9-valent HPV vaccine
Background, transition issues and additional vaccination

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Overview

- **Background**
  - Overview of HPV vaccines
  - Review of 9-valent vaccination recommendations (Feb 2015)
  - Program transition to 9-valent HPV vaccine
- **Additional 9-valent HPV vaccination**
  - Burden of disease
  - Clinical trial data

HPV vaccines licensed in the US

	Bivalent 2vHPV (Cervarix)	Quadrivalent 4vHPV (Gardasil)	9-valent 9vHPV (Gardasil 9)
L1 VLP types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck & Co.	Merck & Co.
Adjuvant	AS04: 500 µg aluminum hydroxide 50 µg 3-*O*-desacyl-4'-monophosphoryl lipid A	AAHS: 225 µg amorphous aluminum hydroxyphosphate sulfate	AAHS: 500 µg amorphous aluminum hydroxyphosphate sulfate
Schedule	3-dose series	3-dose series	3-dose series

~99% of HPV vaccine administered in US through 2014 was quadrivalent HPV vaccine

L1, Major capsid protein; VLP, virus like particle

9-valent HPV vaccine licensure and recommendations

- **Licensed by FDA, December 2014**
- **Recommended by ACIP, February 2015**
  - MMWR Policy Note published March 27, 2015
- **AAP HPV vaccine recommendations, 2015**
  - Consistent with ACIP recommendations

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426445
MMWR 2015;64:300-4
http://www2.aap.org/immunization/illnesses/hpv/hpv.html

Licensed age groups for available HPV vaccines

	Bivalent (Cervarix)	Quadrivalent (Gardasil)	9-valent (Gardasil 9)
Licensure	Females 9-25 years	Females 9-26 years Males 9-26 years	Females 9-26 years Males 9-15 years

- At the time of the first application to FDA, 9vHPV immunogenicity trials in males 16-26 years had not been completed
- Immunogenicity data for males 16-26 years were presented to ACIP and submitted to FDA
- In February 2015, ACIP recommended use of 9vHPV in the currently recommended age groups – through 21 years for males*
  - Use in males 16-26 years is off label at this time

*through age 26 for MSM and immunocompromised males and those with HIV infection

Updated ACIP recommendations February 2015

- Routine vaccination at age 11 or 12 years* with a 3-dose series
- Vaccination recommended through age 26 for females and through age 21 for males not previously vaccinated
- Vaccination recommended for men who have sex with men and immunocompromised men (including HIV-infected) through age 26
- Vaccination of females is recommended with 2vHPV, 4vHPV (as long as this formulation is available), or 9vHPV
- Vaccination of males is recommended with 4vHPV (as long as this formulation is available) or 9vHPV

*vaccination series can be started at 9 years of age

MMWR 2015;64:300-4

Updated ACIP recommendations February 2015

If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV, for protection against HPV 16 and 18, any HPV vaccine product may be used to continue or complete the series for females; 4vHPV or 9vHPV may be used to continue or complete the series for males.

MMWR 2015;64:300-4

TRANSITION FROM QUADRIVALENT TO 9-VALENT HPV VACCINE

9-valent HPV vaccine introduction

- **Licensed by FDA in December 2014**
- **Recommended by ACIP in February 2015**
  - MMWR Policy Note published March 27, 2015
- **Included in the VFC contract in April 2015**
  - May 2015, >50% of awardees placed orders that included 9vHPV
- **Managed care***
  - As of June 2015, >85% of managed care plans have decided to cover 9vHPV

VFC, Vaccines for Children
*Information provided by Merck & Co., Inc

Manufacturer plans

- Merck intends to maintain 4vHPV in the US market until:
  - 9vHPV is approved by FDA for use in males 16-26 years (to match all indications for 4vHPV)
  - 6 months have passed from FDA approval of the male 16-26 year indication (to allow for series completion with 4vHPV)
- 4vHPV expected to be on market until mid-2016
  - Pending FDA approval of the male 16-26 year indication

