# HPV IMMUNOGENICITY DATA REVIEW

## IMMUNE RESPONSE FOLLOWING EXTENDED INTERVAL SCHEDULE OR SINGLE DOSE OF HPV VACCINE

**UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER**

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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# Background and Objectives

There are currently three licensed and WHO pre-qualified human papillomavirus (HPV) vaccines available globally: a bivalent vaccine (2vHPV), a quadrivalent vaccine (4vHPV), and a nonavalent vaccine (9vHPV). The vaccines were originally licensed to be given in a three-dose regimen; based on data from clinical trials and updated licensure status, the Centers for Disease Control and Prevention (CDC) revised the recommendations to a 2-dose regimen for adolescents who start the series before their 15th birthday in 2016[1]. Additional alternative dosing schedules are being explored to address vaccine shortages and difficulty in maintaining vaccination schedules, particularly in low- and middle-income countries. However, there is a lack of evidence on the efficacy and effectiveness of these schedules in comparison to the standard 2- and 3-dose schedules, and comparisons of data from across studies has been difficult due to lack of standardized assays and variable immunogenicity endpoint measures.

In order to better inform strategic decision-making surrounding alternative HPV vaccination schedules, the START team conducted a systematic review and meta-analysis of the published literature in order to address the following research questions:

## RESEARCH QUESTIONS

1. Is the immune response for HPV types 16 and 18 after an extended interval schedule (i.e. at least 12 months between dose 1 and 2) noninferior or otherwise comparable to the immune response after the standard dose schedule (either 3 doses at 0,1/2,6 months or 2 doses at 0,6 months)?

2. Is the immune response for HPV types 16 and 18 after a single dose noninferior or otherwise comparable to the immune response after the standard dose schedule (either 3 doses at 0,1/2,6 months or 2 doses at 0,6 months)?

# Methods

## SYSTEMATIC REVIEW

### SEARCH STRATEGY AND STUDY SELECTION

In accordance with PRISMA guidelines[2], the START team conducted a systematic review to identify post-vaccination immunogenicity data for human papillomavirus (HPV) vaccines among human participants. We searched the PUBMED/MEDLINE database for English-language publications indexed through November 7, 2019; the search was replicated on April 29, 2019 to capture any

additional articles indexed during the review process. Full details of the search strategy are outlined in **Appendix A**.

Abstracts and full-text publications were screened independently using Excel and Covidence software. Per PRISMA guidelines, all publications were screened by at least two reviewers; conflicts were resolved via a third-party review.

Studies meeting the criteria for inclusion in the review were human studies reporting geometric mean titers (GMT) for HPV-16 and -18 following administration of one of the licensed HPV vaccines. Our exclusion criteria were: Not HPV vaccine; non-human study; therapeutic vaccine; no GMT data; review article; non-English publication; non-serum sampling site; duplicate data/data reported previously; non-licensed vaccine; no data for HPV types 16 and 18, assay other than enzyme-linked immunosorbent assay (ELISA), total IgG (IgG), or competitive Luminex immunoassay (cLIA); non-standard dosing schedules (i.e. schedules that were not considered extended interval, single dose, or standard schedule); and non-intramuscular administration route.

Because the target population for the meta-analysis comparisons was HPV-seronegative girls ages 9-15 (or 15-26 where data was unavailable for girls ages 9-15), only studies reporting data in these populations were included in the meta-analysis; GMT data reported among boys or groups containing both boys and girls were excluded. For studies in which GMT estimates or 95% confidence intervals were not explicitly reported in the text of the publication, relevant data was requested from the corresponding authors; studies for which data has not yet been obtained were excluded from the present analysis.

## META-ANALYSIS AND NONINFERIORITY COMPARISON

### DATA ABSTRACTION AND STATISTICAL ANALYSIS

Data was extracted and verified by two reviewers; conflicts were resolved via a third reviewer. We abstracted study metadata including: titles; author; publication year; PMID number; NCT number; assay type; vaccine type and manufacturer; HPV type tested or reported (i.e. HPV-16 or HPV-18); sex; age; sample size; baseline HPV status; country; HIV status; presence of other comorbidities; number of doses received before antibody testing; dosing schedule; time between receipt of first vaccine and antibody testing; GMT point estimate; 95% confidence intervals; and units.

We extracted GMTs reported at one-month post-last dose, 36 months post-first dose, and 72 months post-first dose in order to evaluate short-term, mid-term, and long-term immunogenicity, respectively. Data reported within 12 months of the mid-term time point or within 24 months of the long-term time point were collected if 36- and 72-month data was not available, respectively; for example, if a study

reported GMTs at month 30 but not month 36, the month 30 GMT would be extracted for the mid-term time point. Data reported at 48 months was considered mid-term.

All comparisons and pooled estimates were calculated using international units (IU/mL). Conversion rates for mMU/mL and EU/mL to IU/mL were obtained from the literature[3,4]; only studies reporting GMT in mMU/mL, EU/mL, or IU/mL were included in the meta-analysis.

