

# **Comparison of immunogenicity of 2-dose and 3-dose regimens of 9-valent HPV vaccine**

**Advisory Committee on Immunization Practices  
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## Licensure and Recommendation for 9vHPV Vaccine (Gardasil 9): Similar to qHPV Vaccine (Gardasil)

- The 9-valent HPV (9vHPV) vaccine (3-dose regimen) was licensed in Dec 2014 in the United States, in 2015 in Canada, the EU, Australia, Chile and Hong-Kong, and in 2016 in Ecuador, Korea and New Zealand under the name GARDASIL-9 to prevent
  - *Cervical/vulvar/vaginal/anal cancers caused by HPV 16/18/31/33/45/52/58*
  - *Cervical/vulvar/vaginal/anal dysplasia caused by HPV 6/11/16/18/31/33/45/52/58*
  - *Genital warts caused by HPV 6/11*
- In Feb 2015, the Advisory Committee on Immunization Practices (ACIP) recommended Gardasil 9 for routine vaccination
- Licensure of 9vHPV vaccine is under review in other countries

# Assessment of 2-dose Regimen for HPV Vaccines

- Change in WHO recommendation in Oct 2014 (*HPV vaccines: WHO position paper. Wkly Epidemiol Rec 2014; 89:465-492*)
  - 2 doses (interval 6 months) in girls 9-14 years of age
    - *If dose 2 is administered <5 months after dose 1, a third dose should be given >6 months after the first dose*
    - *No maximum recommended interval (≤12-15 months suggested to complete schedule promptly and prior to becoming sexually active)*
  - 3 doses in individuals ≥15 years of age and those known to be immunocompromised and/or HIV infected
- No current licensure or recommendation of 2-dose regimen in the US
  - 2-dose immunogenicity study of qHPV vaccine was conducted
    - *Demonstrated non-inferior immunogenicity of 2-dose regimen in girls 9-13 years of age vs. 3-dose regimen in women 16-26 years of age*
    - *Ref: Dobson et al. (2013) JAMA 309:1793-1802*
  - Results not submitted to the FDA (considering the imminent submission of the 9vHPV vaccine initial filing to the FDA)

# Assessment of 2-Dose Regimen of 9vHPV Vaccine

- 9vHPV vaccine was developed as a 3-dose vaccine
  - *Development started in 2007 (at that time, 3-dose regimen was standard for HPV vaccines)*
    - *Dec 2014: initial licensure of Gardasil 9 (3-dose regimen)*
    - *Dec 2015: licensure extended to males 16-26 years of age*
- 9vHPV vaccine 2-dose regimen assessment
  - *Immunobridging study ongoing (Protocol 010)*
    - *Results of primary immunogenicity analyses (4 weeks post-last dose) expected to be reviewed by the FDA in 2016*
    - *Study to continue for 2 more years for assessment of antibody persistence and immune memory*
  - *Separate long-term effectiveness planned in a larger study (Protocol 025)*

# 9vHPV 2-dose Study: Study Design [1 of 2]

Enrollment	Open-label study; all received 9vHPV vaccine				
	Cohort	Age (years)	Gender	N	Dosing regimen (months)
	1	9-14	F	300	0, 6
	2	9-14	M	300	0, 6
	3	9-14	F/M	300	0, 12
	4 (control)	16-26	F	300	0, 2, 6
	5 (exploratory)	9-14	F	300	0, 2, 6
Vaccine administration	<ul style="list-style-type: none"> <li>● 2 or 3 vaccination visits: <i>±4-week window around the Month 6 and Month 12 visits; 3-week window around the Month 2 visit</i></li> <li>● 1 additional dose of 9vHPV vaccine at Mo 36 to assess immune memory (<i>antibody levels assessed 1 week &amp; 1 month later</i>)</li> </ul>				

