HPV IMMUNOGENICITY DATA REVIEW

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STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

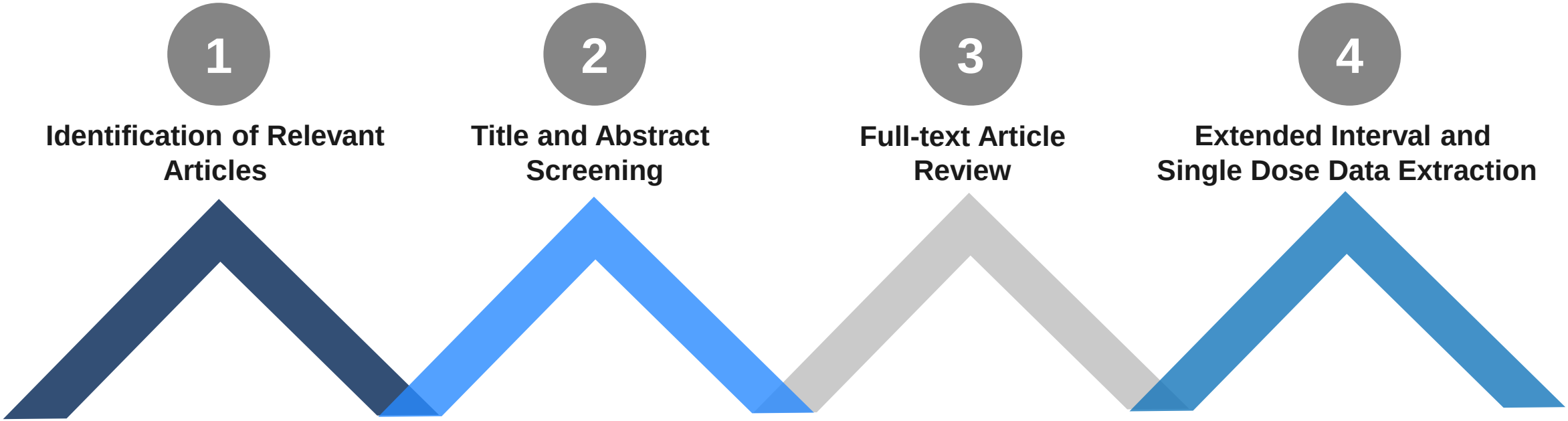
PROJECT OBJECTIVES

1. Conduct systematic literature review to identify studies containing post-HPV vaccination immunogenicity data

2. Identify and summarize relevant immunogenicity data for single dose and extended interval schedules

3. Extract relevant immunogenicity data from identified studies and perform meta-analysis to inform HPV vaccination guidelines

METHODS



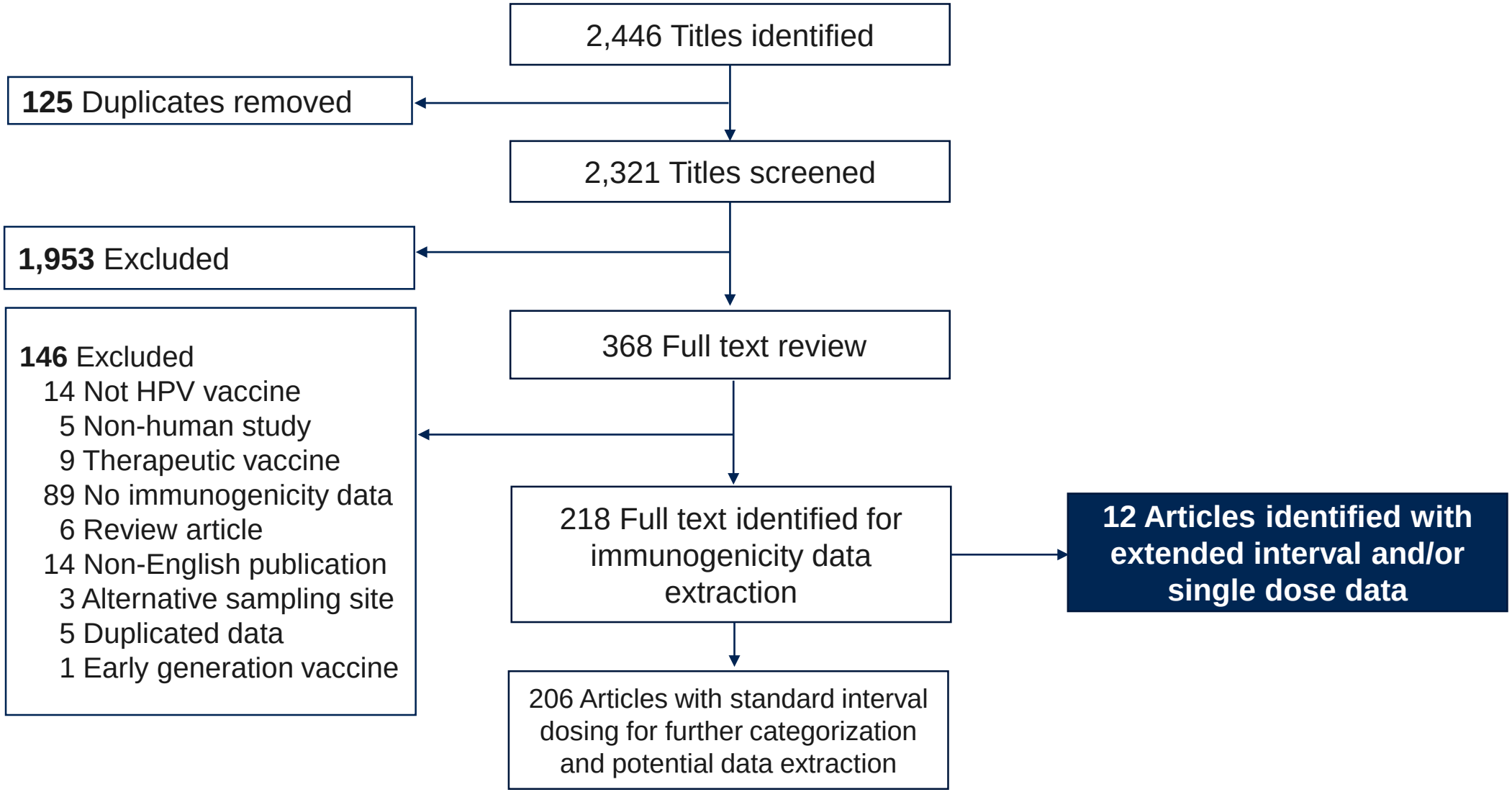
- Developed key search terms
- Pulled relevant studies from PubMed database

- Excluded articles based on predefined criteria:
  - *Not HPV vaccine*
  - *Non-human vaccine*
  - *Therapeutic vaccine*
  - *No immunogenicity data*
  - *Review article*

- Excluded articles based on further criteria:
  - *Non-English publication*
  - *Alternative sampling site*
  - *Duplicated data*
  - *Early generation vaccine*

- Identified all studies with immunogenicity data for single dose as well as dosing schedules ≥12m between 1st and 2nd dose

METHODS: PRISMA DIAGRAM



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KEY VARIABLES EXTRACTED

- HPV type tested, assay type, and assay name
- Vaccine type and manufacturer
- Study participant demographics: sex, age, baseline HPV status, other comorbidities
- Dose schedule, doses received, and time since first vaccine
- Values and CIs (where applicable) for seroconversion or antibody titers, including units

KEY IMMUNOGENICITY DATA COMPARISONS

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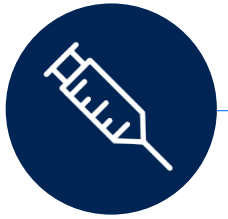
DATA COMPARISON METHODS



Studies with same vaccine, assay, and long-term titer readouts chosen for relevant comparisons

GMT extracted from comparator figures, aggregated using geometric mean weighted by sample size; data aggregated across age groups, sex, baseline serostatus due to limited data availability

Data converted to IU/mL where possible based on published conversion factors for mMu/mL and EU/mL

EXTENDED INTERVAL STUDIES

Authors	Year	Vaccine	Countries	N	Age (yrs)	Sex	Schedule	Assay	Units	Conversion	Lab
Huang	2017	GSK/2v	N. America, Europe, Asia	330-462	9-14, 15-25	F	(0,6), (0,12), (0,1,6)	ELISA	EU/mL	Pinto 2019	GSK
Iversen	2016	Merck/9v	N. America, S. America, Europe, Asia	129-273	9-14, 16-26	M,F	(0,6), (0,12), (0,2,6)	cLIA	mMu/mL	Brown 2014	Merck
Gilca	2018	Merck/9v/4v	Canada	31	13-18	F	(0, 3-8)	ELISA	IU/mL	N/A	CDC
Gilca	2014	Merck/4v	Canada	199-207	9-10	F	(0,6)	Total IgG	LU/mL	None[1]	Unknown
LaMontagne	2013	Merck/4v	Vietnam	206-229	11-13	F	(0,2,6), (0,3,9), (0,6,12), (0,12,24)	cLIA	mMu/mL	Brown 2014	Merck
Toh	2017	Merck/4v, GSK/2v	Fiji	32-66	15-19	F	0-3 doses	PBNA	ED50	None	MCRI[2]

1. No conversion rate available for LU to IU.
2. Murdoch Childrens Research Institute, Melbourne, Australia. No conversion rate available for ED50 to IU.