### STATISTICAL ANALYSIS AND NONINFERIORITY COMPARISON

Pooled GMT estimates and 95% confidence intervals were calculated using a fixed-effects modelling approach. Linear regression models were built using inverse variance weighting and model-based standard errors to estimate pooled GMT ratios. Models were stratified by alternate schedule (i.e. extended interval or single dose), HPV type (i.e. 16 or 18), vaccine type (i.e. 2vHPV, 4vHPV, or 9vHPV), and time point (i.e. one-month post-last dose, 36 months post-first dose, or 72 months post-first dose). Thus, 36 possible models were evaluated. While adjusting the models for relevant covariates was considered, adjustment was ultimately not possible due to limited sample size.

Per discussions with HPV subject matter experts and consistency with prior HPV vaccine literature, noninferiority was assessed by estimating the ratio of pooled GMTs comparing extended interval or single dose to standard schedules at the same time point[5]; the comparison was considered to have demonstrated noninferiority if the lower bound of the 95% confidence interval was greater than or equal to 0.5.

The target population for the meta-analysis was HPV-seronegative girls ages 9-15 years; where possible, noninferiority comparisons were limited to studies in this population. Where data was not available in this population, sensitivity analyses were conducted among women age 15-25.

All analyses were conducted in SAS statistical software version 9.4.

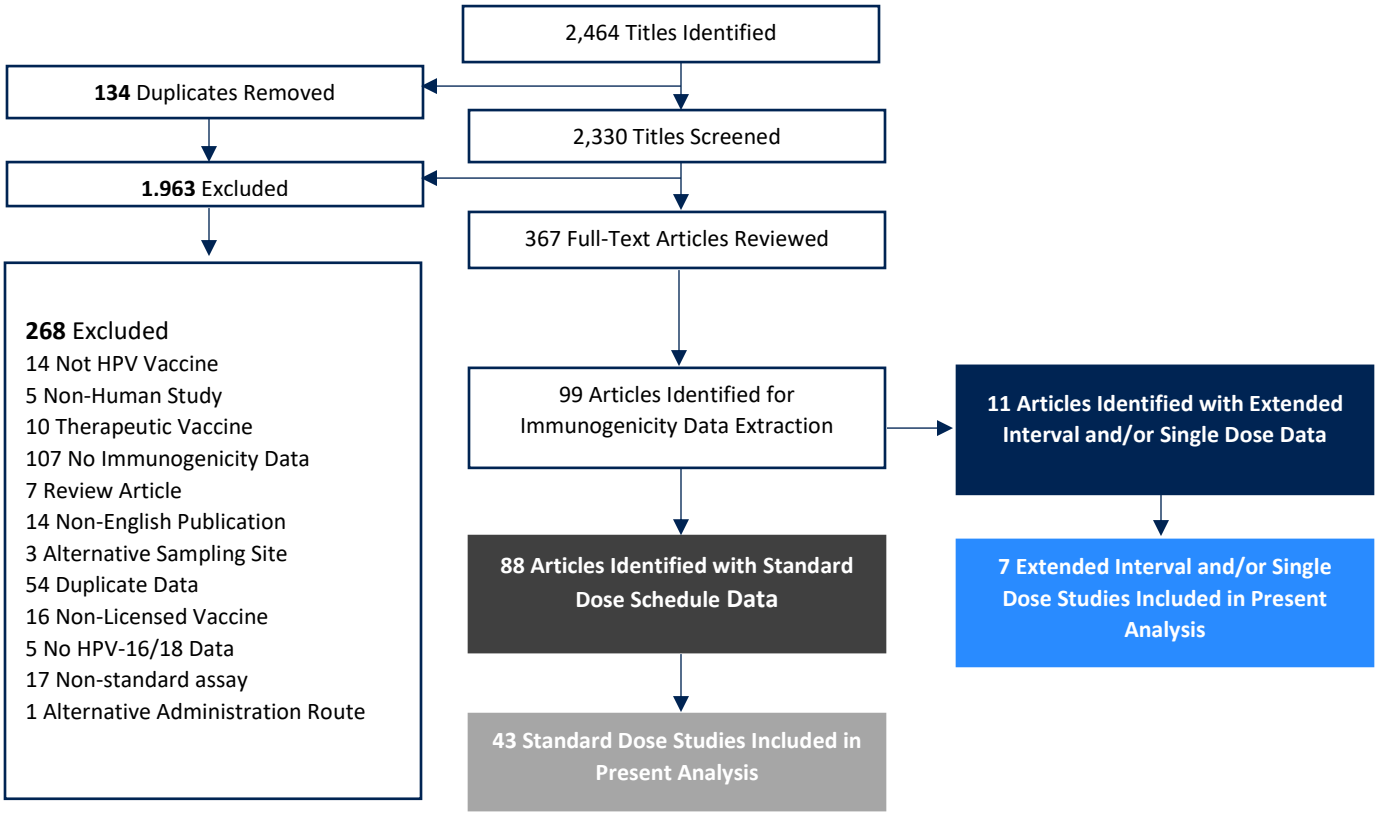
# Key Findings and Limitations

## STUDY IDENTIFICATION

We identified 2,464 studies using the search criteria (Figure 1). After removing duplicates and screening titles and abstracts, 367 studies were included for full-text review. Of these, 268 were excluded; the most common reasons for exclusion were lack of relevant immunogenicity data (107) and duplicate data or data previously reported (54). 99 studies were included; 11 of these included data for single dose and/or extended interval schedules in addition to standard schedules. Identified extended interval and single dose studies are summarized in **Appendices B and C**.

