed policy changes.

Results

Benefits considered critical outcomes in GRADE were prevention of cervical precancers and cancers, oropharyngeal cancer, anal cancer, vaginal/vulvar cancer, and penile cancers (Table 1). Additional important outcomes included HPV infections and anogenital warts/condyloma. Immunogenicity was considered a surrogate marker for prevention of important and critical outcomes, when immunobridging studies were available comparing immunogenicity in the group of interest (i.e., boys or girls aged 9 through 14 years) with a comparison group in which efficacy has been demonstrated in clinical trials (i.e., women aged 15 or 16 through 26 years).

For 9vHPV, one immunobridging study was identified that was also the basis of the FDA decision on 2-dose approval;(5) for 4vHPV, two immunobridging studies were identified;(6, 7) and for 2vHPV, four immunogenicity studies were identified (Table 2).(8-11) Included data showed high seroconversion rates among all cohorts and non-inferior geometric mean antibody titers (GMTs) for all HPV vaccine types in boys and girls receiving 2-dose schedules compared with groups in which efficacy was demonstrated in clinical trials. (Table 3). These studies received a final GRADE evidence type of 3. (Table 4) Same-age comparisons of seroconversion rates and GMTs among boys and girls receiving a 2-dose schedule compared with a 3-dose schedule were not included in GRADE but are shown as supplemental data (Table 5).

Overall GRADE evidence type was 3 (Table 6). Favorable safety profiles for HPV vaccines have been well-established,(12, 13) and no data suggest that adverse events increase with a 2-dose schedule compared with a 3-dose schedule. When benefits are similar and potential for adverse events is lower, then the balance of benefits over harms is greater.

Considerations for formulating recommendations for a 2-dose schedule of HPV vaccine included the following key factors: balance of benefits over harms, GRADE evidence type, values and preferences, and cost-effectiveness considerations (Table 7).

Table 1. Important and critical outcomes related to HPV vaccination		
Outcome	**Importance**	**Included in evidence profile**
Benefits		
Immunogenicity (Seroconversion / Geometric Mean Titers / Avidity)	Important	Yes
HPV infections	Important	No*
Anogenital warts/condyloma	Important	No*
Cervical precancer (Cervical intraepithelial neoplasia [CIN] 2/3 or adenocarcinoma in situ [AIS] 2/3)	Critical	No†
Cervical cancer	Critical	No†
Oropharyngeal cancer	Critical	No†
Anal cancer	Critical	No†
Vaginal/vulvar cancer	Critical	No†
Penile cancer	Critical	No†
* No data available for dosing interval or age range specified in policy question † No data available on these HPV-associated outcomes		

Table 2. Characteristics of included studies

Vaccine	Author, year (reference)	Study design (N=total enrolled)	Participants	Number of HPV vaccine doses (dosing schedule)	Main outcomes
9vHPV	Iversen, 2016(5)	Immunobridging study, 15 countries (N=1518)[a]	Girls, age 9–14 years, Boys, age 9–14 years, Women, age 16–26 years	2 doses (M 0, 6) 2 doses (M 0, 12) 3 doses (M 0, 2, 6)	Immunogenicity (seroconversion and GMTs)
4vHPV	Dobson, 2013(6)	Immunobridging study, Canada (N=830)[b]	Girls age 9–13 years, Women age 16–26 years	2 doses (M 0,6) 3 doses (M 0, 2, 6)	Immunogenicity (seroconversion and GMTs)
	Hernández-Ávila, 2016(7)	Immunobridging study, Mexico (N=450)[c]	Girls age 9–10 years, Women age 18–24 years	2 doses (M 0, 6) 3 doses (M 0, 2, 6)	Immunogenicity (seroconversion and GMTs)
2vHPV	Romanowski, 2016(8)	Immunobridging study, Canada and Germany (N=961)[d]	Girls age 9–14 years, Women age 15–25 years	2 doses (M 0, 6) 3 doses (M 0, 1, 6)	Immunogenicity (seroconversion and GMTs)
	Puthanakit, 2016(9)	Immunobridging study, Canada, Germany, Italy, Taiwan, Thailand (N=1447)[e]	Girls age 9–14 years, Women age 15–25 years	2 doses (M 0, 6) 2 doses (M 0, 12) 3 doses (M 0, 1, 6)	Immunogenicity (seroconversion and GMTs)
	Lazcano-Ponce, 2014(10)	Immunobridging study, Mexico (N=2000)[f]	Girls age 9–10 years, Women age 18–24 years	2 doses (M 0, 6) 3 doses (M 0, 1, 6)	Immunogenicity (seroconversion and GMTs)
	Boxus, 2014(11)	Observational (N=203 specimens from 180 individuals)[g]	Girls age 10–14 years, Women age ≥15 years	2 doses (M 0, 6) 3 doses (M 0, 1, 6)	Immunogenicity (avidity)