Information provided by Merck & Co., Inc

CDC suggestions provided to awardees for implementation during the transition from 4vHPV to 9vHPV

- Providers who have 4vHPV stock but prefer to vaccinate their VFC patients with 9vHPV should be able to order 9vHPV
- For those providers who choose to implement 9vHPV but still have 4vHPV stock, doses of 4vHPV can be used to complete the series for patients who started a series with 4vHPV, or can be used in males since the additional protection from 9vHPV will mostly benefit females

VFC, Vaccines for Children

ADDITIONAL 9-VALENT HPV VACCINATION

Additional 9vHPV vaccination: 9vHPV for persons who completed an HPV vaccination series

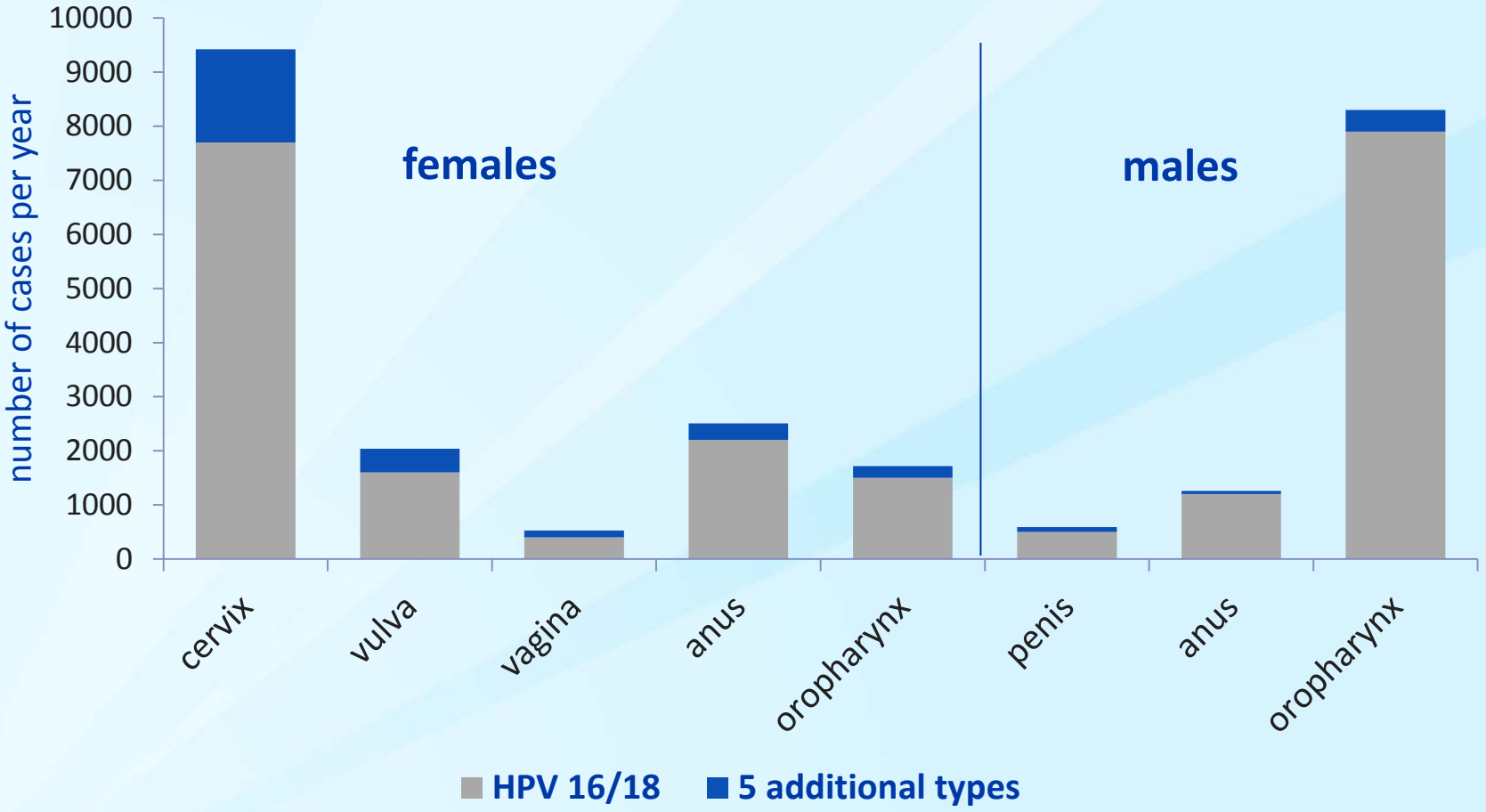
- Due to abbreviated meeting, not discussed in February 2015
- MMWR Policy Note does not include information on this topic
- There is no indication for additional 9vHPV vaccination in the vaccine label
- Common question from vaccination providers/parents