# 9vHPV 2-dose Study: Study Design [2 of 2]

<p><b>Duration</b></p>	<p>37-month study</p>
<p><b>Primary objectives</b></p>	<p>Non-inferiority of GMTs at 1 month after the last dose in girls and boys who received a 2-dose regimen vs. young women who received a 3-dose regimen</p> <p><i>Same approach as that previously accepted for licensure of 3-dose regimen of Gardasil 9</i></p> <p><i>Non-inferiority criterion: exclude 1.5-fold decrease (2- vs. 3-dose)</i></p> <p>3 non-inferiority tests</p> <p><i>Girls (0, 6) vs. Women (0, 2, 6)</i></p> <p><i>Boys (0, 6) vs. Women (0, 2, 6)</i></p> <p><i>Girls/Boys (0, 12) vs. Women (0, 2, 6)</i></p>
<p><b>Exploratory analyses</b></p>	<p>Compare GMTs 1 month after last dose in</p> <p><i>Girls (0, 6) vs. Girls (0, 2, 6)</i></p> <p><i>Girls (0, 12) vs. Girls (0, 2, 6)</i></p> <p>Antibody persistence at Months 24 and 36</p> <p>Assess evidence of immune memory (<i>additional dose at Mo 36</i>)</p> <p><i>No hypothesis testing for the exploratory analyses</i></p>