[a] NCT 1984697, funded by Merck; results presented publicly at ACIP in February 2016
[b] NCT 00501137, funded by Ministries of Health in British Columbia, Nova Scotia, and Quebec (Laboratory testing: Merck)
[c] NCT 01717118, funded by Ministry of Health in Mexico and National Institute of Public Health in Mexico (Laboratory testing: Merck)
[d] NCT 00541970, funded by GlaxoSmithKline
[e] NCT 01381575, funded by GlaxoSmithKline
[f] NCT 01717118, funded by Ministry of Health in Mexico (Laboratory testing: GlaxoSmithKline)
[g] Specimens from NCT 00541970, NCT 00196924, NCT 00196937, funded by GlaxoSmithKline

GMTs, Geometric Mean Titers; M, months after dose 1; NCT, National Clinical Trial number

Table 3. Included data, immunogenicity				
Vaccine	**Outcome**	**Number of subjects (number of studies)**	**Comparison groups**	**Benefits**
9vHPV	Immunogenicity (seroconversion to 9vHPV types)	1102 (1)	Girls and boys 2 doses (M 0, 6) and Girls and boys 3 doses (M 0, 12) and Women 3 doses (M 0, 2, 6)	≥97.9% seropositive at 1 month post last dose in all groups in the per-protocol population
	Immunogenicity (GMTs for 9vHPV types)	560 (1)	Girls 2 doses (M 0,6) versus Women 3 doses (M 0, 2, 6)	Non-inferiority criteria met for all 9vHPV types at 1 month post last dose
		559 (1)	Boys 2 doses (M 0, 6) versus Women 3 doses (M 0, 2, 6)	Non-inferiority criteria met for all 9vHPV types at 1 month post last dose
		555 (1)	Girls and boys 2 doses (M 0, 12) versus Women 3 doses (M 0, 2, 6)	Non-inferiority criteria met for all 9vHPV types at 1 month post last dose
4vHPV	Immunogenicity (seroconversion to 4vHPV types)	806 (2)	Girls 2 doses (M 0,6) and Women 3 doses (M 0, 2, 6)	≥97.1% seropositive at 1 month post last dose in all groups in the per-protocol population
	Immunogenicity (GMTs for 4vHPV types)	806 (2)	Girls 2 doses (M 0, 6) versus Women 3 doses (M 0, 2, 6)	Non-inferiority criteria met for all 4vHPV types at 1 month post last dose and later (latest M 36)
2vHPV	Immunogenicity (seroconversion to 2vHPV types)	2840 (3)	Girls 2 doses (M 0, 6 or 12) and Women 3 doses (M 0, 1, 6)	100% seropositive at 1 month post last dose in all groups in the per-protocol population
	Immunogenicity (GMTs for 2vHPV types)	2840 (3)	Girls 2 doses (M 0, 6 or 12) versus Women 3 doses (M 0, 1, 6)	Non-inferiority criteria met for both 2vHPV types at 1 month post last dose and later (latest M 60)
	Immunogenicity (antibody avidity for 2vHPV types)	180 (1)	Girls 2 doses (M 0, 6) and Women 3 doses (M 0, 1, 6)	No differences in avidity index, suggesting similar quality of antibody response at M 7, 24, and 48 in 2-dose versus 3-dose recipients