SINGLE DOSE STUDIES

Authors	Year	Vaccine	Countries	N	Age (yrs)	Sex	Schedule	Assay	Units	Conversion	Lab
Sankaranarayanan	2016	Merck/4v	India	3452-4950	10-18	F	(0), (0,2), (0,6), (0,2,6)	PBNA	Not reported	None	RGCB[1]
Hurt	2016	Merck/4v	USA	411-1260	17-26	F	1-3 doses	ELISA	NA	None[2]	Johns Hopkins
LaMontagne	2014	GSK/2v	Uganda	36-195	10-11	F	1-3 doses	ELISA	EU/mL	Pinto 2019	NCI
Safaeian	2018	GSK/2v	Costa Rica	79-2043	18-25	F	(0), (0,1), (0,6), (0,1,6)	ELISA	EU/mL	Pinto 2019	NCI

1. Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, India. Units not reported in manuscript. No conversion rate available for PBNA assay.
2. No titers reported; only seroconversion rates available.

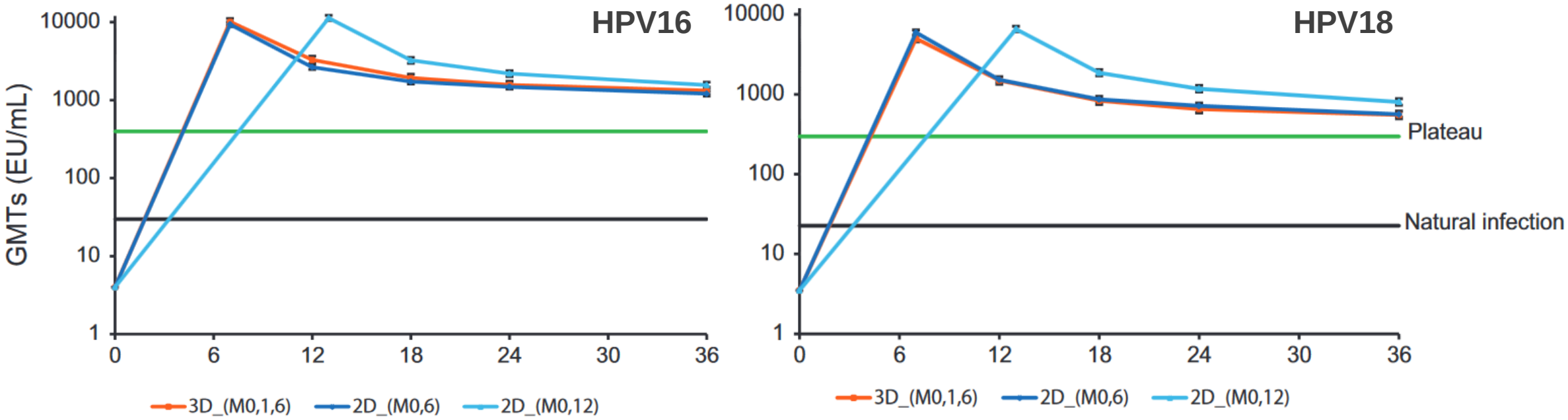
COMPARISON STUDIES

Author	Year	Vaccine	Countries	N	Age (yrs)	Sex	Schedule	Assay	Units	Conversion	Lab
Naud	2014	GSK/2v	Brazil	183	15-25	F	0,1,6	ELISA	EU/mL	Pinto 2019	Unknown
Petaja	2011	GSK/2v	Europe	46-49	10-14	F	0,1,6	ELISA	EU/mL	Pinto 2019	GSK
Romanowski	2016	GSK/2v	Canada, Germany	76-79	10-15	F	0,1,6	ELISA	EU/mL	Pinto 2019	GSK
Skinner	2014	GSK/2v	Australia, N. America, Europe, S. America, Asia	348-361	25+	F	0,1,6	ELISA	EU/mL	Pinto 2019	Unknown
Hildesheim	2014	GSK/2v	Costa Rica	354-379	18-25	F	0,1,6	ELISA	EU/mL	Pinto 2019	Unknown
Petersen[1]	2017	Merck/9v	Australia, N. America, Europe, S. America, Asia, Africa	2405-4884	9-15, 16-26	F	0,1,6	cLIA	mMU/mL	Brown 2014	Merck, PPD[2]
Dobson	2013	Merck/4v	Canada	86-254	9-13, 16-26	F	0,2,6	cLIA	mMU/mL	Brown 2014	Merck
Leung	2015	Merck/4v	Europe, Asia	322-331	9-14	F	0,2,6	ELISA	EU/mL	Leung 2018	GSK
Gilca	2018	Merck/9v	Canada	173	9-11	M,F	0,6	ELISA	IU/mL	N/A	CDC
Olsson	2007	Merck/4v	Europe, S. America	104	16-23	F	0,2,6	cLIA	mMU/mL	Brown 2014	Unknown
Ferris	2017	Merck/4v	N. America, S. America, Europe, Asia	803	9-15	M,F	0,2,6	cLIA	mMU/mL	Brown 2014	Unknown
Ruiz-Sternberg	2018	Merck/4v	N. America, S. America	1307-1524	18-26	F	0,2,6	cLIA	mMU/mL	Brown 2014	Unknown

1. Petersen et al 2017 reports aggregated data from trials **NCT00543543, NCT00943722, NCT00988884, NCT01073293, and NCT01304498**
2. Assay performed by Merck staff at PPD laboratory.

2vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

2vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response Compared to Standard Schedule
Intra-study Comparison: Huang et al 2017 (N. America, Europe Asia)



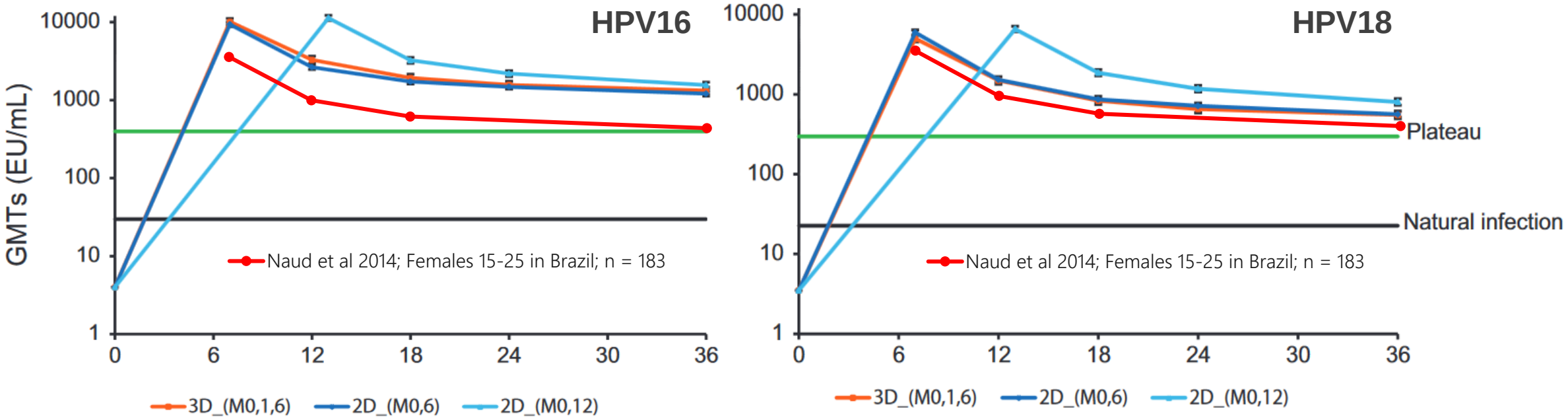
1. Graphs present GMT over time in Huang et al 2017 (N. America, Europe, Asia).

2. Plateau measured as GMT at time 45-50m where efficacy was demonstrated among women age 15-25yrs receiving 3 doses of bivalent vaccine in previous trial; plateau titer values were 398 EU/mL and 297 EU/mL for HPV16 and 18, respectively.

3. Natural infection measured as GMT among women age 15-25 yrs. who had cleared HPV infection in a previous trial; natural infection values were 30 and 23 EU/mL for HPV16 and 18, respectively.

2vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

2vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response Compared to Standard Schedule
Inter-study Comparison: Naud et al 2014 (Brazil)



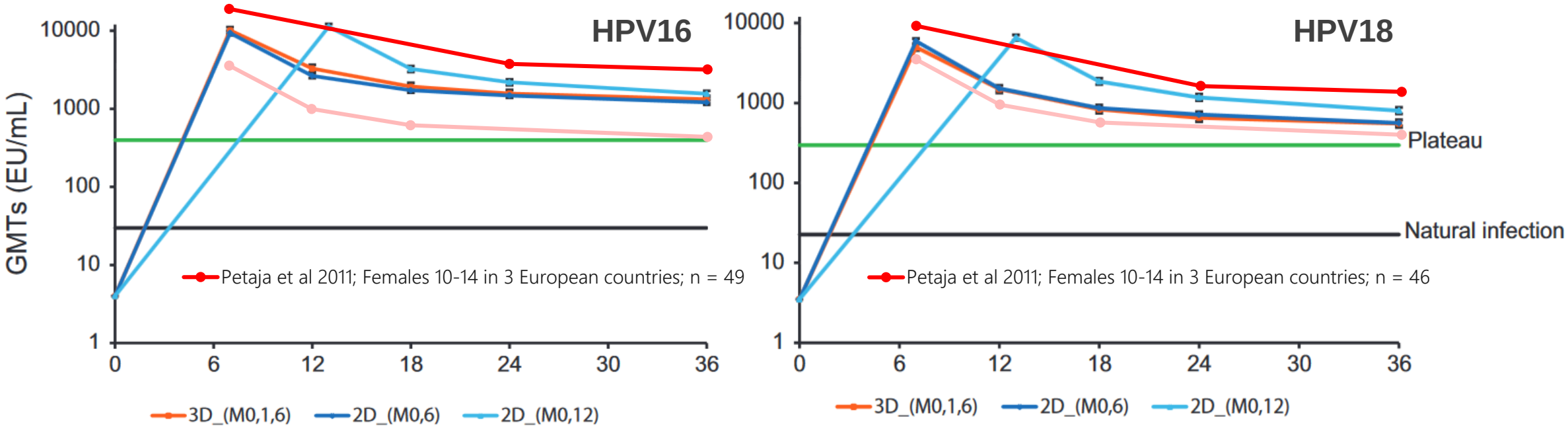
1. Graphs present GMT over time in Huang et al 2017 (N. America, Europe, Asia) compared to GMTs from standard (M0,1,6) schedule Naud et al 2014 (Brazil).