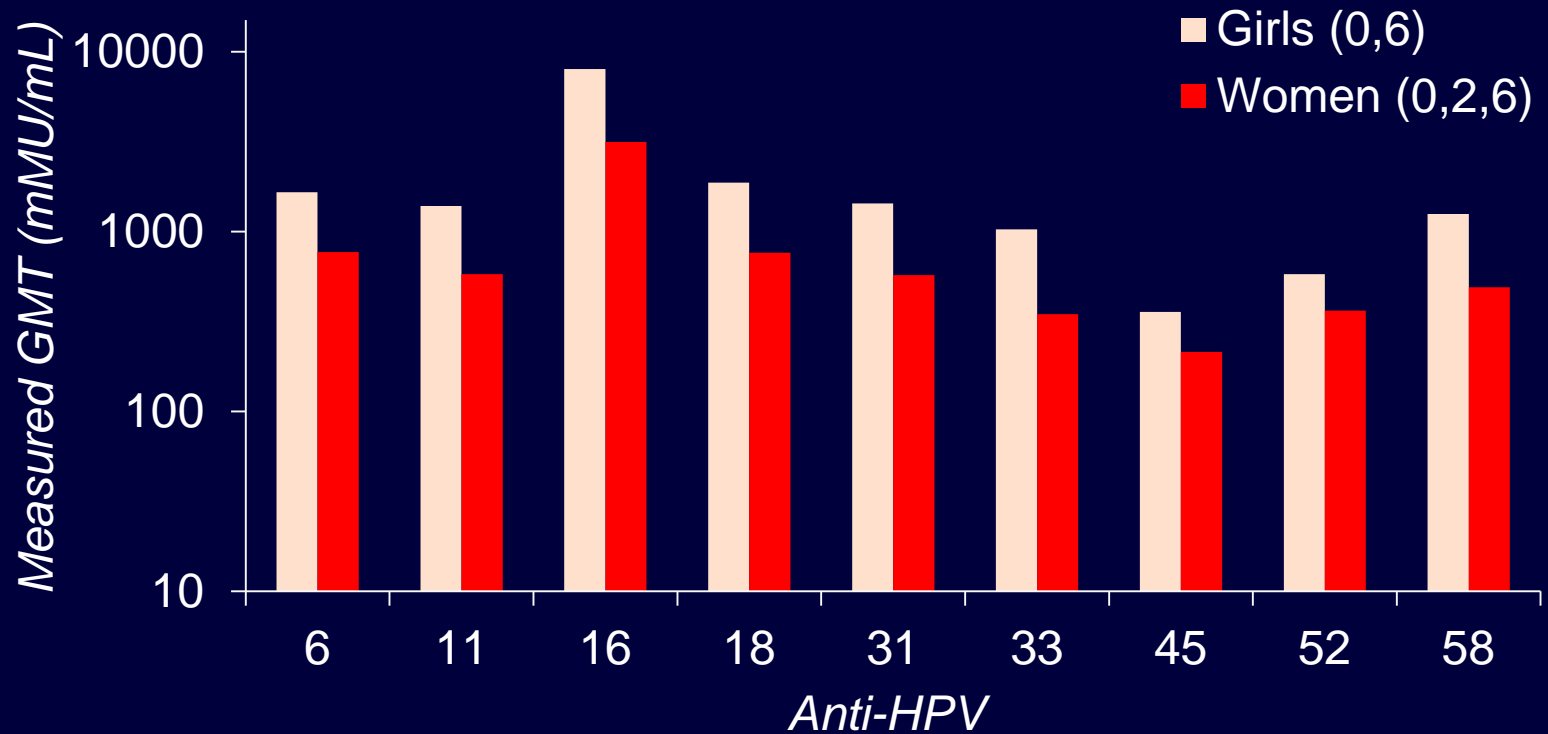
# **EVALUATION OF PRIMARY OBJECTIVES**

***2 DOSES IN GIRLS AND BOYS 9-14 YEARS OF AGE VS.***

***3 DOSES IN YOUNG WOMEN 16-26 YEARS OF AGE***

# 9vHPV 2-dose Study: Non-inferior GMT at 1 Month Post-Last Dose in 2-dose (0, 6) Girls vs. 3-dose (0, 2, 6) Women

The non-inferiority criterion was met for all 9 HPV types (all  $p < 0.001$ )