GMTs, Geometric Mean Titers; M, months after dose 1

Table 4. Type of evidence

Vaccine	Finding	Design (number of studies)	Initial evidence level	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations[a]	Evidence type
9vHPV	Non-inferior immunogenicity, 9vHPV types	Obs (1)	3	No serious	No serious	No serious[b]	No serious	None	3
4vHPV	Non-inferior immunogenicity, 4vHPV types	Obs (2)	3	No serious	No serious	No serious[b]	No serious	None	3
2vHPV	Non-inferior immunogenicity, 2vHPV types	Obs (4)	3	No serious	No serious	No serious[b]	No serious	None	3

[a] Strength of association, dose-response, plausible residual confounding, publication bias

[b] Not downgraded for indirectness since immunobridging studies use a comparison group in which clinical efficacy has been established

Obs, Observational

Table 5. Supplemental data, immunogenicity				
Vaccine	**Outcome**	**Number of subjects (number of studies)**	**Comparison groups**	**Benefits**
9vHPV	Immunogenicity (seroconversion to 9vHPV types)	1091 (1)	Girls and boys 2 doses (M 0, 6 or 12) and Girls 3 doses (M 0, 2, 6)	≥99.2% seropositive at 1 month post last dose in all groups in the per-protocol population
	Immunogenicity (GMTs for 9vHPV types)	549 (1)	Girls 2 doses (M 0, 6) versus Girls 3 doses (M 0, 2, 6)	Lower GMTs in 2-dose group for 4/9 9vHPV types at 1 month post last dose
		544 (1)	Girls and boys 2 doses (M 0, 12) versus Girls 3 doses (M 0, 2, 6)	Lower GMTs in 2-dose group for 1/9 9vHPV types at 1 month post last dose
4vHPV	Immunogenicity (seroconversion to 4vHPV types)	790 (2)	Girls 2 doses (M 0, 6) and Girls 3 doses (M 0, 2, 6)	≥97.1% seropositive at 1 month post last dose in all groups in the per-protocol population
	Immunogenicity (GMTs for 4vHPV types)	495 (1)	Girls 2 doses (M 0, 6) versus Girls 3 doses (M 0, 2, 6)	Non-inferiority met for 3/4 4vHPV types (but not HPV 18) by M 18; non-inferiority met for 2/4 4vHPV types (but not HPV 6 or HPV 18) by M 36
		295 (1)	Girls 2 doses (M 0, 6) versus Girls 3 doses (M 0, 2, 6)	Non-inferiority met for 2/4 4vHPV types (but not HPV 6 or 18) at M 7; non-inferiority met for all 4vHPV types at M 21
2vHPV	Immunogenicity (seroconversion to 2vHPV types)	1533 (2)	Girls 2 doses (M 0, 6) and Girls 3 doses (M 0, 1, 6)	100% seropositive at 1 month post last dose in all groups in the per-protocol population
	Immunogenicity (GMTs for 2vHPV types)	1384 (1)	Girls 2 doses (M 0, 6) versus Girls 3 doses (M 0, 1, 6)	GMT ratios lower in 2-dose group but non-inferiority met for both 2vHPV types at M 21

GMTs, Geometric Mean Titers; M, months after dose 1

Table 6. Summary of evidence for a 2-dose schedule of HPV vaccine					
Comparison	**Outcome**	**Study design (number of studies)**	**Findings**	**Evidence type**	**Overall evidence type**
2 doses of HPV vaccine (age 9–14 years) versus 3 doses of HPV vaccine (age 15–26 years)	Immunogenicity, 9vHPV types	Observational (1)	Non-inferior immunogenicity	3	**3**
	Immunogenicity, 4vHPV types	Observational (2)	Non-inferior immunogenicity	3	
	Immunogenicity, 2vHPV types	Observational (4)	Non-inferior immunogenicity	3	