2. Plateau measured as GMT at time 45-50m where efficacy was demonstrated among women age 15-25yrs receiving 3 doses of bivalent vaccine in previous trial; plateau titer values were 398 EU/mL and 297 EU/mL for HPV16 and 18, respectively.

3. Natural infection measured as GMT among women age 15-25yrs who had cleared HPV infection in a previous trial; natural infection values were 30 and 23 EU/mL for HPV16 and 18, respectively.

2vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

2vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response Compared to Standard Schedule
Inter-study Comparison: Petaja et al 2011 (Europe)



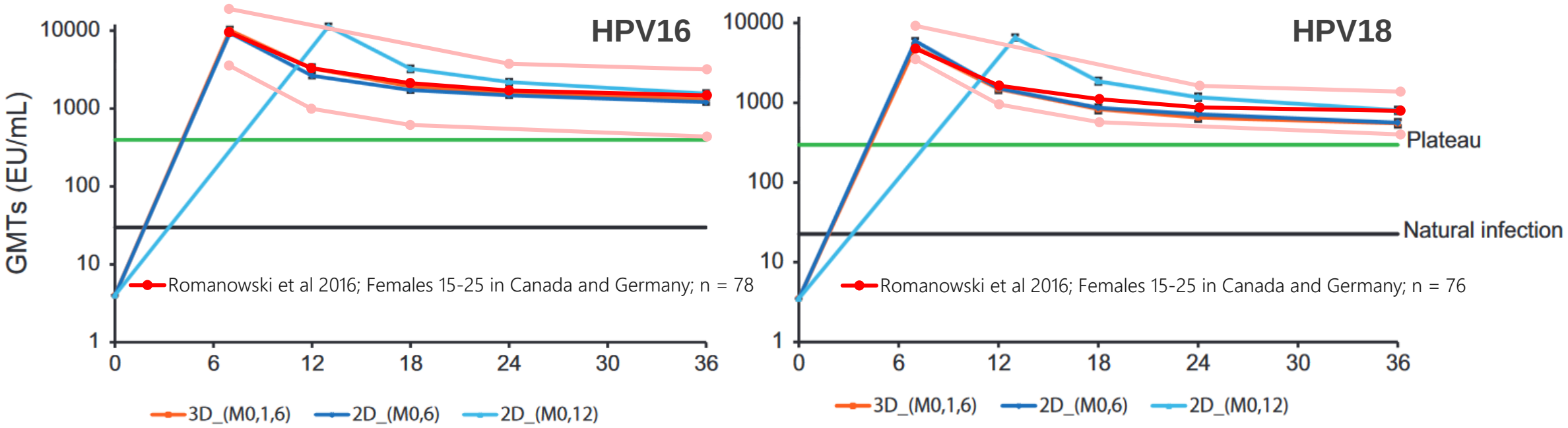
1. Graphs present GMT over time in Huang et al 2017 (N. America, Europe, Asia) compared to GMTs from standard (M0,1,6) schedule in Petaja et al 2011 (Europe).

2. Plateau measured as GMT at time 45-50m where efficacy was demonstrated among women age 15-25yrs receiving 3 doses of bivalent vaccine in previous trial; plateau titer values were 398 EU/mL and 297 EU/mL for HPV16 and 18, respectively.

3. Natural infection measured as GMT among women age 15-25yrs who had cleared HPV infection in a previous trial; natural infection values were 30 and 23 EU/mL for HPV16 and 18, respectively.

2vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

2vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response Compared to Standard Schedule
Inter-study Comparison: Romanowski et al 2016 (Canada, Germany)



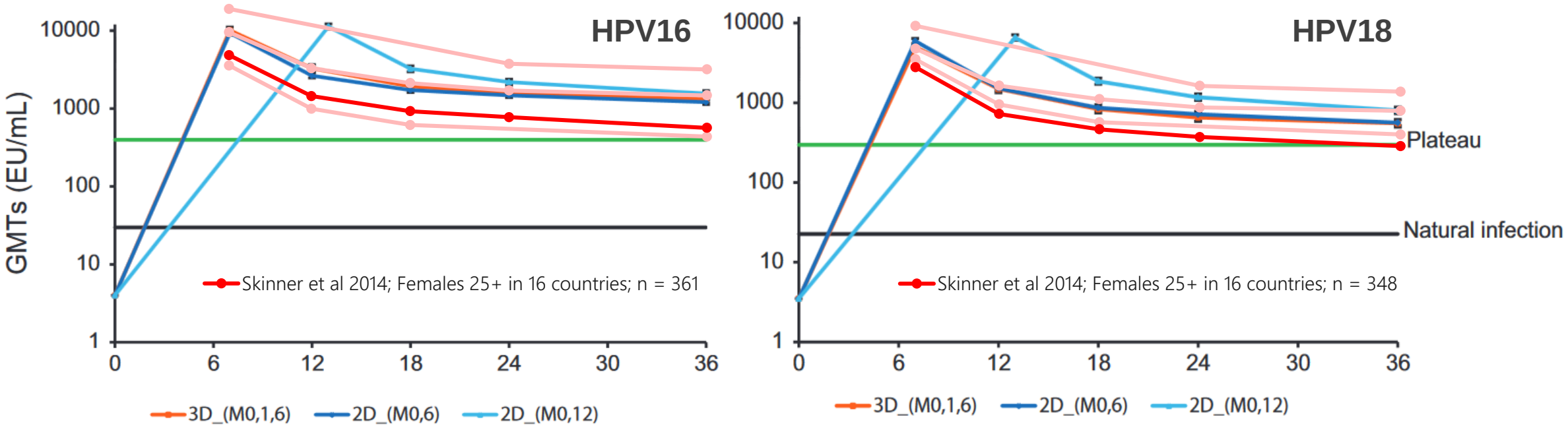
1. Graphs present GMT over time in Huang et al 2017 (N. America, Europe, Asia) compared to GMTs from standard (M0,1,6) schedule in Romanowski et al 2016 (Canada, Germany).

2. Plateau measured as GMT at time 45-50m where efficacy was demonstrated among women age 15-25yrs receiving 3 doses of bivalent vaccine in previous trial; plateau titer values were 398 EU/mL and 297 EU/mL for HPV16 and 18, respectively.

3. Natural infection measured as GMT among women age 15-25yrs who had cleared HPV infection in a previous trial; natural infection values were 30 and 23 EU/mL for HPV16 and 18, respectively.

2vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

2vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response Compared to Standard Schedule
Inter-study Comparison: Skinner et al 2014 (Multi-site)



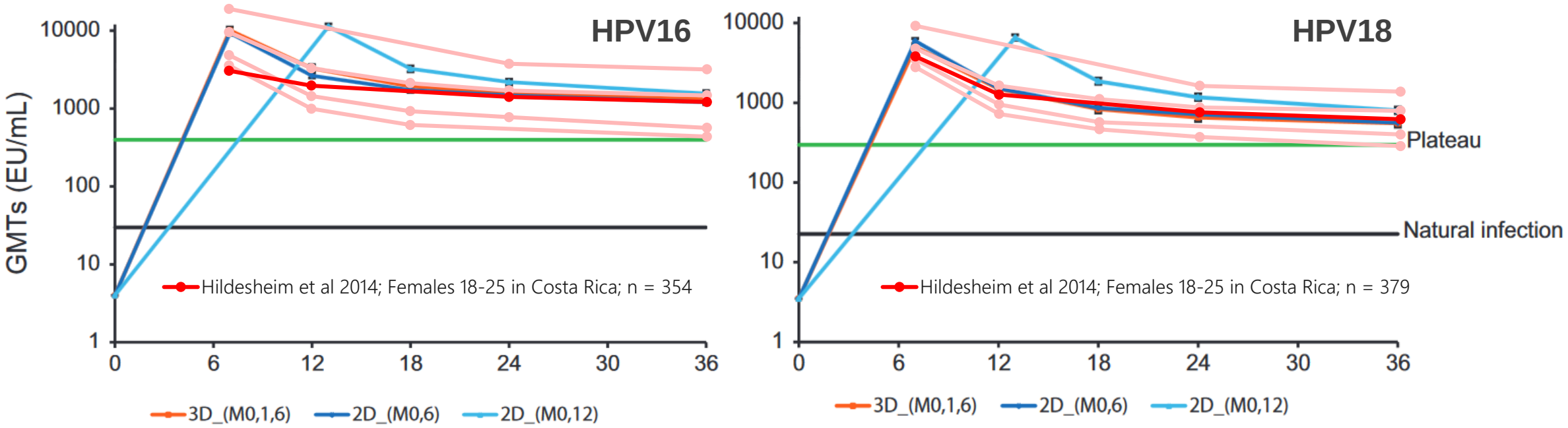
1. Graphs present GMT over time in Huang et al 2017 (N. America, Europe, Asia) compared to GMTs from standard (M0,1,6) schedule in Skinner et al 2014 (Australia, N. America, S. America, Europe, Asia).