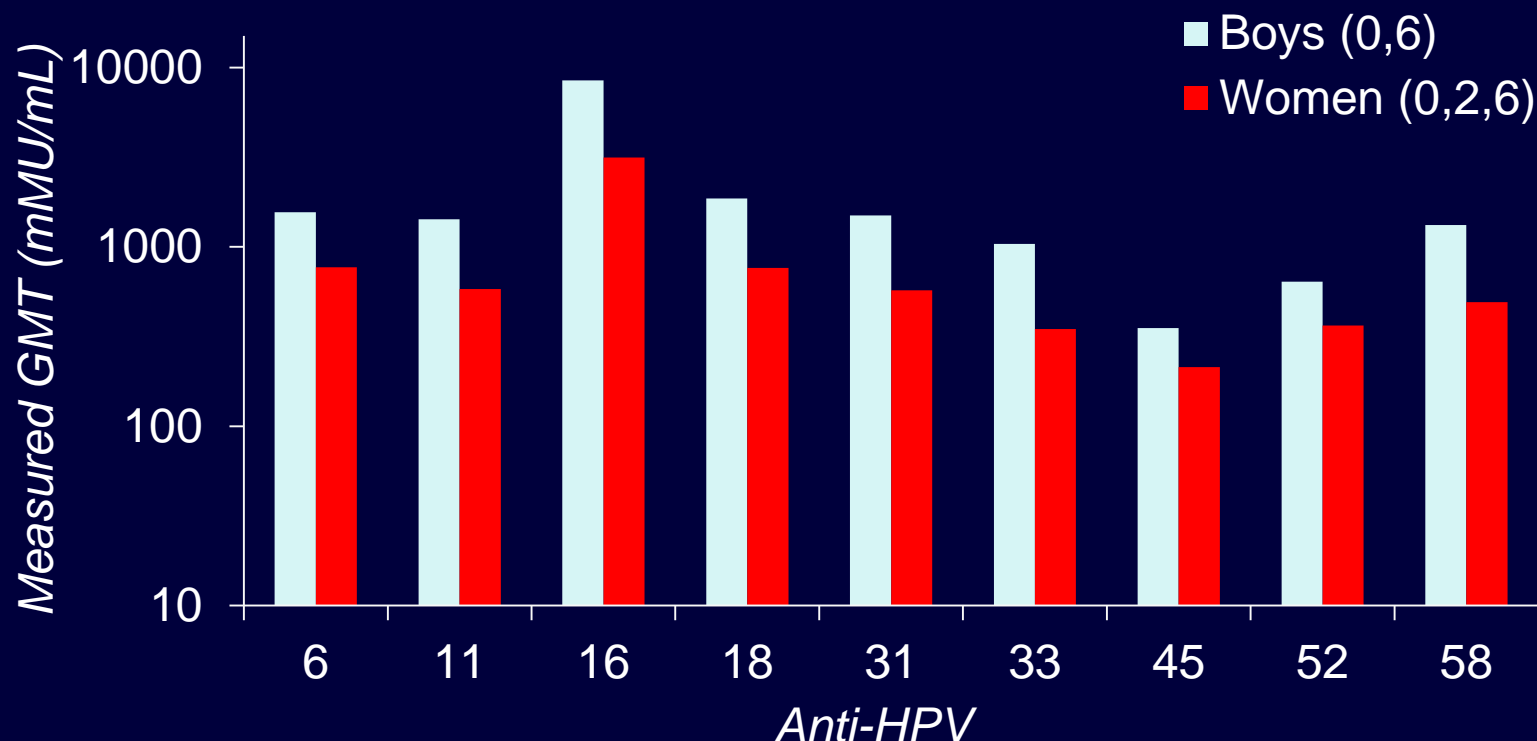


Fold difference (girls/women)	<b>2.15</b>	<b>2.39</b>	<b>2.54</b>	<b>2.46</b>	<b>2.51</b>	<b>2.96</b>	<b>1.67</b>	<b>1.60</b>	<b>2.55</b>
95% CI	(1.83, 2.53)	(2.03, 2.82)	(2.14, 3.00)	(2.05, 2.96)	(2.10, 3.00)	(2.50, 3.50)	(1.38, 2.03)	(1.36, 1.87)	(2.15, 3.01)



# 9vHPV 2-dose Study: Non-inferior GMT at 1 Month Post-Last Dose in 2-dose (0, 6) Boys vs. 3-dose (0, 2, 6) Women

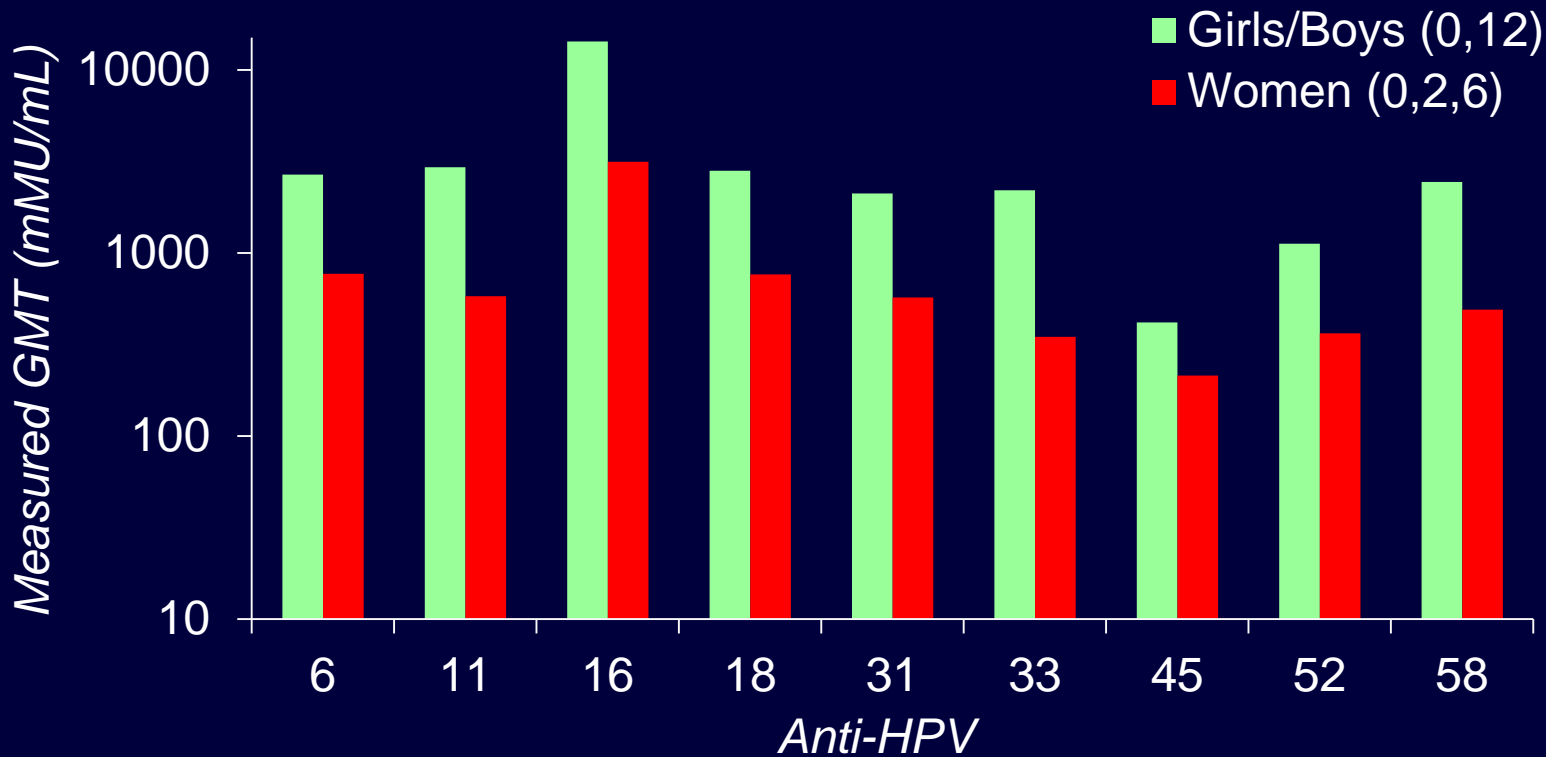
The non-inferiority criterion was met for all 9 HPV types (all  $p < 0.001$ )