Of the 100 identified studies, 29 did not explicitly report GMT or 95% confidence intervals in the text of the publication; of these 29 studies for which data was requested, 23 requests are still outstanding. After excluding outstanding data requests and studies for which data on the target population (HPV-seronegative girls 9-15 or 15-26) was unavailable, 50 of the 99 identified studies were included in the present meta-analysis; seven of these studies include extended interval or single dose data in addition to standard schedule data. Of the four single dose and/or extended interval studies not included in the meta-analysis, two were excluded due to lack of IU/mL conversion factor for the PBNA assay (Toh et al. 2017, Sankaranarayanan et al. 2016), one was excluded due to lack of available GMT data (Hurt et al. 2016) and one was excluded due to lack of confirmed baseline HPV serostatus (LaMontagne et al. 2014).

**Figure 1: PRISMA Diagram**



# RESULTS: EXTENDED INTERVAL

Results for extended interval comparisons are reported below by vaccine type. Full results for each comparison, including figures and tables, are presented in **Appendix D.**

### 2V-HPV

For the bivalent vaccine, seven standard schedule studies were included in the one-month post-last dose comparison and four were included in the 36 months post-first dose comparison. Puthanakit et al. 2016 and Huang et al. 2017 were used as the extended interval studies for one-month post-last dose and 36 months post-first dose, respectively (see **Appendix B**). Pooled GMT estimates for HPV-16 were 1,569 IU/mL (95% CI: 716 – 3,428) and 214 IU/mL (95% CI: 65 – 702) at one-month post-last dose and 36 months post-first dose, respectively. Pooled GMT estimates for HPV-18 were 912 IU/mL (95% CI: 579 – 1,435) and 110 IU/mL (95% CI: 53 – 228) at one-month post-last dose and 36 months post-first dose, respectively. Extended interval was noninferior to the standard dose schedule for HPV-18 at one-month post-last dose (Ratio: 0.92 [95% CI: 0.60 – 1.41]) and 36 months post-first dose (Ratio: 1.15 [95% CI: 0.69 - 1.92]). Noninferiority was not demonstrated for HPV-16 at either one-month post-last dose (Ratio: 0.86 [95% CI: 0.41 – 1.79]) or 36 months post-first dose (Ratio: 0.97 [95% CI: 0.43 – 2.22]), though this may be due to small sample size (i.e. few studies with extended interval data). No data was available for 72 months post-first dose.

### 4V-HPV

For the quadrivalent vaccine, seven standard schedule studies were included in the one-month post-last dose comparison and three were included in both the 36 and 72 months post-first dose comparisons. LaMontagne et al. 2013 was used as the extended interval study for one-month post-last dose and 72 months post-first dose; Neuzil et al. 2011 was used as the extended interval study for 36 months post-first dose (see **Appendix B**). Pooled GMT estimates for HPV-16 were 757 IU/mL (95% CI: 220 – 2,607), 297 IU/mL (95% CI: 74 – 1,187), and 248 IU/mL (95% CI: 99 – 621) at one-month post-last dose, 36 months post-first dose, and 72 months post-first dose, respectively. Pooled GMT estimates for HPV-18 were 265 IU/mL (95% CI: 122 – 573), 36 IU/mL (95% CI: 14 – 91), and 37 IU/mL (95% CI: 13 – 103) at one-month post-last dose, 36 months post-first dose, and 72 months post-first dose, respectively. Extended interval was noninferior to the standard dose schedule for HPV-18 at one-month post-last dose (Ratio: 1.13 [95% CI: 0.57 – 2.23]). Noninferiority was also demonstrated for both HPV-16 and HPV-18 at 36 months post-first dose (HPV-16 ratio: 2.83 [95% CI: 0.95 – 8.44]; HPV-18 ratio: 2.01 [95% CI: 0.92 – 4.37]). Similarly, noninferiority was demonstrated for both HPV-16 and HPV-18 at 72 months post-first dose (HPV-16 ratio: 2.14 [95% CI: 1.25 – 3.66]; HPV-18 ratio: 2.56 [95% CI: 1.39 – 4.72]). Noninferiority was not demonstrated for HPV-16 at one-month post-last dose (Ratio: 0.81 [95% CI: 0.28 – 2.37]), though this may be due to small sample size (i.e. few studies with extended interval data).

### 9V-HPV

For the nonavalent vaccine, four standard schedule studies were included in the one-month post-last dose comparison. Iversen et al. 2016 was used as the extended interval study (see **Appendix B**). Pooled GMT estimates for HPV-16 and HPV-18 at one-month post-last dose were 2,642 IU/mL (95% CI: 1,687 – 4,136) and 516 IU/mL (95% CI: 322 – 828), respectively. Extended interval was noninferior to the standard dose schedule for both HPV-16 and HPV-18 at one-month post-last dose (HPV-16 ratio: 1.97 [95% CI: 1.37 – 2.84]; HPV-18 ratio: 1.33 [95% CI: 0.91 – 1.96]). No data was available for 36 months post-first dose or 72 months post-first dose.