2. Plateau measured as GMT at time 45-50m where efficacy was demonstrated among women age 15-25yrs receiving 3 doses of bivalent vaccine in previous trial; plateau titer values were 398 EU/mL and 297 EU/mL for HPV16 and 18, respectively.

3. Natural infection measured as GMT among women age 15-25yrs who had cleared HPV infection in a previous trial; natural infection values were 30 and 23 EU/mL for HPV16 and 18, respectively.

2vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

2vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response Compared to Standard Schedule
Inter-study Comparison: Hildesheim et al 2014 (Costa Rica)



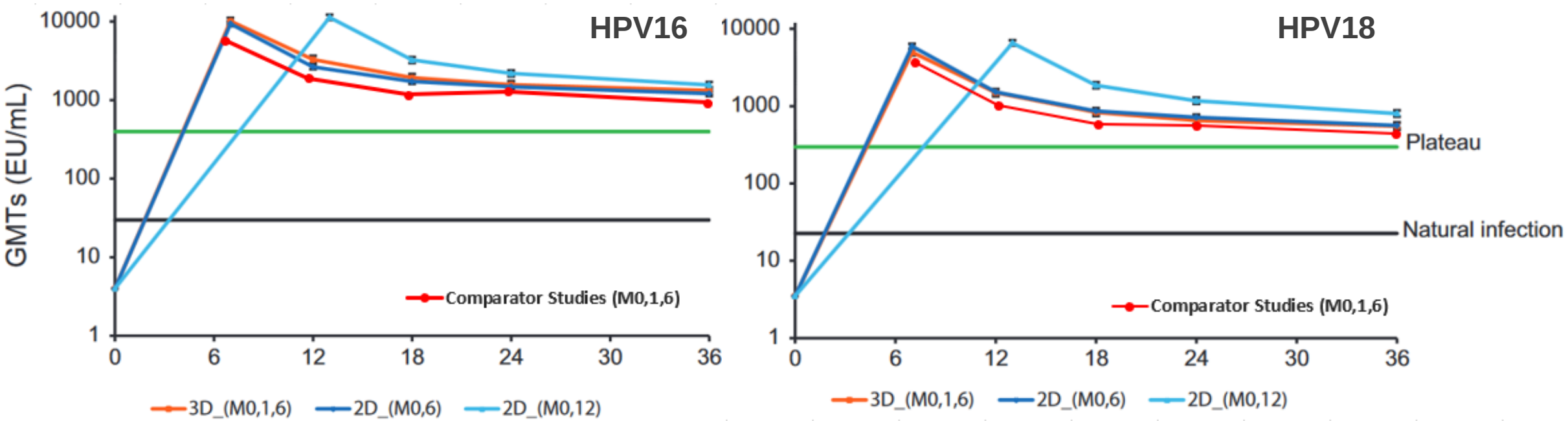
1. Graphs present GMT over time in Huang et al 2017 (N. America, Europe, Asia) compared to GMTs from standard (M0,1,6) schedules in Hildesheim et al 2014 (Costa Rica).

2. Plateau measured as GMT at time 45-50m where efficacy was demonstrated among women age 15-25yrs receiving 3 doses of bivalent vaccine in previous trial; plateau titer values were 398 EU/mL and 297 EU/mL for HPV16 and 18, respectively.

3. Natural infection measured as GMT among women age 15-25yrs who had cleared HPV infection in a previous trial; natural infection values were 30 and 23 EU/mL for HPV16 and 18, respectively.

2vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

2vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response Compared to Standard Schedule
Inter-study Comparison: Aggregated Comparator Data



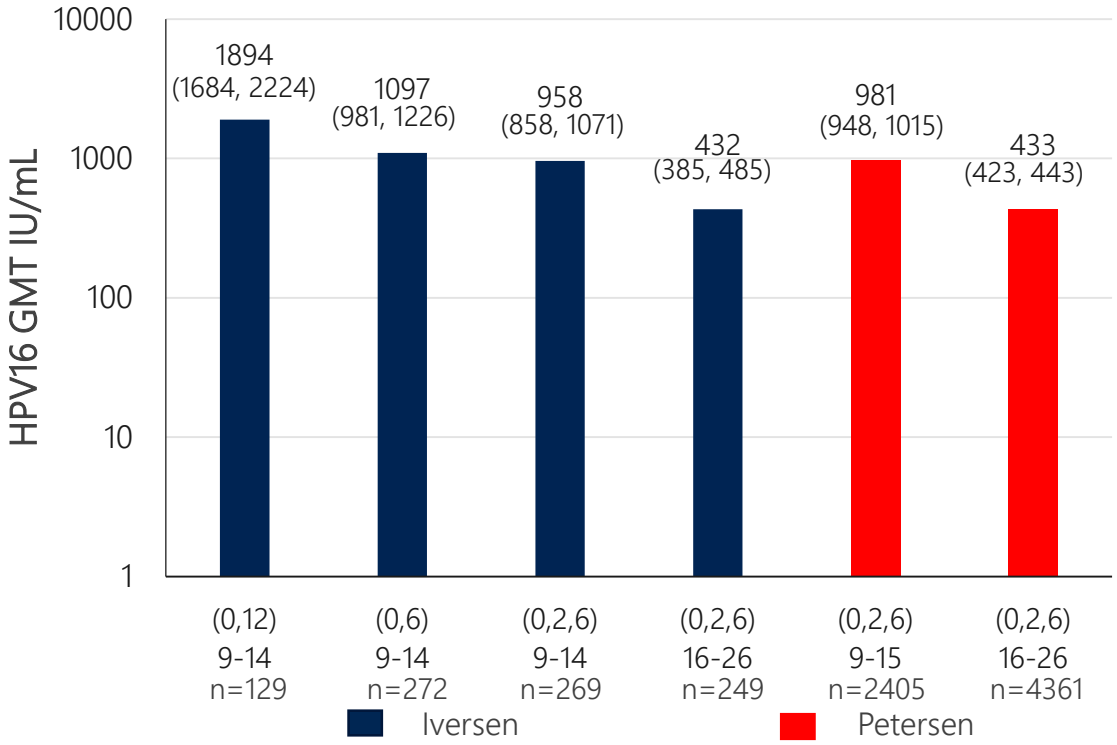
1. Graphs present GMT over time in Huang et al 2017 (N. America, Europe, Asia) compared to aggregated GMTs from standard (M0,1,6) schedules in relevant comparator studies. Comparator studies include Naud et al 2014, Petaja et al 2011, Romanowski et al 2016, Skinner et al 2014, and Hildesheim et al 2014. Comparator studies include data from Australia, N. America, S. America, Europe, and Asia.

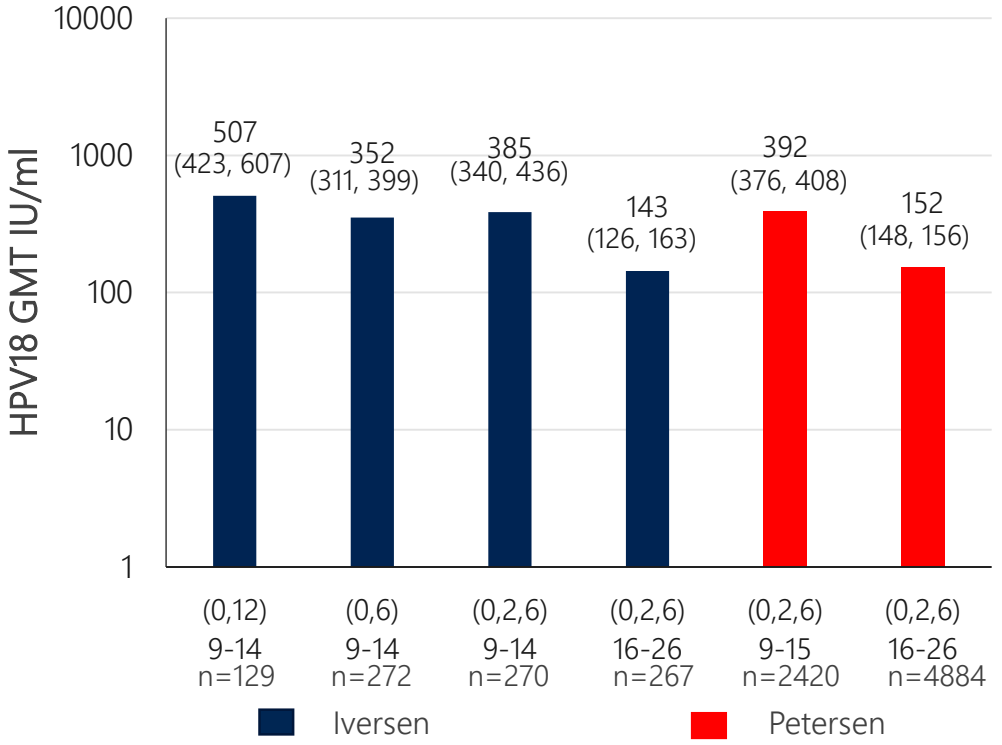
2. Plateau measured as GMT at time 45-50m where efficacy was demonstrated among women age 15-25yrs receiving 3 doses of bivalent vaccine in previous trial; plateau titer values were 398 EU/mL and 297 EU/mL for HPV16 and 18, respectively.