Fold difference (boys/women)	<b>2.02</b>	<b>2.45</b>	<b>2.69</b>	<b>2.44</b>	<b>2.62</b>	<b>2.99</b>	<b>1.65</b>	<b>1.76</b>	<b>2.70</b>
95% CI	(1.73, 2.36)	(2.09, 2.88)	(2.29, 3.15)	(2.04, 2.92)	(2.20, 3.12)	(2.55, 3.50)	(1.37, 1.99)	(1.51, 2.05)	(2.30, 3.16)

# 9vHPV 2-dose Study: Non-inferior GMT at 1 Month Post-Last Dose in 2-dose (0, 12) Girls & Boys vs. 3-dose (0, 2, 6) Women

The non-inferiority criterion was met for all 9 HPV types (all  $p < 0.001$ )



Fold difference (girls&boys/women)	<b>3.47</b>	<b>5.07</b>	<b>4.54</b>	<b>3.69</b>	<b>3.70</b>	<b>6.31</b>	<b>1.96</b>	<b>3.08</b>	<b>4.98</b>
95% CI	(2.93, 4.11)	(4.32, 5.94)	(3.84, 5.37)	(3.06, 4.45)	(3.08, 4.45)	(5.36, 7.43)	(1.61, 2.37)	(2.64, 3.61)	(4.23, 5.86)

