




It's Safe, Don't Wait! Vaccine Safety Data and the New HPV9 Vaccine

Julie A. Boom, M.D.
Associate Professor of Pediatrics
Director, Immunization Project

June 18, 2015

Texas Children's Hospital®

Baylor College of Medicine

Pediatrics

- I am not a speaker for Merck or any other pharmaceutical company
- I do not have any relevant conflicts of interest
- I typically try to only use the generic names, not brand names
- Regarding HPV9, there is only 1 so far


St. John's School

Learning Objectives:

- Reassess current HPV4 safety data as a background
- Appreciate definitions of adverse events, SAEs
- Examine new HPV9 safety data
- Compare HPV4 and HPV 9 vaccine safety data
- Review how to explain HPV vaccine safety data in an understandable way to parents

Adverse Events - Definitions

- Any unfavorable and unintended change in the structure, function or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the vaccine.
- Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine
- Systemic AEs were those not categorized as injection-site AEs.

Adverse events, definitions

- Mild – awareness of symptom, but easily tolerated
- Moderate – discomfort enough to cause interference with usual activities
- Severe – incapacitating with inability to work or do usual activity (abbreviated SAE)
- Swelling or erythema with >2 inches was recorded as severe

https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf

HPV vaccine safety concerns are common

TABLE 2. Top five reasons for not vaccinating adolescents with human papillomavirus (HPV) vaccine* — National Immunization Survey-Teen, United States, 2013

Parents of girls			Parents of boys		
Reason	**%**	**(95% CI)**	**Reason**	**%**	**(95% CI)**
Lack of knowledge	15.5	(13.0–18.5)	Not recommended	22.8	(20.6–25.0)
Not needed or necessary	14.7	(12.5–17.3)	Not needed or necessary	17.9	(15.9–20.1)
Safety concern/Side effects	14.2	(11.8–16.8)	Lack of knowledge	15.5	(13.7–17.6)
Not recommended	13.0	(10.8–15.5)	Not sexually active	7.7	(6.4–9.2)
Not sexually active	11.3	(9.1–13.9)	Safety concern/Side effects	6.9	(5.6–8.5)

Abbreviation: CI = confidence interval.

* Analysis limited to parents reporting that they were not likely to seek HPV vaccination for their teen in the next 12 months or were unsure of their HPV vaccination plans.

"…vaccination coverage for ≥1 dose by 13 years for this cohort could have reached 91.3%"

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6329a3.htm






HPV4 Post-licensure Data

Texas Children's Hospital®

Baylor College of Medicine®

Pediatrics

Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine

Barbara A. Slade, MD, MS
Laura Leidel, RN, FNP-C, MPH
Claudia Vellozzi, MD, MPH
Emily Jane Woo, MD, MPH
Wei Hua, MD, PhD
Andrea Sutherland, MD, MSc, MPH

Context In June 2006, the Food and Drug Administration licensed the quadrivalent human papillomavirus (types 6, 11, 16, and 18) recombinant vaccine (qHPV) in the United States for use in females aged 9 to 26 years; the Advisory Committee on Immunization Practices then recommended qHPV for routine vaccination of girls aged 11 to 12 years.

Objective To summarize reports to the Vaccine Adverse Event Reporting System (VAERS) following receipt of qHPV.

- VAERS passive surveillance 6/1/06 – 12/31/08
- 12,424 reports received (53.9 reports/100,000 doses)
- 772 reports (6.2%) were SAEs, including 32 deaths

JAMA. 2009;302(7):750-757

Texas Children's Hospital®

Baylor College of Medicine

Table 2. Most Common and Other Selected qHPV Adverse Events Following Immunization in the United States, Reported to VAERS June 1, 2006, Through December 31, 2008