3. Natural infection measured as GMT among women age 15-25yrs who had cleared HPV infection in a previous trial; natural infection values were 30 and 23 EU/mL for HPV16 and 18, respectively.

9vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

9vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response at 1 Month Post Last Dose Compared to Standard Schedule (M0,2,6; M0,6); Iversen et al 2016 vs. Petersen et al 2017 (All Study Arms; Australia, N. America, Europe, S. America, Asia, Africa)

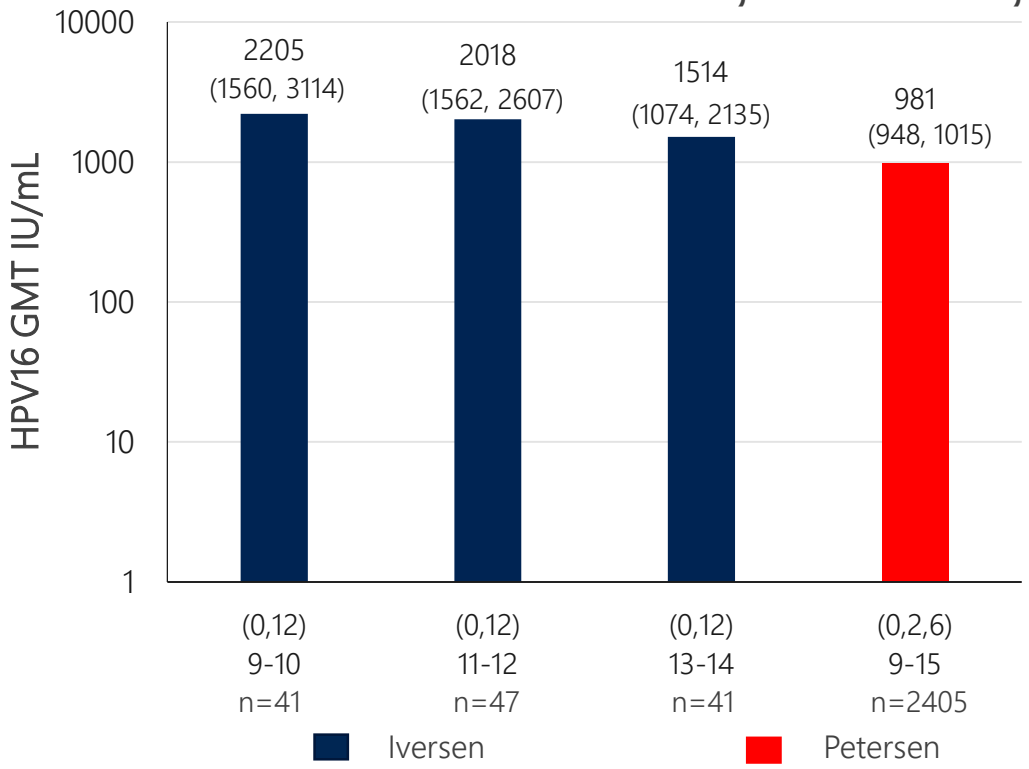


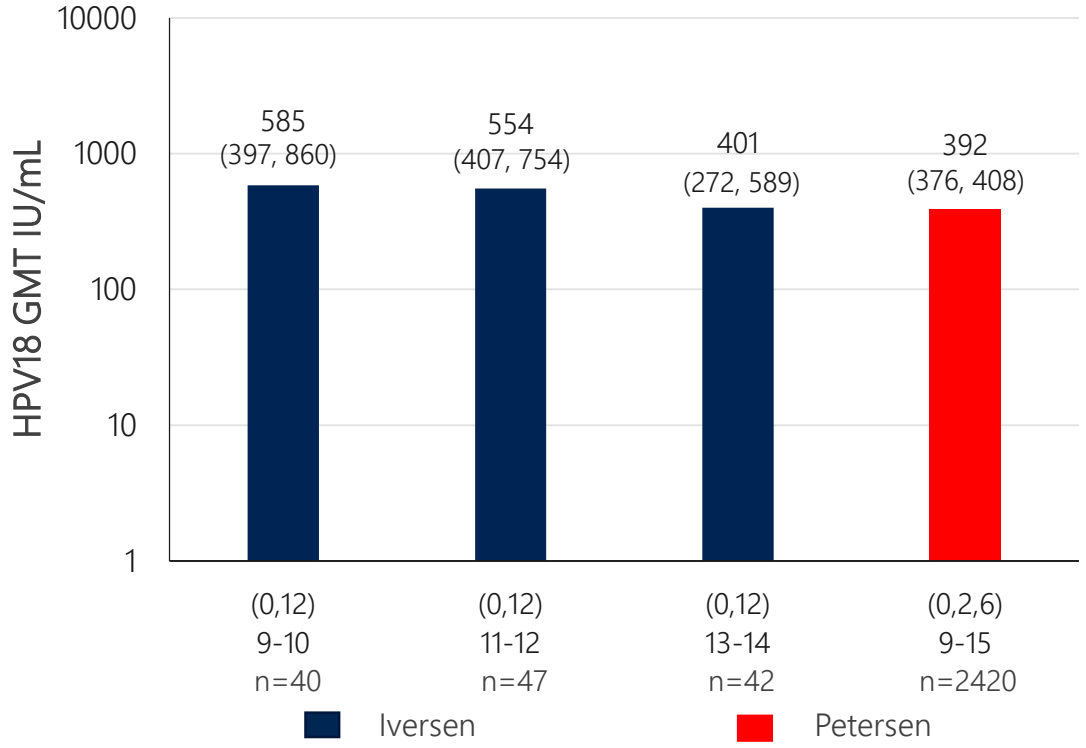


Graphs present GMT at one month post last dose for girls in Iversen et al 2016 compared to aggregated GMTs from standard (M0,2,6) schedules from Petersen et al 2017 (red). Efficacy against HPV infection has been demonstrated in adult women receiving the 3-dose schedule at (0,2,6); both intra- and inter-study comparison indicate a noninferior immune response for extended interval dose. Petersen data aggregates GMT from trials NCT00543543, NCT00943722, NCT00988884, NCT01073293, and NCT01304498. Iversen data included 15 countries. Sample size ranged from 151 to 314. Comparator data included 26 countries in Australia, Europe, South and North America, Asia, and Africa. Sample sizes ranged from 2405 to 4884. All studies used competitive Luminex assays and reported data in mMu/ml. Data converted to IU/ml as per Brown et al 2016 conversion factors: 0.137 (HPV16) and 0.188 (HPV18).

9vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

9vHPV Delivered at (M0,12) Demonstrates Comparable Immune Response at 1 Month Post Last Dose Compared to Standard Schedule (M0,2,6); Iversen et al 2016 vs. Petersen et al 2017 (Young Girls Only; Australia, N. America, Europe, S. America, Asia, Africa)