## 9vHPV 2-dose Study: Seroconversion Rates at 4 Weeks Post-Last Dose

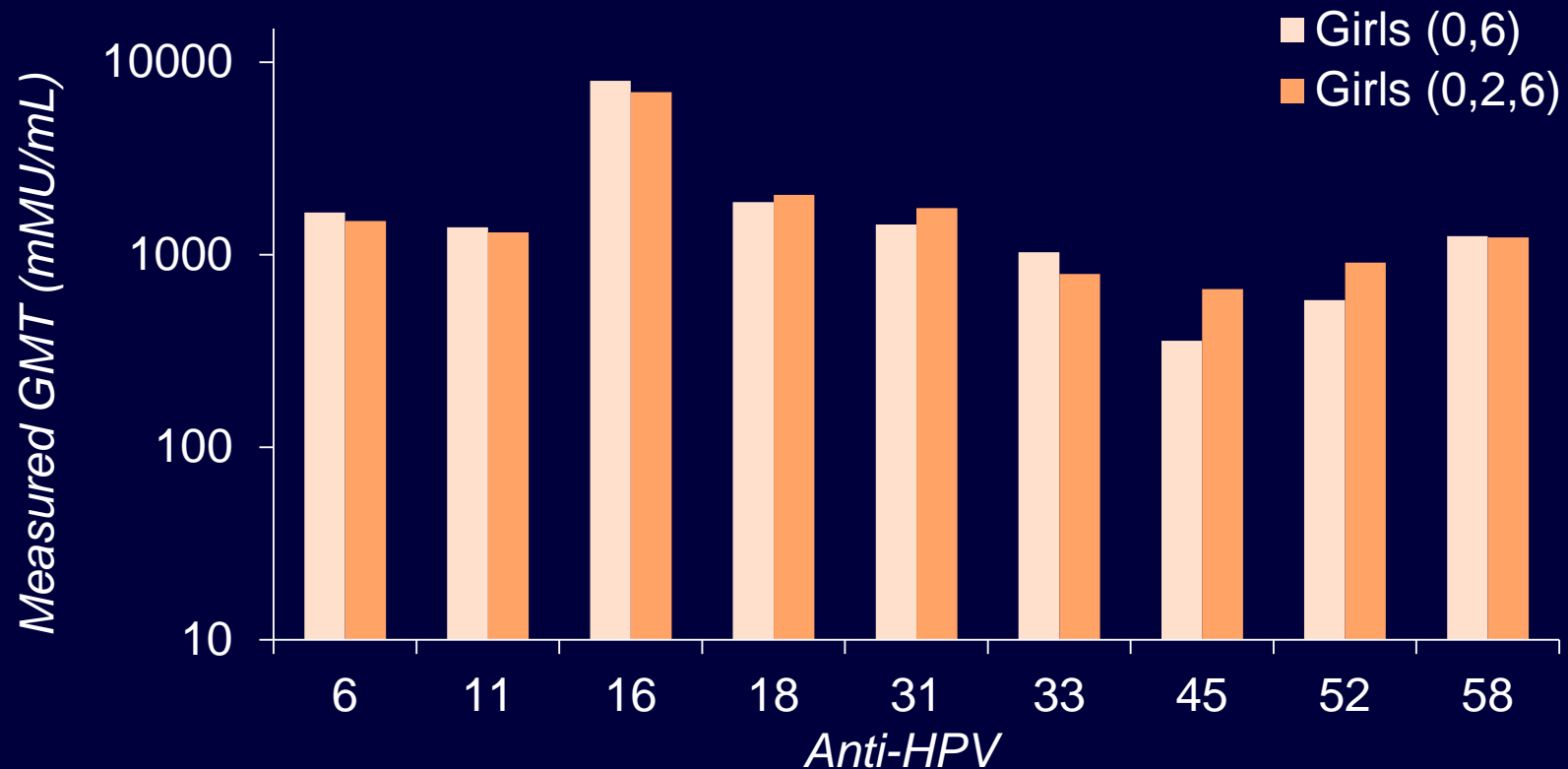
<b>Assay</b>	<b>Girls (0, 6) (N=301)</b>	<b>Boys (0, 6) (N=301)</b>	<b>Girls/Boys (0, 12) (N=300)</b>	<b>Girls (0, 2, 6) (N=300)</b>	<b>Women (0, 2, 6) (N=314)</b>
<b>HPV 6</b>	<b>99.6%</b>	<b>100%</b>	<b>100%</b>	<b>99.2%</b>	<b>99.6%</b>
<b>HPV 11</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>99.6%</b>	<b>99.6%</b>
<b>HPV 16</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>99.6%</b>
<b>HPV 18</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>99.6%</b>	<b>98.5%</b>
<b>HPV 31</b>	<b>99.6%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>99.6%</b>
<b>HPV 33</b>	<b>99.6%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>99.6%</b>
<b>HPV 45</b>	<b>99.3%</b>	<b>99.3%</b>	<b>100%</b>	<b>99.3%</b>	<b>97.9%</b>
<b>HPV 52</b>	<b>99.6%</b>	<b>100%</b>	<b>100%</b>	<b>99.6%</b>	<b>99.6%</b>
<b>HPV 58</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>99.6%</b>	<b>99.6%</b>