Estimated percentages of cancers attributed to HPV in the U.S.

Cancer	HPV attributable % (95% CI)	HPV 16/18 attributable % (95% CI)	HPV 31/33/45/52/58 attributable % (95% CI)
Cervical	91 (88-92)	66 (63-69)	15 (12-17)
Vaginal	75 (63-84)	55 (43-67)	18 (11-30)
Vulvar	69 (62-75)	49 (41-56)	14 (10-20)
Penile	63 (52-73)	48 (37-59)	9 (4-17)
Anal			
Male	89 (77-95)	79 (66-88)	4 (1-13)
Female	92 (85-96)	80 (70-87)	11 (6-19)
Oropharyngeal			
Male	72 (68-76)	63 (59-68)	4 (3-7)
Female	63 (55-71)	51 (43-59)	9 (6-15)

Saraiya et al. JNCI 2015;107

Estimated annual number of cancers attributable to HPV 16/18 and 5 additional HPV types in 9-valent vaccine, U.S.*



*Based on years 2006-2010 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6349a11.htm and data from Saraiya et al. JNCI 2015;107

Summary: attribution of HPV 16/18 and HPV 31/33/45/52/58, United States

- **HPV-associated cancers**
  - 64% of cancers attributable to HPV 16/18
    - 66% of cervical cancer
    - Other cancers: range, 48% penile - 80% anal
  - 10% of cancers attributable to additional 5 types
    - 15% of cervical cancer
    - Other cancers: range, 4% oropharyngeal - 18% vaginal
    - Differences by sex: 14% (n=2800) for females; 4% (n=550) for males
- **≥CIN2 lesions**
  - ~50% attributable to HPV 16/18
  - ~25% attributable to 5 additional types

≥CIN2, cervical intraepithelial neoplasia grade 2 or worse
% among all HPV-associated cancers

MMWR 2015;64:300-4 MMWR RR 2014;63:1-30 Hariri et al. CEBP 2015;393-9

9-valent HPV vaccine clinical development program

- Efficacy trial in females aged 16-26 years
- Immunogenicity/immunobridging trials
- Concomitant use trials
- 9vHPV among females who were vaccinated previously with 4vHPV