## RESULTS: SINGLE DOSE

Results for single comparisons are reported below by vaccine type. Full results for each comparison, including figures and tables, are presented in **Appendix D.** No single dose data was available for girls age 9-15; all results presented below are for girls age 15-26.

### 2V-HPV

For the bivalent vaccine, five standard schedule studies were included in the one-month post-last dose comparison and four were included in the 36 months post-first dose comparison. Safaeian et al. 2018 was used as the single dose study for both comparisons (see **Appendix B**). Pooled GMT estimates for HPV-16 were 28 IU/mL (95% CI: 10 – 78) and 27 IU/mL (95% CI: 7 – 102) at 36 and 72 months post-first dose, respectively. Pooled GMT estimates for HPV-18 were 15 IU/mL (95% CI: 8 – 29) and 43 IU/mL (95% CI: 31 – 59) at 36 and 72 months post-first dose, respectively. Noninferiority was not demonstrated for HPV-16 (36 month ratio: 0.19 [95% CI: 0.08 – 0.44]; 72 month ratio: 0.27 [95% CI: 0.10 – 0.76]) or HPV-18 (36 month ratio: 0.24 [95% CI: 0.14 – 0.41]; 72 month ratio: 0.40 [95% CI: 0.24 – 0.67]). No data was available for one-month post-last dose.

### 4V-HPV

For the quadrivalent vaccine, six standard schedule studies were included in the 36-month post-last dose comparison. Gilca et al. 2018 was used at the single dose study (see **Appendix B**). Pooled GMT estimates at 36 months post-first dose were 18 IU/mL (95% CI: 0.1 – 3,269) and 5 IU/mL (95% CI: 0 – 8,684) for HPV-16 and HPV-18, respectively. Noninferiority was not demonstrated for HPV-16 (Ratio: 0.19 [95% CI: 0.08 – 0.44]) or HPV-18 (Ratio: 0.24 [95% CI: 0.14 – 0.41]). No data was available for one-month post-last dose or 72 months post-first dose.

### 9V-HPV

No single dose data was available for the nonvalent vaccine.

## SUMMARY

Findings from the meta-analysis suggest that extended interval schedules may be noninferior to standard schedules for most vaccine types, HPV types, and time points. Noninferiority was demonstrated for HPV-18 at short-term and mid-term time points for the bivalent vaccine; for HPV-16 at short-term and mid-term time points as well as HPV-18 at the mid-term time point for the quadrivalent vaccine; and for both HPV types at the short-term time point for the nonavalent vaccine. Where noninferiority was not demonstrated, lower bounds of 95% confidence intervals were within 0.1 of the threshold. Noninferiority was not demonstrated for single dose for any vaccine type, HPV type, or time point.

## LIMITATIONS

The present meta-analysis is subject to a variety of limitations, the most salient of which is a lack of extended interval and single dose data for robust comparisons among HPV-seronegative girls age 9-15 stratified by vaccine type and time points for assessment of immune response.

The lack of extended interval and single dose data in the published literature has several implications for the results of the meta-analysis that may limit the interpretability of the findings. First, relevant data was not available for each vaccine at each time point. For example, no extended interval data was available for two of the licensed vaccines at 72 months post-first dose; thus, the present meta-analysis does not address the long-term comparability of immune response with an extended interval schedule for those vaccines. Additionally, inclusion of only one study per comparison limits the statistical stability of the comparison. Because the definition of the noninferiority outcome relies directly on interpretation of the 95% confidence interval associated the ratio of GMT estimates, the lack of statistical precision may preclude the ability to reliably assess noninferiority. The meta-analysis employed fixed-effects models for the noninferiority comparisons; given the high heterogeneity of the studies included in the analysis, a random-effects model is generally preferable. However, random-effects models are not possible when one of the comparison groups relies on a single study (as was the case with each comparison in the present analysis). Further, inclusion of only one study per comparison precludes the ability to adjust for relevant covariates in the regression models.

The analysis is further limited by the lack of established correlate of protection against HPV infection. Without establishing a correlate of protection, it is difficult to know whether the differences in pooled GMT estimates would impact clinical outcomes.

## CONCLUSION

While findings from the meta-analysis suggest that extended interval schedules may be noninferior to standard schedules (particularly for the 4vHPV and 9vHPV vaccines), these results should be interpreted with caution given the lack of extended interval data available in the published literature. Similarly, the lack of single dose data as well as the lack of established correlate of protection may preclude a robust understanding of the immune response following a single dose of the HPV vaccine. Further head-to-head clinical trials comparing alternative dosing schedules to standard schedules are needed to better understand the comparability of immune response.