# **EXPLORATORY ANALYSES**

***2 DOSES IN GIRLS 9-14 YEARS OF AGE VS.***

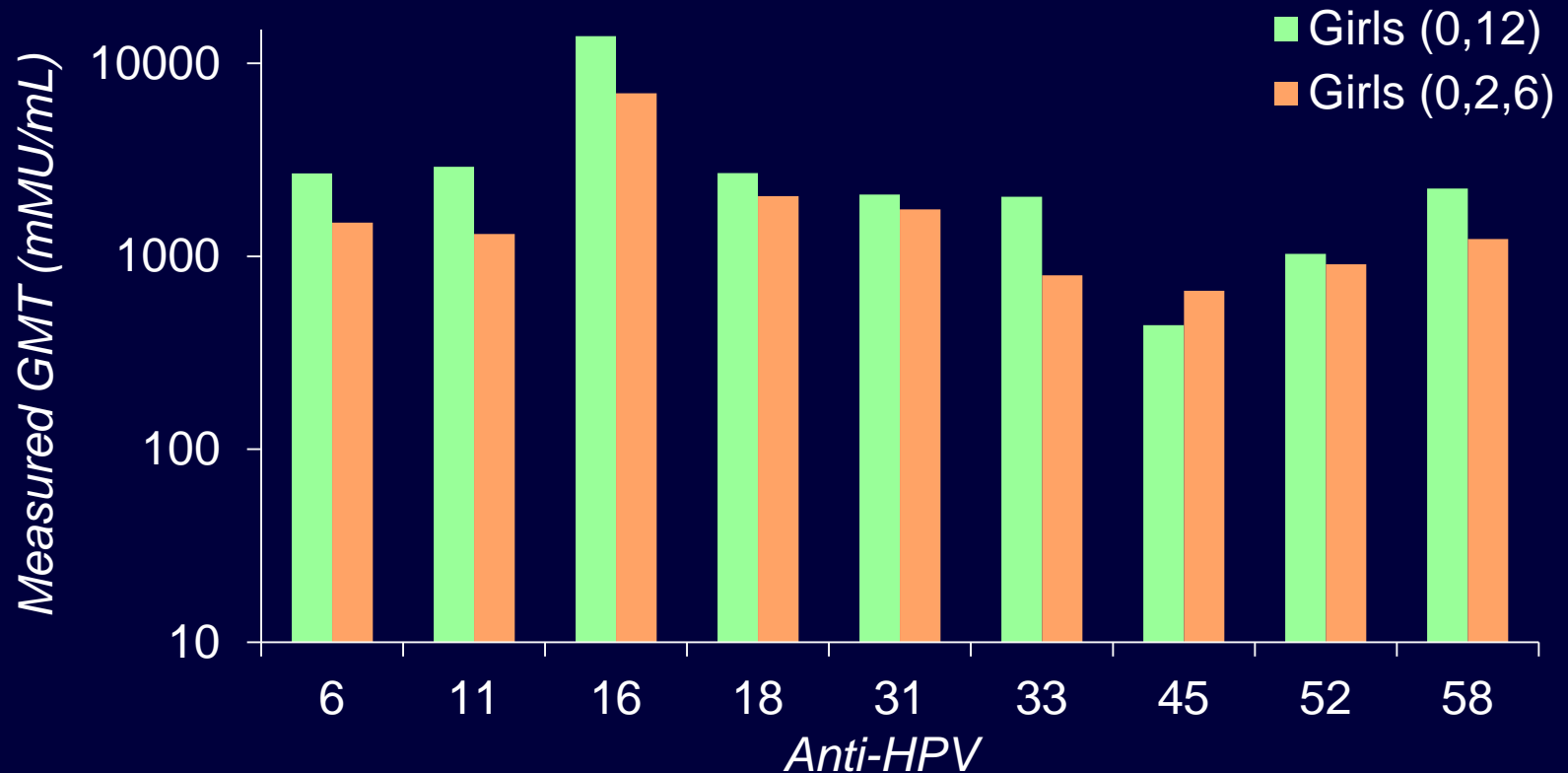
***3 DOSES IN GIRLS 9-14 YEARS OF AGE***

# 9vHPV 2-dose Study: GMT Comparison at 1 Month Post-Last Dose in 2-dose (0, 6) Girls vs. 3-dose (0, 2, 6) Girls



Fold difference (0,6)/(0,2,6)	<b>1.11</b>	<b>1.06</b>	<b>1.14</b>	<b>0.91</b>	<b>0.82</b>	<b>1.29</b>	<b>0.54</b>	<b>0.64</b>	<b>1.02</b>
95% CI	(0.94, 1.30)	(0.90, 1.25)	(0.98, 1.34)	(0.77, 1.09)	(0.69, 0.97)	(1.10, 1.52)	(0.45, 0.65)	(0.55, 0.75)	(0.87, 1.20)