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

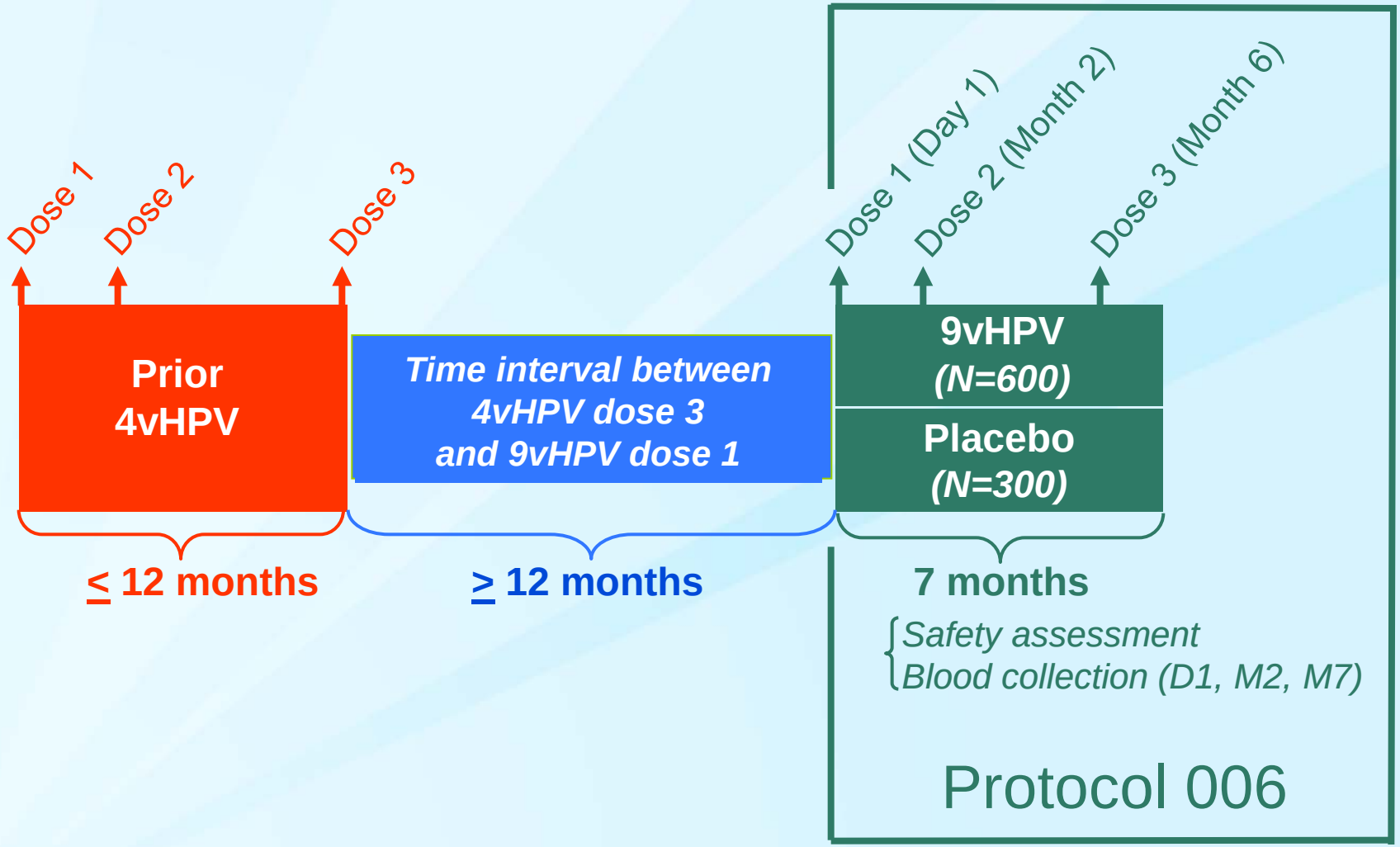
Protocol 006: 9vHPV in prior 4vHPV recipients

Study Objectives	To evaluate the safety of 9vHPV in prior 4vHPV recipients To evaluate immunogenicity of 9vHPV with respect to HPV 31,33,45,52,58 in prior 4vHPV recipients
Study Population	924 females 12–15 years: ~180 16–26 years: ~720
Study Design	Double-blinded RCT (randomized 2:1 to 9vHPV/saline placebo) 0,2,6 month schedule Antibody measured at enrollment, post dose 1 and post dose 3