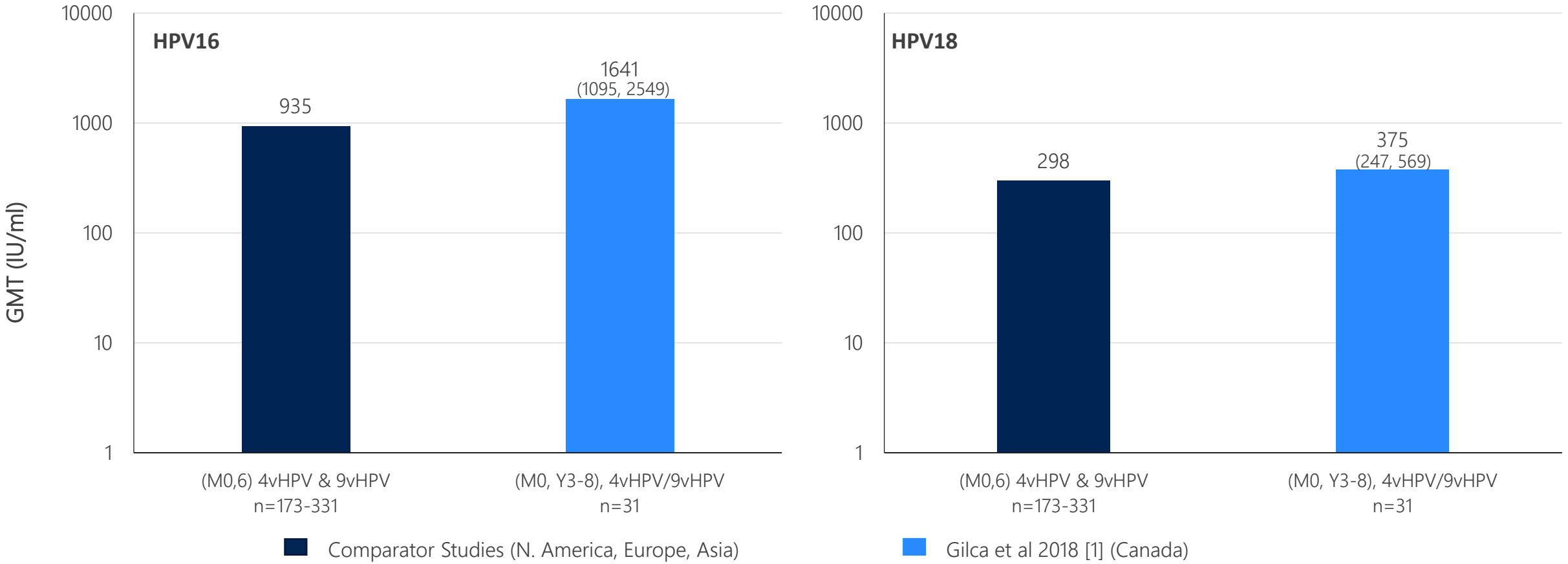




Graphs present GMT at one month post last dose for girls in Iversen et al 2016 (M0,12), disaggregated by age, compared to aggregated GMTs from standard (M0,2,6) schedules from Petersen et al 2017 (red). Petersen data aggregates GMT from trials NCT00543543, NCT00943722, NCT00988884, NCT01073293, and NCT01304498. Iversen data included 15 countries. Sample size ranged from 151 to 314. Comparator data included 26 countries in Australia, Europe, South and North America, Asia, and Africa. Sample sizes ranged from 2405 to 4884. All studies used competitive Luminex assays and reported data in mMu/ml. Data converted to IU/ml as per Brown et al 2016 conversion factors: 0.137 (HPV16) and 0.188 (HPV18).

4v/9vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

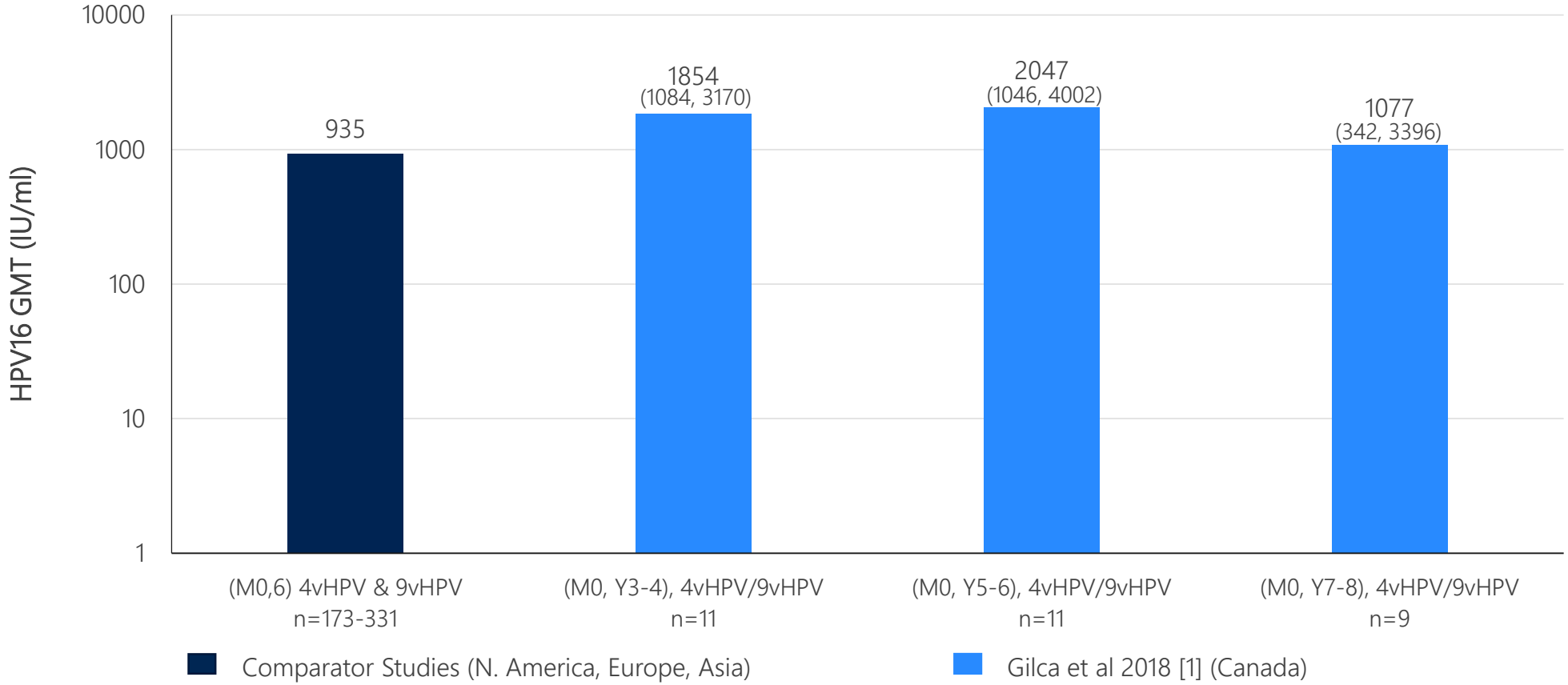
9vHPV Delivered 3-8Y After 4vHPV Demonstrates Comparable Immune Response at 1 Month Post Last Dose Compared to (M0,6) Studies Using ELISA (N. America, Europe, Asia)



Graphs present GMT at one month post last dose in Gilca et al 2018 [1] (girls age 13-18) compared to alternate extended schedules in relevant comparator studies. Comparator studies include Gilca et al 2018 [2] (girls and boys age 9-11) and Leung et al 2015 (girls age 9-14). Gilca 2018 [1] conducted in Canada with a sample size of 31. Comparator data included 5 countries in North America, Europe, and Asia. Sample sizes ranged from 173 to 331. All studies used ELISA and reported in EU/ml or IU/ml.

4v/9vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

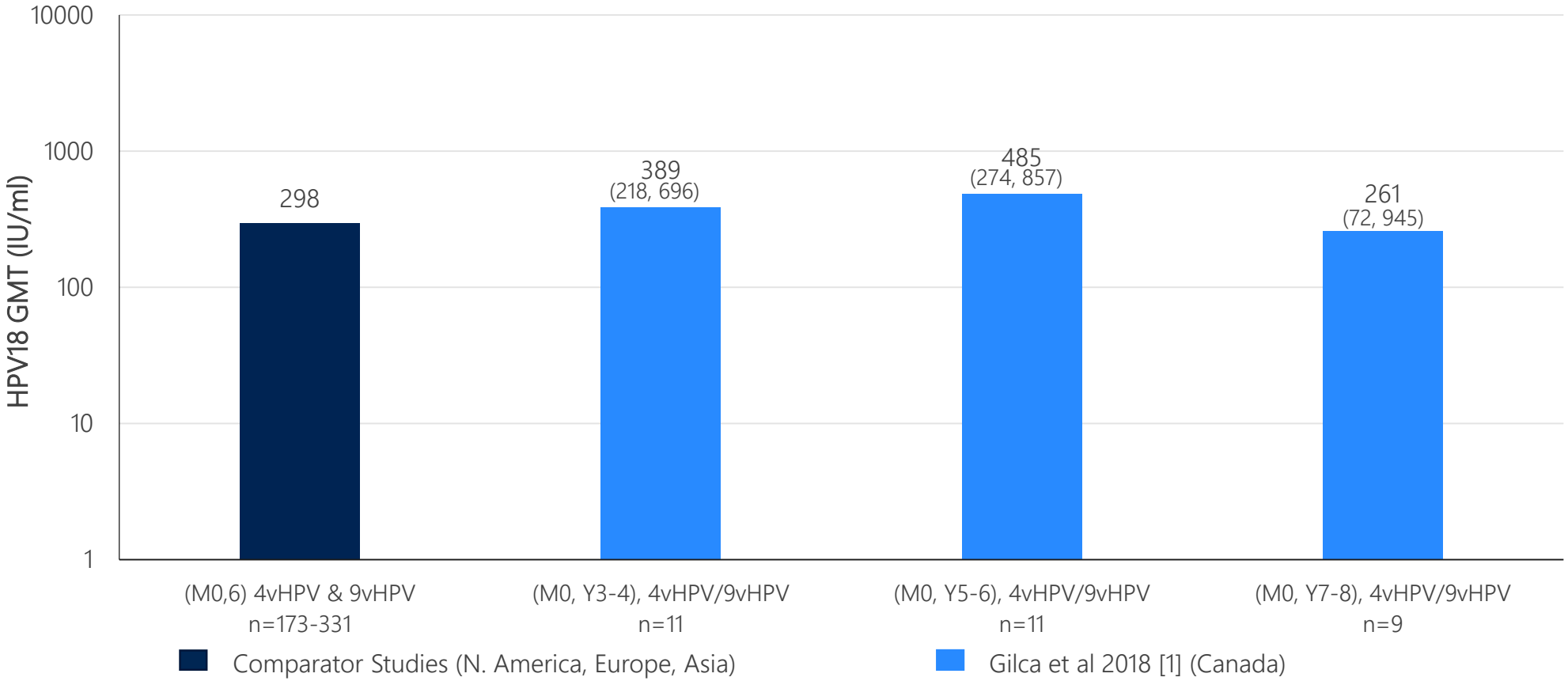
9vHPV Delivered 3-4Y, 5-6Y, 7-8Y After 4vHPV Demonstrates Comparable Immune Response at 1 Month Post Last Dose Compared to (M0,6) Studies Using ELISA (HPV16; N. America, Europe, Asia)



Graphs present GMT at one month post last dose in Gilca et al 2018 [1] (girls age 13-18), disaggregated by receipt of last dose, compared to alternate extended schedules in relevant comparator studies. Comparator studies include Gilca et al 2018 [2] (girls and boys age 9-11) and Leung et al 2015 (girls age 9-14). Gilca 2018 [1] conducted in Canada with a sample size of 31. Comparator data included 5 countries in North America, Europe, and Asia. Sample sizes ranged from 173 to 331. All studies used ELISA and reported in EU/ml or IU/ml.