AEFI[a]	No. (%)			Total, No.	Reporting Rate[c]
	Serious Adverse Events	Nonserious Events	qHPV Alone[b]		
Syncope, syncope vasovagal	93 (5)	1803 (95)	1396 (74)	1896	8.2
Local reaction[d]	41 (2)	1700 (98)	1338 (77)	1741	7.5
Dizziness	96 (6)	1476 (94)	1147 (73)	1572	6.8
Nausea	119 (10)	1045 (90)	908 (78)	1164	5.0
Headache	150 (16)	787 (84)	688 (73)	937	4.1
Hypersensitivity reaction[e]	47 (6)	678 (94)	582 (80)	725	3.1
Urticaria	22 (4)	590 (96)	501 (82)	612	2.6
Venous thromboembolic event	39 (69)	17 (31)	55 (98)	56	0.2
Autoimmune disorder	19 (37)	32 (63)	45 (88)	51	0.2
Guillain-Barré syndrome	31 (74)	11 (26)	25 (60)	42	0.2
Anaphylaxis	8 (29)	20 (71)	18 (64)	28	0.1
Death	32 (100)	0	23 (72)	32	0.1
Transverse myelitis	10 (100)	0	10 (100)	10	0.04
Pancreatitis	9 (100)	0	9 (100)	9	0.04
Motor neuron disease	2 (100)	0	2 (100)	2	0.009

JAMA. 2009;302(7):750-757

HPV4 Safety Data – post-licensure monitoring, 2006-2014

- HPV4 – 67M doses distributed 6/06- 3/14
- HPV2 – 719,000 doses distributed 10/09-3/14
- VAERS – received 25,176 adverse events reports from 6/06 – 3/14
- HPV4 accounted for 99% of doses & VAERS reports
- 92.4% of HPV reports were classified as nonserious

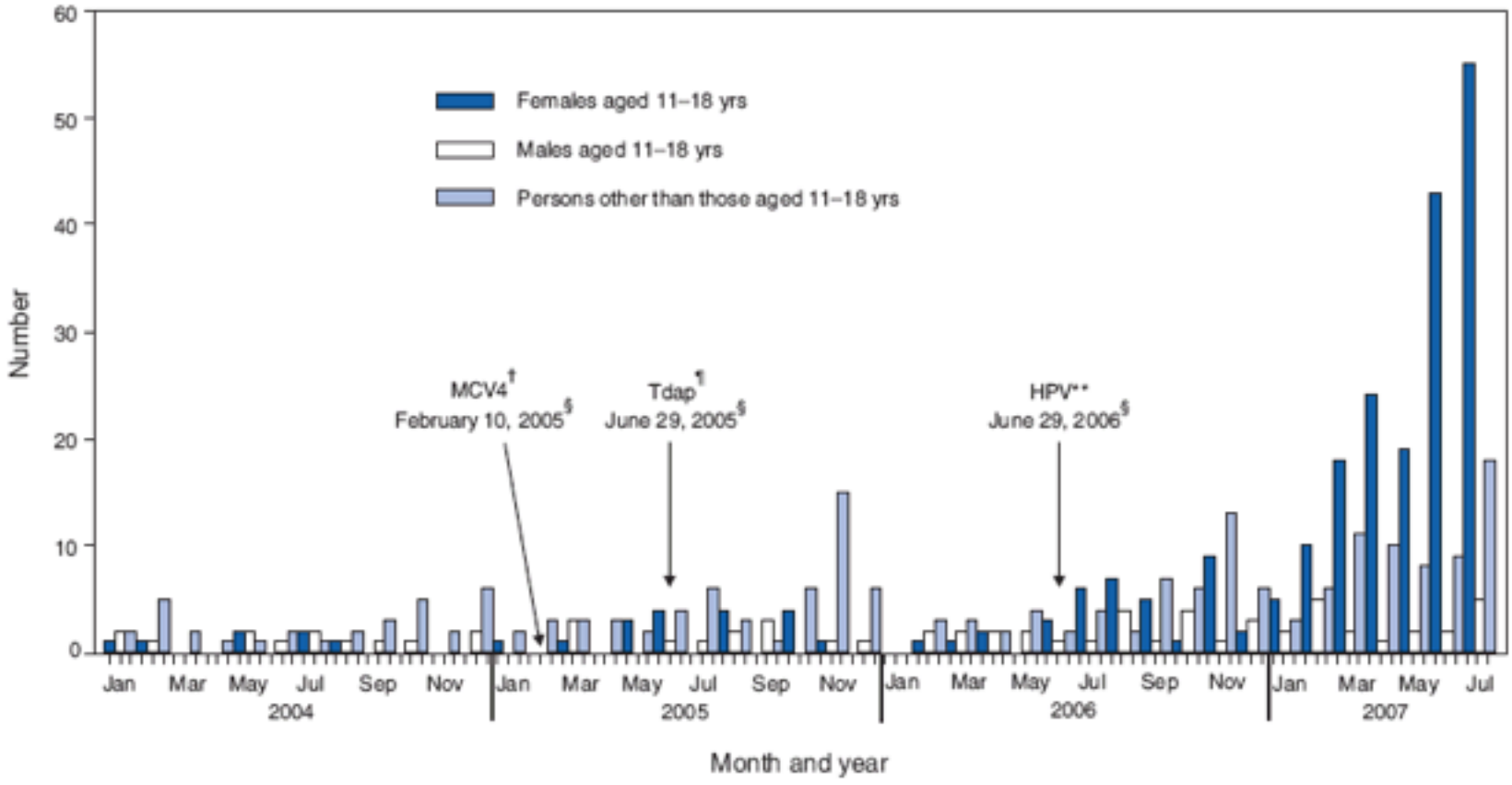
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6329a3.htm