- Manufacturer did not seek an indication for 9vHPV in prior 4vHPV recipients

RCT, randomized controlled trial

Protocol 006: Study design

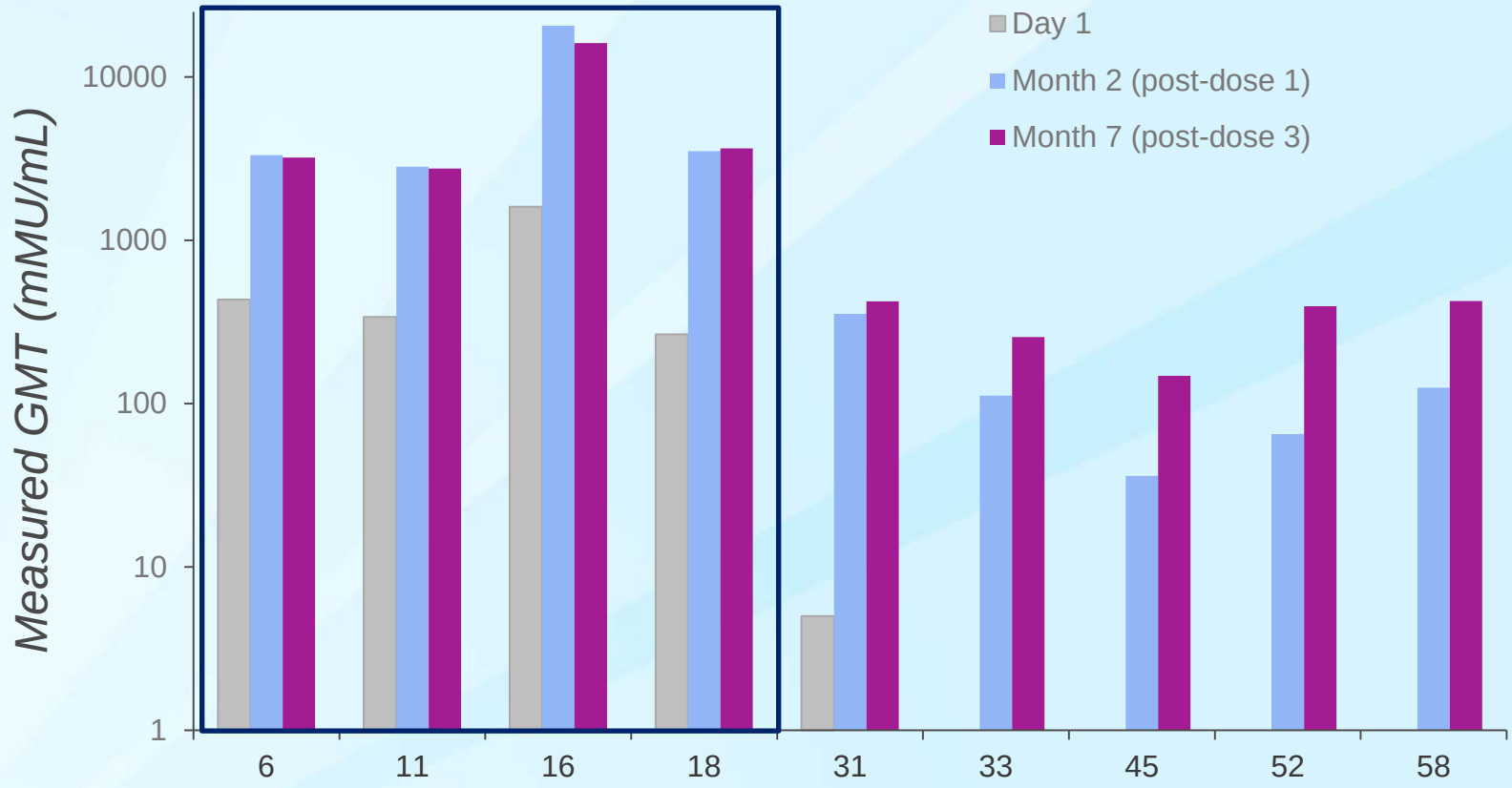


Protocol 006: 9vHPV in prior 4vHPV recipients Summary immunogenicity findings

- **Post dose 1**
  - Seropositivity to HPV 31,33,45,52,58: 98%, 95%, 68%, 94%, 99%
- **Post dose 2**
  - Sera not collected
- **Post dose 3**
  - >98% seropositive to all 5 types

9vHPV immunogenicity in prior 4vHPV recipients at enrollment, following dose 1 and dose 3

