Summary of clinical trial data and GRADE for 9-valent HPV vaccine

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Outline

- Summary of 9vHPV clinical trial data
  - Outcome, immunogenicity
  - Safety
- Review of GRADE for 9vHPV (October 2014)
- Considerations for 9vHPV recommendation

9vHPV clinical trials

Study	Design	N	Sex	Age	Objectives
9vHPV pivotal efficacy study					
001	RCT	14215	F	16–26 years	Efficacy, immunogenicity, safety
9vHPV immunobridging studies in adolescents					
002	Obs	2999	F F, M	16–26 years 9–15 years	9vHPV adult-to-adolescent immunobridging, safety
009	RCT	600	F	9–15 years	4vHPV-to-9vHPV immunobridging, safety
9vHPV immunobridging studies in adult males					
003	Obs	2520	F, M	16–26 years	9vHPV female-to-male immunobridging, safety
9vHPV concomitant use studies					
005	Obs	1241	F, M	11–15 years	Concomitant use: Menactra, Adacel
007	Obs	1054	F, M	11–15 years	Concomitant use: Repevax
9vHPV in prior 4vHPV recipients					
006	RCT	924	F	12–26 years	9vHPV in prior 4vHPV recipients

RCT = randomized controlled trial; Obs = observational study

9vHPV FDA Label: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

9vHPV Clinical Trial: https://clinicaltrials.gov/ct2/show/NCT01651949?term=v503&rank=3

Protocol 001: Pivotal efficacy trial in females aged 16–26 years in per protocol population[a]

HPV vaccine type	Outcome	Incidence in 9vHPV[b] (n/N)	Incidence in 4vHPV[b] (n/N)	Vaccine efficacy % (95% CI)
31/33/45/52/58	≥CIN2	1/5948	27/5943	96.3 (79.5–99.8)
	≥CIN2, VIN2/3, VaIN2/3	1/6016	30/6017	96.7 (80.9–99.8)
	6-month persistent infection	26/5939	642/5953	96.2 (94.4–97.5)
6/11/16/18	≥CIN2[c]	1/5715	0/5732	--
	Anogenital warts[d]	4/4744	0/4805	--

≥CIN = cervical intraepithelial neoplasia 2/3 or adenocarcinoma in situ; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia

[a]Received all 3 vaccine doses within 1 year of enrollment, were PCR negative and seronegative to HPV 31, 33, 45, 52, 58 prior to dose 1, and remained PCR negative to the relevant HPV type(s) through one month post-dose 3.
[b]Incidence over median 40 months of follow-up
[c]HPV 16/18-related
[d]HPV 6/11-related

9vHPV FDA Label: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

Protocol 001: Immunogenicity in females aged 16–26 years 9vHPV compared with 4vHPV

	9vHPV			4vHPV		
Outcome	n	(%)	GMT	n	(%)	GMT
Anti-HPV 6	3993	(99.8)	893	3975	(99.8)	875
Anti-HPV 11	3995	(100)	666	3982	(99.9)	830
Anti-HPV 16	4032	(100)	3131	4062	(100)	3157
Anti-HPV 18	4539	(99.8)	805	4541	(99.7)	679

- **>99% seroconversion to HPV 6, 11, 16, 18 in both groups**
- **Non-inferiority criterion met for HPV 6, 11, 16, 18 (*P*<0.001)**

Data from per protocol population; Antibody measured by cLIA at month 7

9vHPV summary findings

- **Efficacy**
  - ~97% protection against HPV 31, 33, 45, 52, 58-related outcomes
  - Similar protection against HPV 6, 11, 16, 18-related disease
- **Non-inferior immunogenicity**
  - For HPV 6, 11, 16, 18 compared with 4vHPV in 16–26 and 9–15 year olds
  - For all 9 HPV vaccine types in adolescent females and males compared to adult females and in adult males compared to adult females
- **Concomitant use**
  - No impact on immunogenicity and safety when 9vHPV administered concomitantly with meningococcal vaccine (Menactra), Tdap vaccine (Adacel), and Tdap-IPV vaccine (Repevax)

9vHPV safety summary

- **Generally well tolerated in >15,000 recipients**
  - Adverse event profile similar to 4vHPV across age, gender, race, ethnicity
  - More injection site-related swelling and erythema in females who received 9vHPV (most mild/moderate in intensity)
  - Lower frequency of adverse events in males compared to females (similar to 4vHPV)

9vHPV policy questions for GRADE

- **Should 9vHPV be recommended routinely for 11–12 year olds?** *(routine vaccination)*