Most commonly reported symptoms:

- Injection site reactions
- Dizziness
- Syncope – may include tonic/clonic movements
- Nausea
- Headache

Postvaccination syncope

FIGURE. Number of postvaccination syncope* episodes reported to the Vaccine Adverse Event Reporting System, by month and year of report — United States, January 1, 2004–July 31, 2007



http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5717a2.htm

Texas Children's Hospital®

Baylor College of Medicine



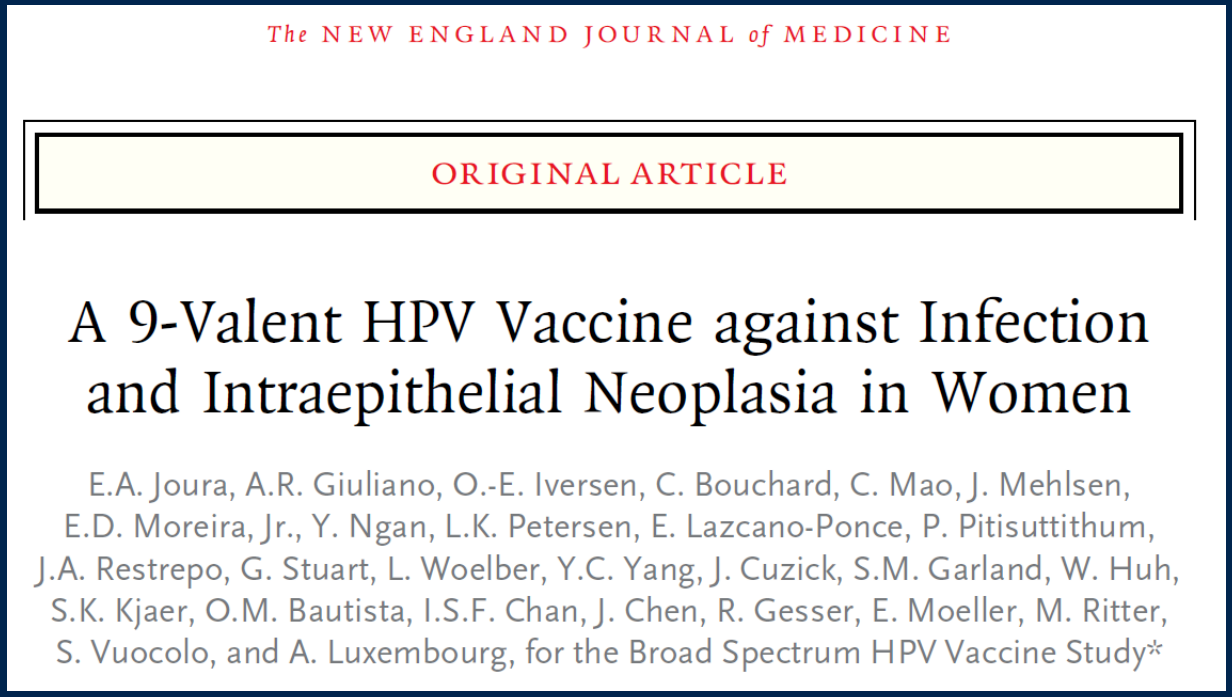



Texas Children's Hospital®

Baylor College of Medicine

HPV9 Pre-licensure Data

Pediatrics



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women

E.A. Joura, A.R. Giuliano, O.-E. Iversen, C. Bouchard, C. Mao, J. Mehlsen, E.D. Moreira, Jr., Y. Ngan, L.K. Petersen, E. Lazcano-Ponce, P. Pitisuttithum, J.A. Restrepo, G. Stuart, L. Woelber, Y.C. Yang, J. Cuzick, S.M. Garland, W. Huh, S.K. Kjaer, O.M. Bautista, I.S.F. Chan, J. Chen, R. Gesser, E. Moeller, M. Ritter, S. Vuocolo, and A. Luxembourg, for the Broad Spectrum HPV Vaccine Study*

- Study #001, randomized, international, multi-center, double-blind trial comparing HPV4 to HPV9
- n = 14, 215 females 16-26 years who had never had a Pap or only had normal Pap results

Joura EA et al. N Engl J Med 2015;372:711-23

Texas Children's Hospital

Baylor College of Medicine

Table 4. Adverse Events.*

Event	9vHPV Vaccine (N=7071)	qHPV Vaccine (N=7078)
	no. of participants (%)	
Participants with one or more adverse events†	6640 (93.9)	6419 (90.7)