Females 12 to 15 years of age



Fold difference (post-dose 3/ post-dose 1):	**0.96**	**0.98**	**0.78**	**1.04**	**1.20**	**2.29**	**4.16**	**6.08**	**3.40**

9vHPV immunogenicity in prior 4vHPV recipients at enrollment, following dose 1 and dose 3

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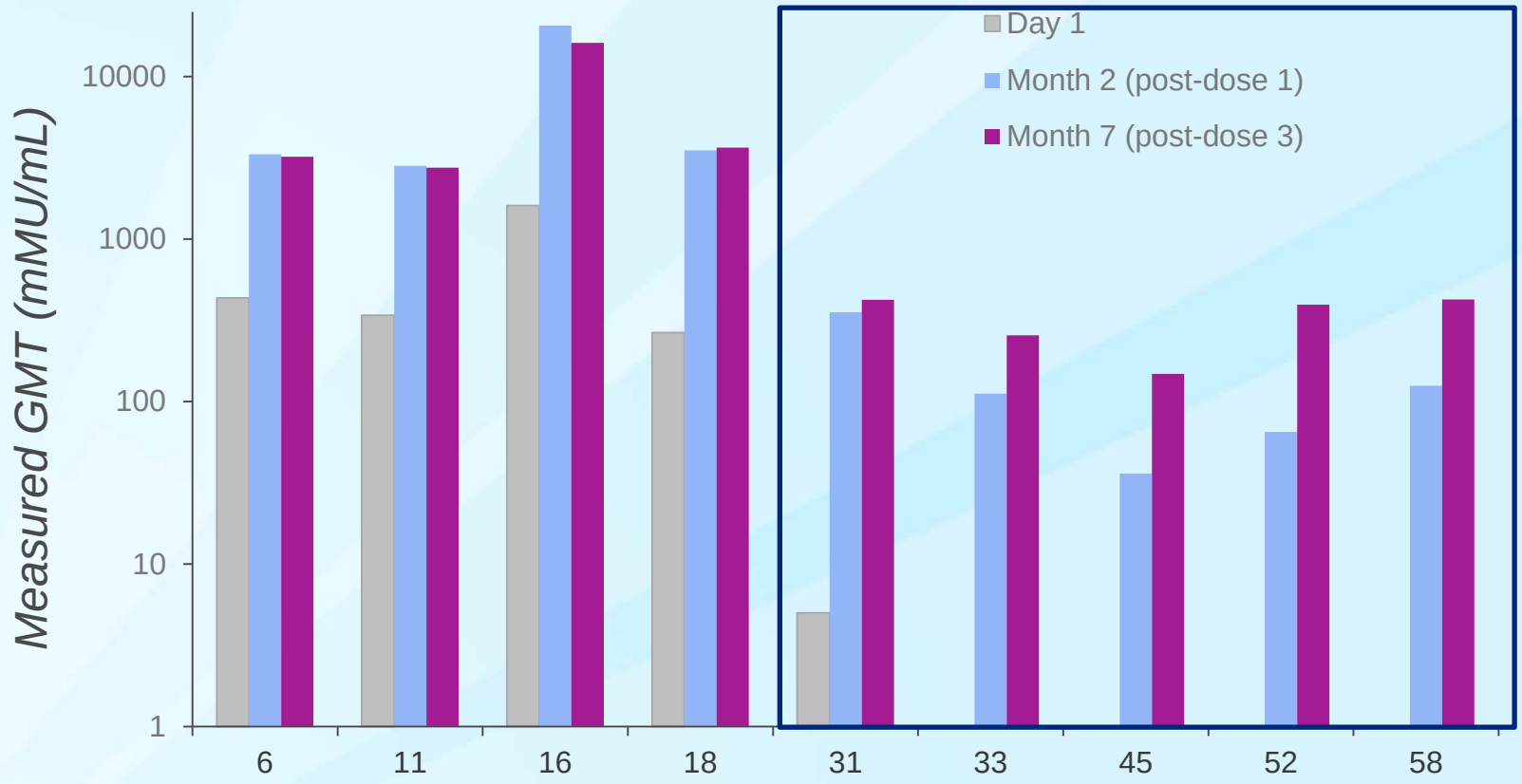