## REFERENCES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5. Lazcano-Ponce E, Torres L, Stanley M, 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 &. 2014;32:725-732. doi:10.1016/j.vaccine.2013.11.059

# Appendices

## APPENDIX A: SEARCH STRING

(papillomavirus[ti] OR “papilloma virus”[ti] OR “papilloma viruses”[ti] OR hpv[ti] OR papillomaviridae/immunology[mh:noexp] OR human papillomavirus 16[mh] OR human papillomavirus 18[mh] OR human papillomavirus 6[mh] OR papillomavirus infections[mh])

AND

(vaccination[mh] OR immunization[mh] OR vaccines[mh] OR vaccine*[ti] OR vaccination*[ti] OR immuniz*[ti] OR papillomavirus vaccines[mh])

AND

(antibody formation[mh] OR viral antibodies/blood[mh] OR viral antibodies/immunology[mh] OR antibod* OR immunity[mh] OR immunity[tw] OR “immune response” OR “immune responses” OR “immunological response” OR “immunological responses” OR immunology[tw] OR immunogenic*[tw] OR seroconversion[tw] OR seropositivity[tw] OR seropositive[tw] OR outcome[tw] OR efficacy[tw])

AND

(clinical trial[pt] OR epidemiologic studies[mh])

# APPENDIX B: SUMMARY OF IDENTIFIED EXTENDED INTERVAL AND SINGLE DOSE STUDIES

## *Extended Interval Studies*

| Authors | Year | Vaccine | Countries | N | Age (yrs) | Sex | Schedule | Assay | Units | Lab |
|---|---|---|---|---|---|---|---|---|---|---|
| **Huang; Puthanakit[1]** | **2017; 2016[1]** | **2vHPV** | **N. America, Europe, Asia** | **330-462** | **9-14, 15-25** | **F** | **(0,6), (0,12), (0,1,6)** | **ELISA** | **EU/mL** | **GSK** |
| **Iversen** | **2016** | **9vHPV** | **N. America, S. America, Europe, Asia** | **129-273** | **9-14, 16-26** | **M,F** | **(0,6), (0,12), (0,2,6)** | **cLIA** | **mMU/ML** | **Merck** |
| **Gilca[2]** | **2018** | **9vHPV, 4vHPV** | **Canada** | **31** | **13-18** | **F** | **(0, 3-8y)** | **ELISA** | **IU/mL** | **CDC** |
| **LaMontagne /Neuzil[3]** | **2013; 2011[2]** | **4vHPV** | **Vietnam** | **206-229** | **11-13** | **F** | **(0,2,6), (0,3,9), (0,6,12), (0,12,24)** | **cLIA** | **mMU/mL** | **Merck** |
| Toh | 2017 | 4vHPV, 2vHPV | Fiji | 32-66 | 15-19 | F | 0-3 doses | PBNA | ED50 | MCRI[4] |

Bold indicates that study was included in meta-analysis.
1. Huang 2017 is a follow-up study of the same cohort from Puthanakit 2016.
2. Gilca 2018 contains both single dose and extended interval data and was thus used for both comparisons.
3. LaMontagne 2013 is a follow-up study of the same cohort from Neuzil 2011.
4. Murdoch Childrens Research Institute, Melbourne, Australia.

## *Single Dose Studies*

| Authors | Year | Vaccine | Countries | N | Age (yrs) | Sex | Schedule | Assay | Units | Lab |
|---|---|---|---|---|---|---|---|---|---|---|
| Sankaranarayanan | 2016 | 4vHPV | India | 3452-4950 | 10-18 | F | (0), (0,2), (0,6), (0,2,6) | PBNA | Not reported | RGCB[1] |
| Hurt | 2016 | 4vHPV | USA | 411-1260 | 17-26 | F | 1-3 doses | ELISA | NA[2] | Johns Hopkins |
| LaMontagne | 2014 | 2vHPV | Uganda | 36-195 | 10-11 | F | 1-3 doses | ELISA | EU/mL | NCI |
| **Safaeian** | **2018** | **2vHPV** | **Costa Rica** | **79-2043** | **18-25** | **F** | **(0), (0,1), (0,6), (0,1,6)** | **ELISA** | **EU/mL** | **NCI** |
| **Gilca[3]** | **2018** | **9vHPV, 4vHPV** | **Canada** | **31** | **13-18** | **F** | **(0, 3-8y)** | **ELISA** | **IU/mL** | **CDC** |

Bold indicates that study was included in meta-analysis.
1.Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, India.
2. No GMTs reported in study; only seroconversion rates available.
3. Gilca 2018 contains both single dose and extended interval data and was thus used for both comparisons.

# APPENDIX C: LIST OF IDENTIFIED STUDIES


Apter, D. et al. “Efficacy of Human Papillomavirus 16 and 18 (HPV-16/18) AS04-Adjuvanted Vaccine against Cervical Infection and Precancer in Young Women: Final Event-Driven Analysis of the Randomized, Double-Blind PATRICIA Trial.” Clinical and Vaccine Immunology : CVI, vol. 22, no. 4 PG-361-73, 2015, pp. 361–73, doi:10.1128/CVI.00591-14.