- **Should 9vHPV be recommended for females aged 13–26 years and males aged 13–21 years who have not been previously vaccinated?** *(catch-up vaccination)*

Overall quality of evidence for 9vHPV routine vaccination in females

Comparison		Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	Benefits	**HPV 6/11/16/18** **Cervical cancer** **Cervical precancer** **Anogenital warts**	4vHPV RCT (3)[a] 9vHPV RCT (2), Obs (4)[b]	Non-inferior immunogenicity	2–3	2
		HPV 31/33/45/52/58 **Cervical cancer** **Cervical precancer**	9vHPV RCT (1)[c] 9vHPV RCT (1), Obs (4)[d]	Non-inferior immunogenicity	1–2	
	Harms	**SAE**	9vHPV RCT (1), Obs (2)[e]	No cases	2	
		Anaphylaxis		No cases		

[a]Data from 4vHPV Protocols 007 (RCT), 013 (RCT), 015 (RCT)
[b]Supportive 9vHPV Protocols 001 (RCT), 002 (Obs), 003 (Obs), 005 (Obs), 007 (Obs) 009 (RCT)
[c]Data from 9vHPV Protocol 001 (RCT)
[d]Supportive 9vHPV Protocols 002 (Obs), 003 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)
[e]Data from 9vHPV Protocols 002 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)

Overall quality of evidence for 9vHPV catch up vaccination in females

Comparison		Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	Benefits	**HPV 6/11/16/18** **Cervical precancer** **Cervical cancer** **Anogenital warts**	4vHPV RCT (3)[a] 9vHPV RCT (1), Obs (2)[b]	High efficacy for 4vHPV; non-inferior immunogenicity for HPV 6/11/16/18 and comparable risk for outcomes	2–3	2
		HPV 31/33/45/52/58 **Cervical precancer** **Cervical cancer**	9vHPV RCT (1)[c] 9vHPV Obs (2)[d]	Decreased risk for HPV 31/33/45/52/58-related outcomes	1–2	
	Harms	**SAE**	9vHPV RCT (1), Obs (2)[e]	Few cases	2	
		Anaphylaxis		No vaccine-related cases		

[a]Data from 4vHPV Protocols 007 (RCT), 013 (RCT), 015 (RCT)
[b]Supportive 9vHPV Protocols 001 (RCT), 002 (Obs), 003 (Obs)
[c]Data from 9vHPV Protocol 001 (RCT)
[d]Supportive 9vHPV Protocols 002 (Obs), 003 (Obs)
[e]Data from 9vHPV Protocols 001 (RCT), 002 (Obs), 003 (Obs)

Overall quality of evidence for 9vHPV routine vaccination in males

Comparison		HPV 6/11/16/18 Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	Benefits	**Anal cancer** **Anogenital warts**	RCT (1)[a] RCT (1), Obs (1)[b]	Non-inferior immunogenicity	2–3	3
	Harms	**SAE**	RCT (1), Obs (4)[c]	No cases	2	
		Anaphylaxis		No cases		

[a]Data from 4vHPV Protocol 020 (RCT)
[b]Supportive 9vHPV Protocols 001 (RCT), 002 (Obs)
[c]Data from Protocols 002 (Obs), 005 (Obs), 007 (Obs), 009 (RCT)

Overall quality of evidence for 9vHPV catch up vaccination in males

Comparison		HPV 6/11/16/18 Outcome	Design (# studies)	Findings	Evidence type	Overall
9vHPV vs. 4vHPV	Benefits	**Anal cancer Anogenital warts**	4vHPV RCT (1)[a] 9vHPV RCT (1), Obs (1)[b]	High efficacy for 4vHPV; non-inferior immunogenicity	2–3	3
	Harms	**SAE**	9vHPV RCT (1), Obs (2)[c]	Few cases	2	
		Anaphylaxis		No vaccine-related cases		

[a]Data from 4vHPV Protocol 020 (RCT)
[b]Supportive 9vHPV Protocols 001 (RCT), 003 (Obs)
[c]Data from 9vHPV Protocols 001 (RCT), 002 (Obs), 003 (Obs)

GRADE Summary
Considerations for formulating 9vHPV recommendation

Evidence type for benefits and harms	• Data from RCT and immunobridging studies • Evidence type 2 (moderate) for females • Evidence type 3 (low) for males
Balance of benefits versus harms	• Benefits outweigh harms
Values	• ACIP HPV Work Group placed high value on prevention of outcomes due to HPV 6, 11, 16, 18, 31, 33, 45, 52, 58
Cost-effectiveness	• 9vHPV is cost saving compared to 4vHPV
Summary	• Category A recommendation

Acknowledgments

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