4v/9vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

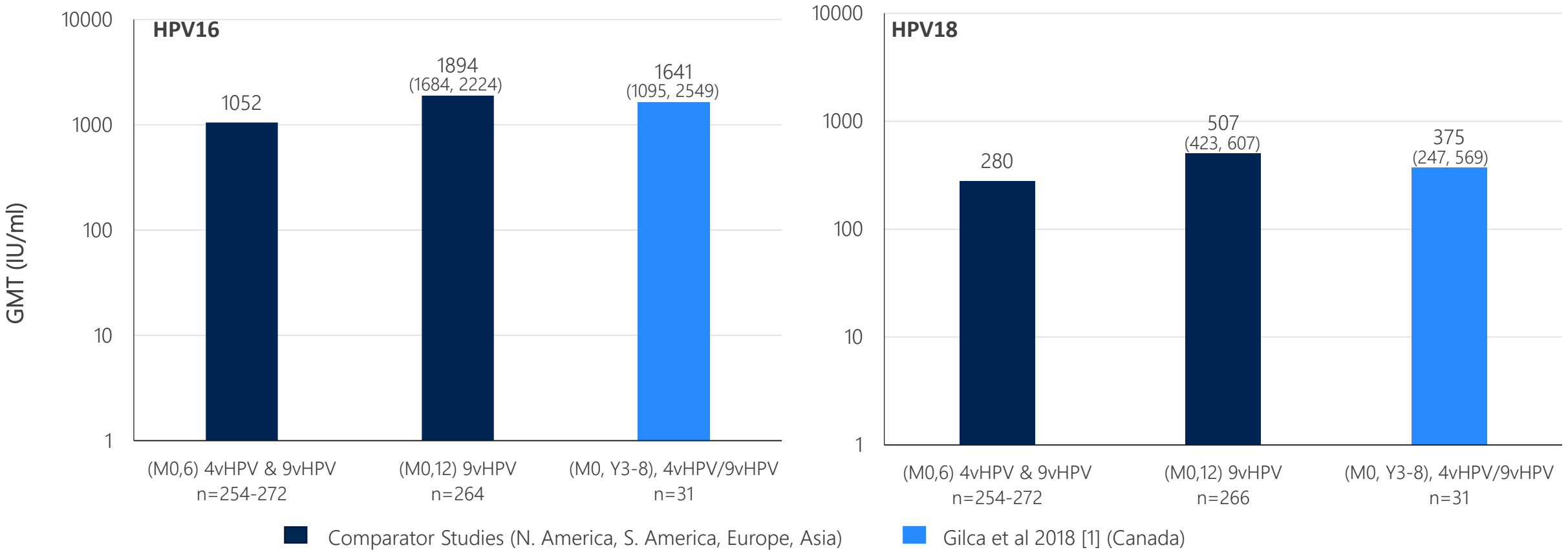
9vHPV Delivered 3-4Y, 5-6Y, 7-8Y After 4vHPV Demonstrates Comparable Immune Response at 1 Month Post Last Dose Compared to (M0,6) Studies Using ELISA (HPV18; N. America, Europe, Asia)



Graphs present GMT at one month post last dose in Gilca et al 2018 [1] (girls age 13-18), disaggregated by receipt of last dose, compared to alternate extended schedules in relevant comparator studies. Comparator studies include Gilca et al 2018 [2] (girls and boys age 9-11) and Leung et al 2015 (girls age 9-14). Gilca 2018 [1] conducted in Canada with a sample size of 31. Comparator data included 5 countries in North America, Europe, and Asia. Sample sizes ranged from 173 to 331. All studies used ELISA and reported in EU/ml or IU/ml.

4v/9vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

9vHPV Delivered 3-8Y After 4vHPV Demonstrates Comparable Immune Response at 1 Month Post Last Dose Compared to (M0,6) and (M0,12) Studies Using cLIA (N. America, S. America, Europe, Asia)



Graphs present GMT at one month post last dose in Gilca et al 2018 [1] (girls age 13-18) compared to alternate extended schedules in relevant comparator studies. Comparator studies include Iversen et al 2016 and Dobson et al 2013 (girls age 9-14). Gilca 2018 [1] was conducted in Canada with a sample size of 31, using ELISA reported in IU/ml. Comparator data included 15 countries in Asia, Africa, South and North America, and the Middle East. Sample sizes ranged from 254 to 272. Comparator studies used cLIA and reported in mMu/ml.

APPENDIX A: SUMMARY OF IDENTIFIED EXTENDED INTERVAL AND SINGLE DOSE STUDIES

IDENTIFIED STUDIES

Extended Interval Studies

1. NCT01381575 (Puthanakit et al 2016, Huang et al 2017)
2. Iversen et al 2016
3. Gilca et al 2018
4. Gilca et al 2014
5. NCT00524745 (Neuzil et al 2011, LaMontagne et al 2013)
6. Toh et al 2017

Single Dose Studies

1. Sankaranarayanan et al 2016
2. Hurt et al 2016
3. LaMontagne et al 2014
4. Safaeian et al 2018

EXTENDED INTERVAL

1 **NCT01381575 (Puthanakit et al 2016, Huang et al 2017)**

Study Characteristics

- Randomized open trial comparing immunogenicity after 2D vs. 3D of bivalent vaccine
- Dosing schedules: (0,6), (0,12), (0,1,6)
- Girls age 9-14 for (0,6), (0,12), women age 15-25 for (0,1,6) from Canada, Germany, Italy, Taiwan, Thailand
- Study group samples ranged from n=330-462

Immunogenicity Data

- Antibody titers (GMT) measured in EU/mL
- Measured at one month after final vaccination in dosing series
- Measured through 36 months after first dose for all schedules
- Data extracted from Puthanakit et al 2016 and Huang et al 2017
- Assay: VLP ELISA, reported as EU/ml (conducted at GSK/Belgium)

EXTENDED INTERVAL

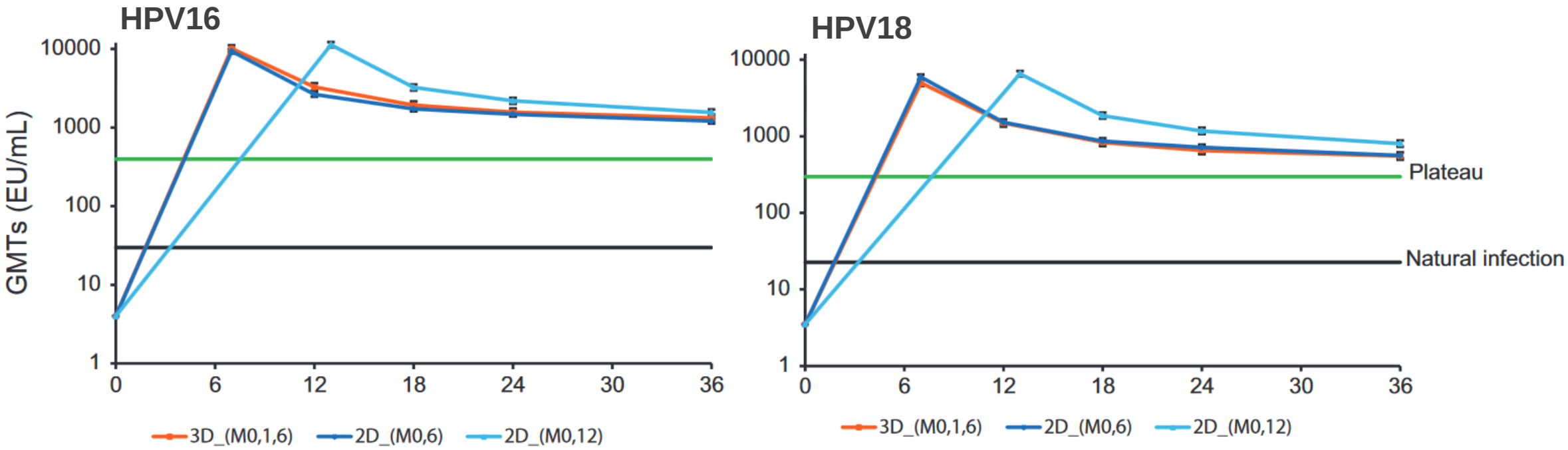
1 NCT01381575 (Puthanakit et al 2016, Huang et al 2017)

HPV Type	Dosing Schedule	Age	Sex	N	Antibody Titers by Time after First Dose, GMT (95% CI)				
					7m	12/13m	18m	24m	36m
16	(0,12)	9-14	F	339	-	11450 (10635, 12327)	3355	2244	1559 (1431, 1699)
16	(0,6)	9-14	F	455	9400 (8818, 10020)	2663	1788	1505	1210 (1125, 1302)
16	(0,1,6)	15-25	F	330	10234 (9258, 11314)	3317	2005	1594	1326 (1194, 1474)
18	(0,12)	9-14	F	355	-	6656 (6154, 7200)	1779	1104	804 (732, 883)
18	(0,6)	9-14	F	462	5909 (5509, 6338)	1526	856	696	563 (516, 613)
18	(0,1,6)	15-25	F	356	5003 (4573, 5473)	1505	783	656	553 (494, 618)

1. Titers presented in EU/mL
2. Confidence intervals reported when available in publication

EXTENDED INTERVAL

1 **NCT01381575 (Puthanakit et al 2016, Huang et al 2017)**



1. Plateau measured as GMT at time 45-50m among women age 15-25 receiving 3 doses of bivalent vaccine in previous trial; plateau titer values were 398 EU/mL and 297 EU/mL for HPV16 and 18, respectively.