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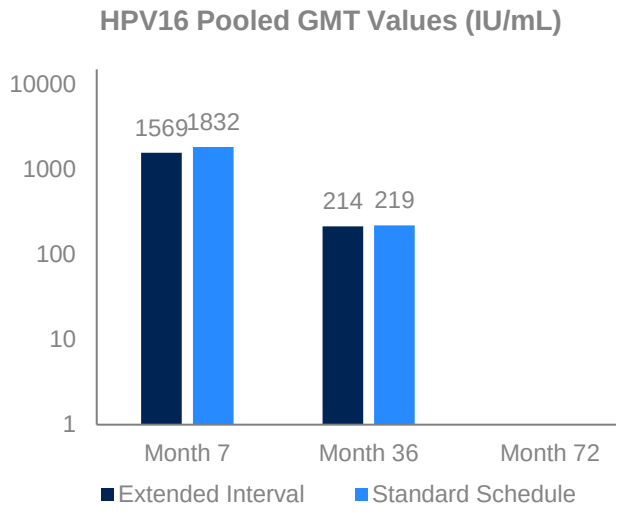
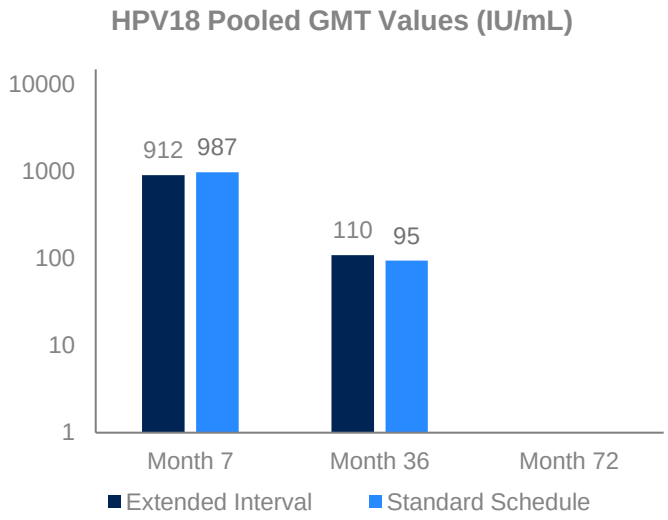
# APPENDIX D: META-ANALYSIS RESULTS

## EXTENDED INTERVAL

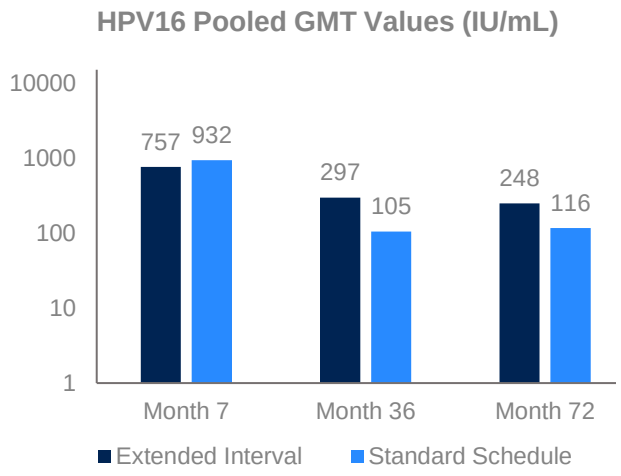
*2vHPV*

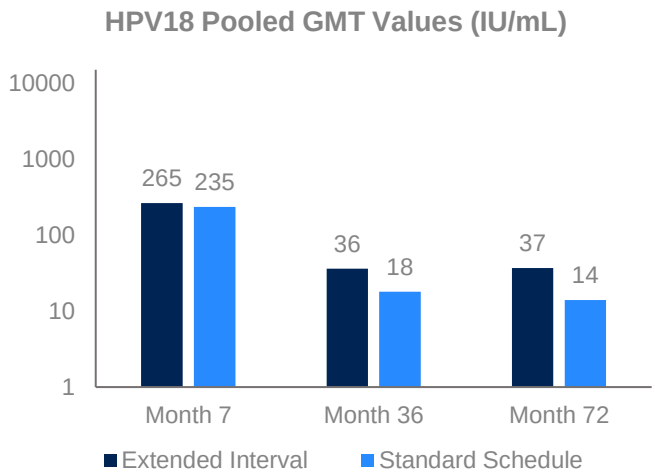



| | HPV-16 | | | HPV-18 | | |
|---|---|---|---|---|---|---|
| | **1 Month Post-Last Dose** | **Month 36** | **Month 72** | **1 Month Post-Last Dose** | **Month 36** | **Month 72** |
| Extended Interval Pooled GMT (95% CI) | 1,569 (716 - 3,428) | 214 (65 - 702) | No Data | 912 (579 - 1,435) | 110 (53 - 228) | No Data |
| Standard Dose Pooled GMT (95% CI) | 1,832 (1264 - 2655) | 219 (119 - 405) | No Data | 987 (798 - 1,221) | 95 (64 - 141) | No Data |
| GMT Ratio (95% CI) | 0.86 (0.41 - 1.79) | 0.97 (0.43 - 2.22) | No Data | 0.92 (0.60 - 1.41) | 1.15 (0.69 - 1.92) | No Data |
| Noninferiority Demonstrated? | **No** | **No** | **No Data** | **Yes** | **Yes** | **No Data** |
| Extended Interval Study | Puthanakit 2016 | Huang 2017 | No Data | Puthanakit 2016 | Huang 2017 | No Data |
| Number of Standard Schedule Studies Included | 7 | 4 | No Data | 7 | 4 | No Data |