Injection-site event‡	6414 (90.7)	6012 (84.9)
Pain§	6356 (89.9)	5910 (83.5)
Mild	3754 (53.1)	4043 (57.1)
Moderate	2300 (32.5)	1682 (23.8)
Severe	302 (4.3)	185 (2.6)
Swelling	2830 (40.0)	2035 (28.8)
Mild: 0 to ≤2.5 cm	1958 (27.7)	1594 (22.5)
Moderate: >2.5 cm to ≤5.0 cm	597 (8.4)	332 (4.7)
Severe: >5.0 cm	272 (3.8)	109 (1.5)
Unknown	3 (0)	0 (0)
Erythema	2407 (34.0)	1810 (25.6)
Mild: 0 to ≤2.5 cm	1921 (27.2)	1555 (22.0)
Moderate: >2.5 cm to ≤5.0 cm	370 (5.2)	197 (2.8)
Severe: >5 cm	114 (1.6)	57 (0.8)
Unknown	2 (0)	1 (0)
Pruritus§	388 (5.5)	282 (4.0)
Mild	301 (4.3)	223 (3.2)
Moderate	80 (1.1)	56 (0.8)
Severe	7 (0.1)	3 (0)

Joura EA et al. N Engl J Med 2015;372:711-23

Table 4. Adverse Events.*

Event	9vHPV Vaccine (N=7071)	qHPV Vaccine (N=7078)
	no. of participants (%)	
Systemic event¶	3948 (55.8)	3883 (54.9)
Any vaccine-related systemic event	2086 (29.5)	1929 (27.3)
Headache	1031 (14.6)	969 (13.7)
Pyrexia	357 (5.0)	301 (4.3)
Nausea	311 (4.4)	261 (3.7)
Dizziness	211 (3.0)	197 (2.8)
Fatigue	166 (2.3)	150 (2.1)
Serious event	233 (3.3)	183 (2.6)
Vaccine-related event	2 (0)	2 (0)
Death‖	5 (0.1)	5 (0.1)
Discontinuation due to adverse event**	8 (0.1)	4 (0.1)
Vaccine-related event	5 (0.1)	3 (0)
Serious event	3 (0)	1 (0)
Serious vaccine-related event	1 (0)	0 (0)

Joura EA et al. N Engl J Med 2015;372:711-23

Why are vaccine associated events slightly higher?

	HPV4 (µg)	HPV9 (µg)
Amorphous Aluminum Hydroxyphosphate Sulfate (AAHS)	225	500
HPV-6	20	30
HPV-11	40	40
HPV-16	40	60
HPV-18	20	40
HPV-31	--	20
HPV-33	--	20
HPV-45	--	20
HPV-52	--	20
HPV-58	--	20