# 9vHPV 2-dose Study: GMT Comparison at 1 Month Post-Last Dose in 2-dose (0, 12) Girls vs. 3-dose (0, 2, 6) Girls



Fold difference (0,12)/(0,2,6)	<b>1.80</b>	<b>2.23</b>	<b>1.98</b>	<b>1.32</b>	<b>1.19</b>	<b>2.56</b>	<b>0.66</b>	<b>1.13</b>	<b>1.83</b>
95% CI	(1.44, 2.23)	(1.82, 2.74)	(1.62, 2.41)	(1.05, 1.65)	(0.96, 1.48)	(2.10, 3.11)	(0.53, 0.84)	(0.93, 1.37)	(1.49, 2.23)

## 9vHPV 2-dose Study: Safety Summary

Adverse Event	Girls (0, 6)	Boys (0, 6)	Girls/Boys (0, 12)	Girls (0, 2, 6)	Women (0, 2, 6)
<b>Subjects with follow-up</b>	<b>294</b>	<b>296</b>	<b>293</b>	<b>300</b>	<b>313</b>
<b>With serious AEs</b>	<b>3 (1.0)</b>	<b>5 (1.7)</b>	<b>3 (1.0)</b>	<b>3 (1.0)</b>	<b>8 (2.6)</b>
<b>With serious vaccine-related AEs</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>
<b>Who died</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>
<b>Discontinued due to an AE</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>1 (0.3)*</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>
<b>Discontinued due to a vaccine-related AE</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>1 (0.3)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>
<b>Discontinued due to a serious AE</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>

*Based on safety follow-up from Day 1 through visit cut-off date (19-Jun-2015)*

*\*Urticaria 1 day post-dose 1*

# Summary – 2-dose Study of 9vHPV Vaccine

## ● Primary Objectives

- Non-inferior HPV 6/11/16/18/31/33/45/52/58 GMTs at 1 month after last vaccination in girls and boys 9 to 14 years of age who received 2 doses of 9vHPV vaccine versus women 16 to 26 years of age who received 3 doses
  - *Supports extending efficacy findings in women who received 3 doses to girls and boys who received 2 doses*

## ● Exploratory Analyses

- Lower HPV GMTs for some HPV types were observed in girls who received 2 doses versus girls who received 3 doses
  - *Clinical significance unknown; may deserve further investigation (e.g., longer follow-up)*

## ● Safety

- 9vHPV vaccine generally well tolerated in all vaccination groups (no vaccine-related SAEs, no death, discontinuation due to an AE <0.1%)
  - *No new safety findings compared with previous clinical studies of the 9vHPV vaccine*



# Key Points to Consider

- Time interval between dose 1 and dose 2
  - *Per WHO and EMA: if for any reason, the interval between doses 1 and 2 is <5 months, a third dose should be given  $\geq 6$  months after dose 1*
  - *Post-marketing effectiveness study of Gardasil indicates lower effectiveness if interval between doses 1 and 2 is <5 months (Blomberg et al Clin Infect Dis 2015; 61:676-682)*
- Ensuring series completion is essential
  - *Post-marketing effectiveness studies of qHPV vaccine indicate lower effectiveness of a single dose*
- Duration of protection provided by 2 doses of 9vHPV vaccine has not been assessed
  - *No efficacy assessment*
  - *No long-term follow-up data*
- Longer term follow-up planned
  - *Immunogenicity assessment through Month 37 in this study*
  - *Separate, larger, long-term effectiveness study planned (in the absence of an immune threshold of protection)*

# Conclusions – 2-dose Regimen of 9vHPV Vaccine

- Administration of a 2-dose series of 9vHPV vaccine in girls and boys 9 to 14 years of age, with the second dose given at 6 or 12 months following the first dose ( $\pm$  4 week window), generates non-inferior anti-HPV 6/11/16/18/31/33/45/52/58 antibody responses compared with the 3-dose regimen in young women 16 to 26 years of age
- Efficacy of 2-dose regimen, durability of responses and long term effectiveness remain to be evaluated in:
  - Long-term follow-up clinical studies
  - Post-licensure epidemiological studies