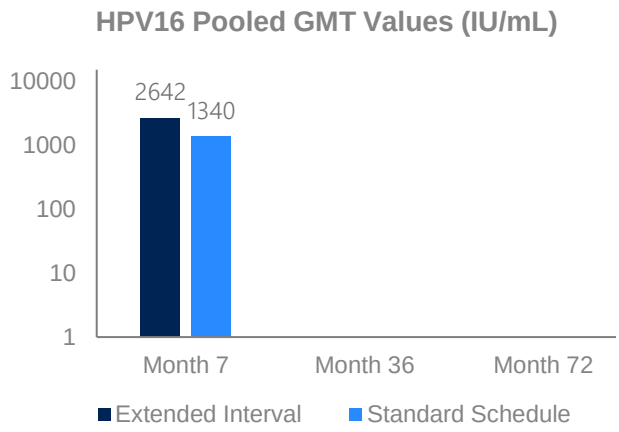
*4vHPV*

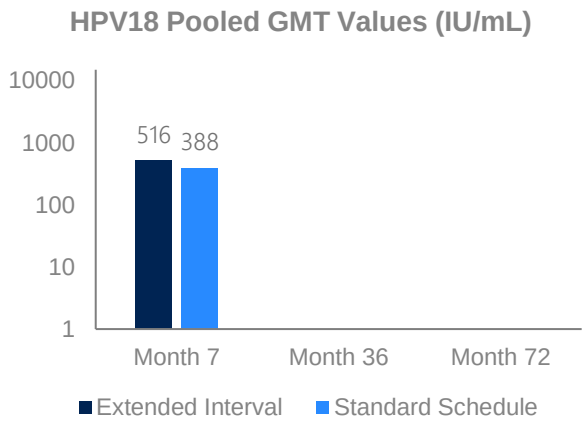



| | HPV-16 | | | HPV-18 | | |
|---|---|---|---|---|---|---|
| | **1 Month Post-Last Dose** | **Month 36** | **Month 72** | **1 Month Post-Last Dose** | **Month 36** | **Month 72** |
| Extended Interval Pooled GMT (95% CI) | 757 (220 - 2,607) | 297 (74 - 1,187) | 248 (99 - 621) | 265 (122 - 573) | 36 (14 - 91) | 37 (13 - 103) |
| Standard Dose Pooled GMT (95% CI) | 932 (723 - 1,202) | 105 (60 - 184) | 116 (55 - 242) | 235 (187-294) | 18 (12 - 28) | 14 (6 - 34) |
| GMT Ratio (95% CI) | 0.81 (0.28 - 2.37) | 2.83 (0.95 - 8.44) | 2.14 (1.25 - 3.66) | 1.13 (0.57 - 2.23) | 2.01 (0.92 - 4.37) | 2.56 (1.39 - 4.72) |
| Noninferiority Demonstrated? | **No** | **Yes** | **Yes** | **Yes** | **Yes** | **Yes** |
| Extended Interval Study | LaMontagne 2013 | Neuzil 2011 | LaMontagne 2013 | LaMontagne 2013 | Neuzil 2011 | LaMontagne 2013 |
| Number of Standard Schedule Studies Included | 7 | 3 | 3 | 7 | 3 | 3 |