Joura EA et al. N Engl J Med 2015;372:711-23

HPV9 Immunobridging studies

- Study V503-009, randomized controlled trial
- 600 girls, 9-15 years
- Hypotheses:
  1. Similar immune response compared to HPV4
  2. Well-tolerated

https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf

Table 1: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

	GARDASIL 9				GARDASIL			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
Girls and Women 16 through 26 Years of Age								
Injection-Site Adverse Reactions	**N=7069**	**N=6997**	**N=6909**	**N=7071**	**N=7076**	**N=6992**	**N=6909**	**N=7078**
Pain, Any	70.7	73.5	71.6	89.9	58.2	62.2	62.6	83.5
Pain, Severe	0.7	1.7	2.6	4.3	0.4	1.0	1.7	2.6
Swelling, Any	12.5	23.3	28.3	40.0	9.3	14.6	18.7	28.8
Swelling, Severe	0.6	1.5	2.5	3.8	0.3	0.5	1.0	1.5
Erythema, Any	10.6	18.0	22.6	34.0	8.1	12.9	15.6	25.6
Erythema, Severe	0.2	0.5	1.1	1.6	0.2	0.2	0.4	0.8
Systemic Adverse Reactions	**n=6995**	**n=6913**	**n=6743**	**n=7022**	**n=7003**	**n=6914**	**n=6725**	**n=7024**
Temperature ≥100°F	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature ≥102°F	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
Girls 9 through 15 Years of Age								
Injection-Site Adverse Reactions	**N=300**	**N=297**	**N=296**	**N=299**	**N=299**	**N=299**	**N=294**	**N=300**
Pain, Any	71.7	71.0	74.3	89.3	66.2	66.2	69.4	88.3
Pain, Severe	0.7	2.0	3.0	5.7	0.7	1.3	1.7	3.3
Swelling, Any	14.0	23.9	36.1	47.8	10.4	17.7	25.2	36.0
Swelling, Severe	0.3	2.4	3.7	6.0	0.7	2.7	4.1	6.3
Erythema, Any	7.0	15.5	21.3	34.1	9.7	14.4	18.4	29.3
Erythema, Severe	0	0.3	1.4	1.7	0	0.3	1.7	2.0
Systemic Adverse Reactions	**n=300**	**n=294**	**n=295**	**n=299**	**n=299**	**n=297**	**n=291**	**n=300**
Temperature ≥100°F	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature ≥102°F	0	0.3	1.0	1.3	0.3	0.3	0	0.7

The data for girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).

https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf

Table 2: Rates (%) of Unsolicited Injection-Site and Systemic Adverse Reactions Occurring among ≥1.0% of Individuals after Any Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

	Girls and Women 16 through 26 Years of Age		Girls 9 through 15 Years of Age	
	GARDASIL 9 N=7071	GARDASIL N=7078	GARDASIL 9 N=299	GARDASIL N=300
Injection-Site Adverse Reactions (1 to 5 Days Post-Vaccination, Any Dose)				
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	0	0
Hematoma	0.9	0.6	3.7	4.7
Mass	1.3	0.6	0	0
Hemorrhage	1.0	0.7	1.0	2.0
Induration	0.8	0.2	2.0	1.0
Warmth	0.8	0.5	0.7	1.7
Reaction	0.6	0.6	0.3	1.0
Systemic Adverse Reactions (1 to 15 Days Post-Vaccination, Any Dose)				
Headache	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0	2.7
Diarrhea	1.2	1.0	0.3	0
Oropharyngeal pain	1.0	0.6	2.7	0.7
Myalgia	1.0	0.7	0.7	0.7
Abdominal pain, upper	0.7	0.8	1.7	1.3
Upper respiratory tract infection	0.1	0.1	0.3	1.0

https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf

HPV9 Immunobridging studies

- Study V503-002, observational study
- 2 groups, n = 2,999:
  - Boys (n=639) and girls (n=1,878) 9-15 years;
  - Women 16-26 years
- Subjects received doses from one of 3 different lots of HPV9
- Hypotheses:
  1. Similar immune response in boys and girls compared to women
  2. Well-tolerated in boys and girls compared to women
  3. Consistent immune response across 3 different lots

https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf

Table 3: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age who Received Gardasil 9

	GARDASIL 9 N=639	Girls
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pain	71.5	89.3
Injection-Site Erythema	24.9	34.1
Injection-Site Swelling	26.9	47.8
Oral Temperature ≥100.0°F[T]	10.4	6.7
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Hematoma	1.3	3.7
Injection-Site Induration	1.1	2.0
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)		
Headache	9.4	11.4
Pyrexia	8.9	5.0
Nausea	1.3	3.0