Table 7. Considerations for formulating recommendations for a 2-dose schedule of HPV vaccine

Key factors	Comments
Balance of benefits versus harms	• 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 and harms	• GRADE evidence type 3
Values and preferences	• ACIP HPV Work Group placed high value on programmatic considerations as well as prevention of outcomes due to vaccine-type HPV
Cost-effectiveness	• Likely cost-effective compared with 3 doses
Summary	• Category A recommendation for a 2-dose schedule of HPV vaccine for girls and boys who initiate the vaccination series at ages 9 through 14 years

Summary

After reviewing the available data, including the result of the GRADE analysis, ACIP voted in October 2016 to recommend a 2-dose schedule of HPV vaccine for girls and boys who initiate the vaccination series at ages 9 through 14 years (Category A recommendation). See *Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices*.
(https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm?s_cid=mm6549a5_w.(14)

References

1. Food and Drug Administration. Prescribing information [package insert]. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, 18) vaccine, recombinant]. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2015. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf.
2. Food and Drug Administration. Prescribing information [package insert]. Gardasil 9 [human papillomavirus 9-valent vaccine, recombinant]. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2016. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf.
3. Food and Drug Administration. Prescribing information [package insert]. Cervarix [human papillomavirus bivalent (types 16, 18) vaccine, recombinant]. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2016. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf.
4. Ahmed F, Temte JL, Campos-Outcalt D, Schunemann HJ, ACIP Evidence-Based Recommendations Work Group. Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC). Vaccine. 2011;29(49):9171-6.
5. Iversen O-E, Miranda MJ, Ulied A, Soerdal T, Lazarus E, Chokephaibulkit K, et al. Immunogenicity of the 9-Valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women. JAMA. 2016;316(22):2411-2421.
6. Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA. 2013;309(17):1793-802.
7. Hernandez-Avila M, Torres-Ibarra L, Stanley M, Salmeron J, Cruz-Valdez A, Munoz N, et al. Evaluation of the immunogenicity of the quadrivalent HPV vaccine using 2 versus 3 doses at month 21: An epidemiological surveillance mechanism for alternate vaccination schemes. Hum Vaccin Immunother. 2016;12(1):30-8.
8. Romanowski B, Schwarz TF, Ferguson L, Peters K, Dionne M, Behre U, et al. Sustained immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine administered as a two-dose schedule in adolescent girls: Five-year clinical data and modeling predictions from a randomized study. Hum Vaccin Immunother. 2016;12(1):20-9.
9. Puthanakit T, Huang LM, Chiu CH, Tang RB, Schwarz TF, Esposito S, et al. Randomized open trial comparing 2-dose regimens of the human papillomavirus 16/18 AS04-adjuvanted vaccine in girls aged 9-14 years versus a 3-dose regimen in women aged 15-25 years. J Infect Dis. 2016;214(4):525-36.
10. Lazcano-Ponce E, Stanley M, Munoz N, Torres L, Cruz-Valdez A, Salmeron J, et al. Overcoming barriers to HPV vaccination: non-inferiority of antibody response to human papillomavirus 16/18 vaccine in adolescents vaccinated with a two-dose vs. a three-dose schedule at 21 months. Vaccine. 2014;32(6):725-32.
11. Boxus M, Lockman L, Fochesato M, Lorin C, Thomas F, Giannini SL. Antibody avidity measurements in recipients of Cervarix vaccine following a two-dose schedule or a three-dose schedule. Vaccine. 2014;32(26):3232-6.
12. Gee J, Weinbaum C, Sukumaran L, Markowitz LE. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. Hum Vaccin Immunother. 2016;12(6):1406-17.
13. Moreira ED, Jr., Block SL, Ferris D, Giuliano AR, Iversen OE, Joura EA, et al. Safety profile of the 9-Valent HPV vaccine: A combined analysis of 7 phase III clinical trials. Pediatrics. 2016;138(2): e20154387.

14. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus (HPV) vaccination: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2016; 65:1405–1408. https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm?s_cid=mm6549a5_w.