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Protocol 006: Injection-site and systemic adverse events

(Following any dose)

Reaction	9vHPV (N=608) %	Saline placebo (N=305) %
Injection-site AE* (1-5 days)		
Pain	90.3	38.0
Swelling	49.0	5.9
Erythema	42.3	8.5
Pruritus	7.7	1.3
Hematoma	4.8	2.3
Reaction	1.3	0.3
Mass	1.2	0.7
Systemic AE (1-15 days)		
Headache	19.6	18.0
Fever	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain	1.5	0,7

*Most injection-site adverse events (AEs) were of mild or moderate intensity

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

Cross-study comparison

Analysis Objectives	To compare the safety of 9vHPV in prior 4vHPV recipients with 9vHPV in 4vHPV naïve females*
	To compare immunogenicity of 9vHPV in prior 4vHPV recipients with 9vHPV in 4vHPV naïve females*
Limitation	Analysis comparing data across different studies

*in other trials from 9vHPV clinical program

9vHPV immunogenicity in prior 4vHPV recipients Cross-study comparison

Age/Type	GMTs after 3 doses of 9vHPV (95% CI)		Ratio
	Naïve to 4vHPV vaccination[a]	Prior 4vHPV vaccination[b]	
16-26 yrs			
HPV 31	**665** (647,683)	**231** (211,253)	**0.3**
HPV 33	**419** (410,429)	**160** (147,174)	**0.4**
HPV 45	**254** (247,262)	**88** (80, 97)	**0.3**
HPV 52	**382** (373,392)	**240** (220,261)	**0.6**
HPV 58	**489** (478,501)	**242** (223,262)	**0.5**
12-15 yrs			
HPV 31	**1538** (1461,1619)	**423** (352,510)	**0.3**
HPV 33	**822** (785,860)	**256** (217,302)	**0.3**
HPV 45	**591** (557,627)	**148** (119,183)	**0.3**
HPV 52	**823** (784,864)	**395** (331,472)	**0.5**
HPV 58	**1111** (1060,1164)	**425** (359,503)	**0.4**

[a]Data from Protocols 001, 002 for 16-26 yr olds and from Protocols 002, 005, 007 for 12-15 yr olds; by cLIA at month 7
[b]Data from Protocol 006

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM429166.pdf

Injection-Site AEs after 9vHPV in prior 4vHPV recipients
Cross-study safety comparison
Females 12 to 26 years
(Days 1 to 5 following any vaccination with 9vHPV vaccine)

Injection-site AE	Naïve to HPV vaccination* (N=9,385) %	Prior 4vHPV vaccination (N=608) %
Pain	88.1	90.3
Erythema	32.3	42.3
Swelling	38.4	49.0

AE, adverse event
*From protocols 001, 002, 005, 007, 009

Merck, unpublished data

Summary (transition)

- Updated HPV vaccine Policy Note published, March 2015
- 9vHPV included in VFC contract, April 2015
- Transition to 9vHPV in public and private sectors ongoing
- Manufacturer expects 4vHPV to be on the US market until mid-2016

VFC, Vaccines for Children

Summary (additional 9vHPV vaccination)

- One trial evaluated 9vHPV in prior 3-dose 4vHPV recipients
  - After 3 doses of 9vHPV, >98% of prior 4vHPV recipients were seropositive to all additional 5 types
  - Acceptable safety profile
- In a cross study comparison of 9vHPV in prior 4vHPV recipients
  - 3 doses of 9vHPV resulted in lower GMTs for the 5 additional types compared with 3 doses of 9vHPV in HPV vaccine naïve females
    - Clinical significance unclear: no immune correlate of protection
  - Safety profile similar except higher rates of injection site reactions

Acknowledgements

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Thank you

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