HPV9 Immunobridging studies

- Study V503-003, observational
- 3 groups, n=2,520
  - Heterosexual men, 16-26 years, n=1,106
  - MSM, 16-26 years, n=313
  - Females, 16-26 years, n=1,101
- Hypotheses:
  1. Similar immune responses in men compared to females
  2. Well-tolerated

https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf

Solicited and unsolicited AEs

	Men (%)	Women (%)
Injection site pain	63.6	83.1
Injection site erythema	20.9	32.4
Injection site swelling	20.4	38
Temperature ≥100.0F	4.4	5.9
Hematoma	0.1	0
Headache	14.4	22.9

https://clinicaltrials.gov/ct2/show/results/NCT01651949?sect=X9843a0156&term=v503-003&rank=1#outcome3

Serious Adverse Events

- Examined collectively for 6 integrated clinical studies
- 13,236 HPV9 recipients had safety follow-up
- 305 (2.3%) reported serious adverse event
  - HPV4 comparison 185/7,378 = 2.5%
- 5 SAEs were vaccine-related: pyrexia, allergy to vaccine, asthmatic crisis, headache and tonsillitis)

Deaths across study population

- 10 deaths occurred across the clinical studies
- 5 in HPV9 group and 5 in HPV4 group
- None were vaccine-related
- HPV9 – MVA, suicide, ALL, hypovolemic septic shock, unexplained sudden death 678 days after last dose
- HPV4 – MVA, airplane crash, cerebral hemorrhage, gunshot wound, stomach adenocarcinoma

Systemic autoimmune disorders

- 2.4% of HPV9 recipients reported new medical conditions
- 3.3% of HPV4 recipients reported new medical conditions
- Both were similar to rates reported following AAHS (adjuvant alone) control or saline placebo in historical clinical trials

HPV9 Immunobridging studies

- Study V503-006, RCT
- 924 girls 12-26 years who had previously received HPV4
- Purpose of the study was to examine participants for serious or non-serious adverse events

Table 4: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Individuals Previously Vaccinated with GARDASIL Who Received GARDASIL 9 or Saline Placebo (Girls and Women 12 through 26 Years of Age)

	GARDASIL 9 N=608	Saline Placebo N=305
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pain	90.3	38.0
Injection-Site Erythema	42.3	8.5
Injection-Site Swelling	49.0	5.9
Oral Temperature ≥100.0°F[T]	6.5	3.0
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)		
Injection-Site Pruritus	7.7	1.3
Injection-Site Hematoma	4.8	2.3
Injection-Site Reaction	1.3	0.3
Injection-Site Mass	1.2	0.7
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)		
Headache	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain, upper	1.5	0.7
Influenza	1.2	1.0

https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf

Concomitant Use

- Study V503-005
- Purpose to examine antibody responses for all vaccines co-administered (Menactra (MCV4), Adacel (Tdap) and HPV9)
- Also to observe for differences in injection site adverse reactions and fever days 1-5 following vaccination

Concomitant use AEs

	Concomitant (%)	Non-concomitant (%)
Injection site erythema	40.0	38.1
Injection site pain	84.5	80.2
Injection site swelling	45.0	41.7
Pyrexia	14.4	15.6
Headache	22.8	17.5

https://clinicaltrials.gov/ct2/show/NCT00365378?term=v501-005&rank=1

Practical safety advice for clinicians:

- Pain occurs in almost everyone (90%)
- Swelling and redness are common too (30-40%)
- Fever and hematomas are uncommon (3-5%)
- Headache may occur in about 20%
- SAEs are very rare
- When in doubt, lay down the patient and give the vaccine in the supine position
- Adhere to 15 minute observation period

http://redbook.solutions.aap.org/chapter.aspx?sectionId=56798089&bookId=886&resultClick=1#56798728

Practical safety advice for parents

- HPV9 is very safe
- HPV9 is similar to HPV4, although more redness and swelling may be seen due to the additional ingredients
- Local AEs are common (expect pain, possible redness and swelling)
- SAEs are rare
- Scientific studies do not support scary stories spread by popular media






Julie Boom, M.D.
jboom@bcm.edu
832-824-2064

Texas Children's Hospital®

Baylor College of Medicine

Pediatrics