*9vHPV*

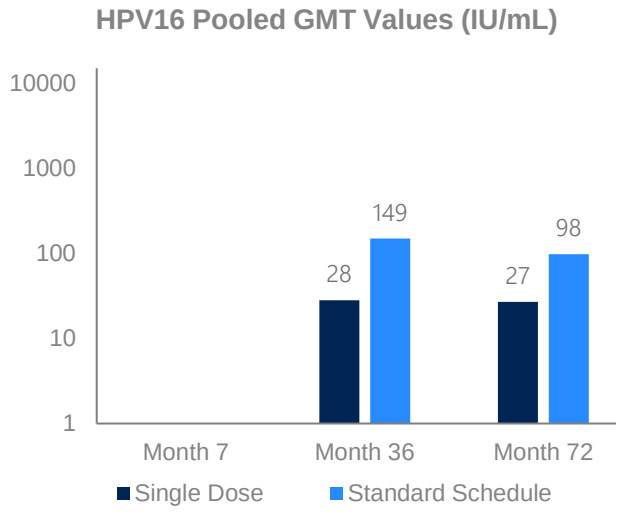


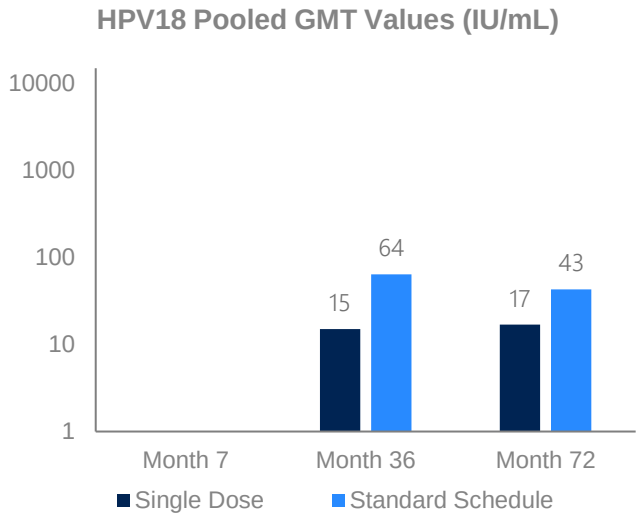




| | HPV-16 | | | HPV-18 | | |
|---|---|---|---|---|---|---|
| | **1 Month Post-Last Dose** | **Month 36** | **Month 72** | **1 Month Post-Last Dose** | **Month 36** | **Month 72** |
| Extended Interval Pooled GMT (95% CI) | 2,642 (1,687 - 4,136) | No Data | No Data | 516 (322 - 828) | No Data | No Data |
| Standard Dose Pooled GMT (95% CI) | 1,340 (1,225 - 1,467) | No Data | No Data | 388 (352 - 427) | No Data | No Data |
| GMT Ratio (95% CI) | 1.97 (1.37 - 2.84) | No Data | No Data | 1.33 (0.91 - 1.96) | No Data | No Data |
| Noninferiority Demonstrated? | **Yes** | **No Data** | **No Data** | **Yes** | **No Data** | **No Data** |
| Extended Interval Study | Iversen 2016 | No Data | No Data | Iversen 2016 | No Data | No Data |
| Number of Standard Schedule Studies Included | 4 | No Data | No Data | 4 | No Data | No Data |

## SINGLE DOSE

*2vHPV*

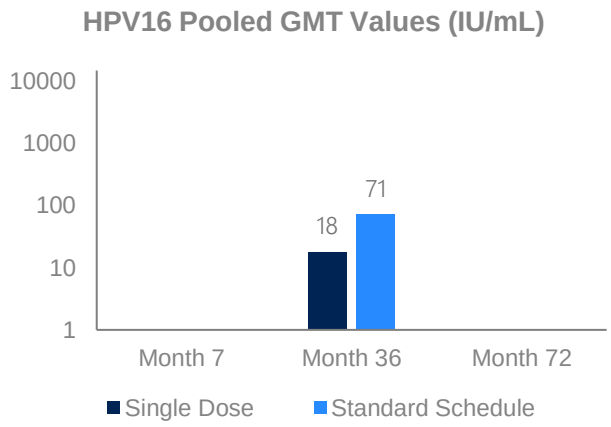


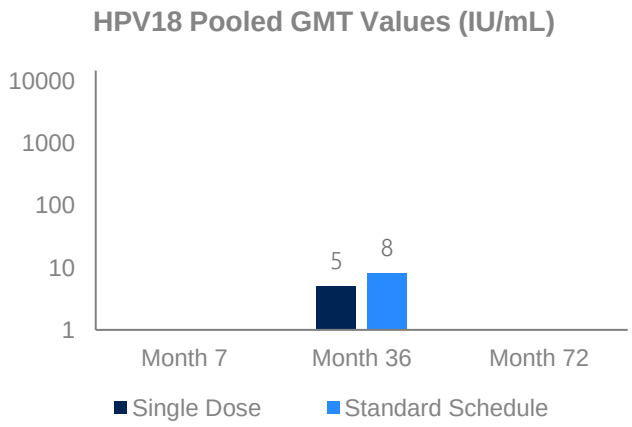




| | HPV-16 | | | HPV-18 | | |
|---|---|---|---|---|---|---|
| | **1 Month Post-Last Dose** | **Month 36** | **Month 72** | **1 Month Post-Last Dose** | **Month 36** | **Month 72** |
| Single Dose Pooled GMT (95% CI) | No Data | 28 (10 - 78) | 27 (7 - 102) | No Data | 15 (8 - 29) | 43 (31 - 59) |
| Standard Dose Pooled GMT (95% CI) | No Data | 149 (111 - 199) | 98 (56 - 170) | No Data | 64 (51 - 81) | 17 (9 - 33) |
| GMT Ratio (95% CI) | No Data | 0.19 (0.08 - 0.44) | 0.27 (0.10 - 0.76) | No Data | 0.24 (0.14 - 0.41) | 0.40 (0.24 - 0.67) |
| Noninferiority Demonstrated? | **No Data** | **No** | **No** | **No Data** | **No** | **No** |
| Single Dose Studies | No Data | Safaeian 2018 | Safaeian 2018 | No Data | Safaeian 2018 | Safaeian 2018 |
| Number of Standard Schedule Studies Included | No Data | 5 | 4 | No Data | 5 | 4 |

No data available for girls 9-15; data presented for girls age 15-26.

*4vHPV*




| | HPV-16 | | | HPV-18 | | |
|---|---|---|---|---|---|---|
| | **1 Month Post-Last Dose** | **Month 36** | **Month 72** | **1 Month Post-Last Dose** | **Month 36** | **Month 72** |
| Single Dose Pooled GMT (95% CI) | No Data | 18 (0.1 - 3,269) | No Data | No Data | 5 (0 - 8,684) | No Data |
| Standard Dose Pooled GMT (95% CI) | No Data | 71 (57 - 89) | No Data | No Data | 8 (6 - 11) | No Data |
| GMT Ratio (95% CI) | No Data | 0.25 (0.00 - 13.33) | No Data | No Data | 0.71 (0.00 - 190.21) | No Data |
| Noninferiority Demonstrated? | **No Data** | **No** | **No Data** | **No Data** | **No** | **No Data** |
| Single Dose Studies | No Data | Gilca 2018 | No Data | No Data | Gilca 2018 | No Data |
| Number of Standard Schedule Studies Included | No Data | 6 | No Data | No Data | 6 | No Data |

No data available for girls 9-15; data presented for girls age 15-26.

*9vHPV*

***No single dose data was available for the 9vHPV vaccine.***