2. Natural infection measured as GMT among women age 15-25 who had cleared HPV infection in a previous trial; natural infection values were 30 and 23 EU/mL for HPV16 and 18, respectively.

EXTENDED INTERVAL

2 **Iversen et al 2016**

Study Characteristics

- Randomized open noninferiority trial conducted at 52 sites across 15 countries comparing immunogenicity following 9-valent vaccine
- Dosing schedules: (0,6), (0,12), (0,2,6)
- Girls and boys age 9-14 for (0,6), (0,12); girls age 9-14 and women age 16-26 for (0,1,6)
- Study group samples ranged from n = 129 - 273

Immunogenicity Data

- Antibody GMT, seroconversion rates for all dosing schedules reported one month after last dose
- Data disaggregated by sex and age (eg 9-10, 11-12, 13-14) in supplementary appendices
- Assay: Multiplexed cLIA, reported as mMu/ml tested at Merck/USA

EXTENDED INTERVAL

2 Iversen et al 2016

HPV Type	Dosing Schedule	Age	Sex	N	Antibody Titers 1m after Last Dose, GMT (95% CI)
16	(0,6)	9-14	F	272	8005 (7161, 8949)
16	(0,6)	9-14	M	273	8475 (7582, 9472)
16	(0,12)	9-14	Both	264	14329 (12796, 16046)
16	(0,12)	9-14	F	129	13828 (11781, 16232)
16	(0,2,6)	9-14	F	269	6996 (6261, 7817)
16	(0,2,6)	16-26	F	249	3154 (2807, 3544)
18	(0,6)	9-14	F	272	1873 (1652, 2124)
18	(0,6)	9-14	M	272	1861 (1641, 2110)
18	(0,12)	9-14	Both	266	2810 (2475, 3191)
18	(0,12)	9-14	F	129	2696 (2252, 3227)
18	(0,2,6)	9-14	F	270	2049 (1810, 2320)
18	(0,2,6)	16-26	F	267	762 (671, 864)

1. Titers presented in mMU/mL

EXTENDED INTERVAL

3 **Gilca et al 2018**

Study Characteristics

- Exploratory immunogenicity study of girls who received one dose of 4vHPV and one dose of 9vHPV 3 to 8 years later
- 31 girls age 13-18 living in Quebec identified through regional vaccine registry
- Study group sample size n = 31

Immunogenicity Data

- Antibody GMT, seroconversion rates measured 3-8 years after first dose, 1 month after second dose
- Data available for HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58
- Assay: multiplex direct IgG ELISA, performed by the Centers for Disease Control and Prevention (CDC, Atlanta, USA), reported as IU/ml (16,18) and AU/ml (6,11)

EXTENDED INTERVAL

3 Gilca et al 2018

HPV Type	Dosing Group	Age	Sex	N	Antibody Titers by Time after First Dose, GMT (95% CI)	
					3-8 years (pre-9vHPV)	3-8 years + 1 months (post-9vHPV)
6	**(0, 36-96)**	13-18	F	31	6 (4, 11)	406 (272, 605)
11	**(0, 36-96)**	13-18	F	31	8 (5, 13)	553 (349, 877)
16	**(0, 36-96)**	13-18	F	31	20 (12, 34)	1641 (1095, 2458)
18	**(0, 36-96)**	13-18	F	31	6 (4, 10)	375 (247, 569)

1. Titers presented in AU/mL for HPV types 6 and 11; presented in IU/mL for HPV types 16 and 18
2. Titer data collected between 3-8 years after initial dose of 4vHPV (mean = 5.4 years)

EXTENDED INTERVAL

4 **Gilca et al 2014**

Study Characteristics

- Randomized open trial comparing immunogenicity of 4vHPV when co-administered with HAV/HBV vaccine
- Girls age 9-10 in Quebec
- Dose schedule: (0,6) with co-administration of HAV/HBV with first dose, or one month following first dose of 4vHPV
- Study group samples ranged from n = 199 - 207

Immunogenicity Data

- Antibody GMT, seroconversion rates measured at 6m, 7m, and 43m after first dose of 4vHPV
- Data available for HPV types 6, 11, 16, 18
- Assay: Luminex Total IgG assay, reported as LU

EXTENDED INTERVAL

4 Gilca et al 2014

HPV Type	Dosing Group	Age	Sex	N	Antibody Titers by Time after First Dose, GMT (95% CI)		
					6 mo.	7 mo.	42 months
6	**(0,6), CoAdm**	9-10	F	207	11 (10,14)	1103 (989, 1230)	77 (66, 91)
11	**(0,6), CoAdm**	9-10	F	207	71 (62, 81)	3897 (3575, 4248)	308 (268, 353)
16	**(0,6), CoAdm**	9-10	F	207	42 (36, 49)	3287 (2977, 3628)	286 (243, 336)
18	**(0,6), CoAdm**	9-10	F	207	12 (10, 14)	887 (791, 994)	45 (37, 55)
6	**(0,6)**	9-10	F	199	-	1220 (1094, 1362)	85 (72, 101)
11	**(0,6)**	9-10	F	199	-	4136 (3773, 4533)	336 (291, 388)
16	**(0,6)**	9-10	F	199	-	3543 (3224, 3893)	330 (283, 384)
18	**(0,6)**	9-10	F	199	-	993 (890, 1109)	60 (50, 71)

1. Titers presented in Luminex Units (LU)
2. Sample size presented for 6, 7m time points; smaller sample sizes for 42m due to loss to follow-up

EXTENDED INTERVAL

5 NCT00524745 (Neuzil et al 2011, LaMontagne et al 2013)

Study Characteristics

- Randomized open trial comparing immunogenicity after 2D vs. 3D of quadrivalent vaccine
- Dosing schedules: (0,2,6), (0,3,9), (0,6,12), (0,12,24)
- Girls age 11-13 in Vietnam
- Study group samples ranged from n = 206-229

Immunogenicity Data

- Antibody titers (GMT) measured pre-dose 3, 1 month post dose 3, 29-32 months post dose 3
- Data available for HPV6, 11, 16, 18
- Data extracted from Neuzil et al 2011 and LaMontagne et al 2013
- Assay: type-specific cLIA, performed by Merck Research Laboratories (United States), reported as mMu/ml

EXTENDED INTERVAL

5 NCT00524745 (Neuzil et al 2011, LaMontagne et al 2013)

HPV Type	Dosing Group	Age	Sex	N	Antibody Titers by Time after Dose 3, GMT (95% CI)			
					Pre-dose 3	1m post-dose 3	20m post-dose 3	29-32m post-dose 3
16	(0,2,6)	11-13	F	227	668 (585, 763)	5808 (4961, 6799)	-	1072 (900, 1278)
16	(0,3,9)	11-13	F	229	889 (791, 999)	5369 (4632, 6222)	-	966 (827, 1128)
16	(0,6,12)	11-13	F	206	928 (756, 1140)	5716 (4877, 6701)	-	1014 (902, 1140)
16	(0,12,24)	11-13	F	213	1572 (1366, 1810)	3693 (3145, 4335)	1755 (1518, 2030)	1311 (1135, 1514)
18	(0,2,6)	11-13	F	227	78 (68, 89)	1730 (1504, 1990)	-	167 (133, 210)
18	(0,3,9)	11-13	F	229	102 (88, 119)	1502 (1302, 1733)	-	170 (139, 208)
18	(0,6,12)	11-13	F	206	137 (114, 166)	1582 (1363, 1835)	-	170 (146,197)
18	(0,12,24)	11-13	F	213	191 (163, 224)	1336 (1192, 1497)	280 (235, 334)	194 (161, 234)

1.Antibody titer presented in mMU/mL
2. Sample sizes presented for pre- and 1 month-post dose 3; smaller sample sizes for 20 and 29-32m due to loss to follow-up

EXTENDED INTERVAL

6 **Toh et al 2017**

Study Characteristics

- Prospective cohort study comparing immunogenicity after a single dose of 2vHPV in girls who previously received 0-4 doses of 4vHPV
- Comparator groups: 0, 1, 2, 3, previous doses of 4vHPV, 6 years before single dose of 2vHPV
- Girls age 15-19 in Fiji
- Study group samples ranged from n = 32-66

Immunogenicity Data

- Antibody titers (GMT) and seroconversion rates prior to 2vHPV, antibody GMT one month after 2vHPV
- Data available for HPV6, 11, 16, 18
- Assay: PBNA, performed by Murdoch Childrens Research Institute, Melbourne, Australia, reported as ED50 units

EXTENDED INTERVAL

6 Toh et al 2017

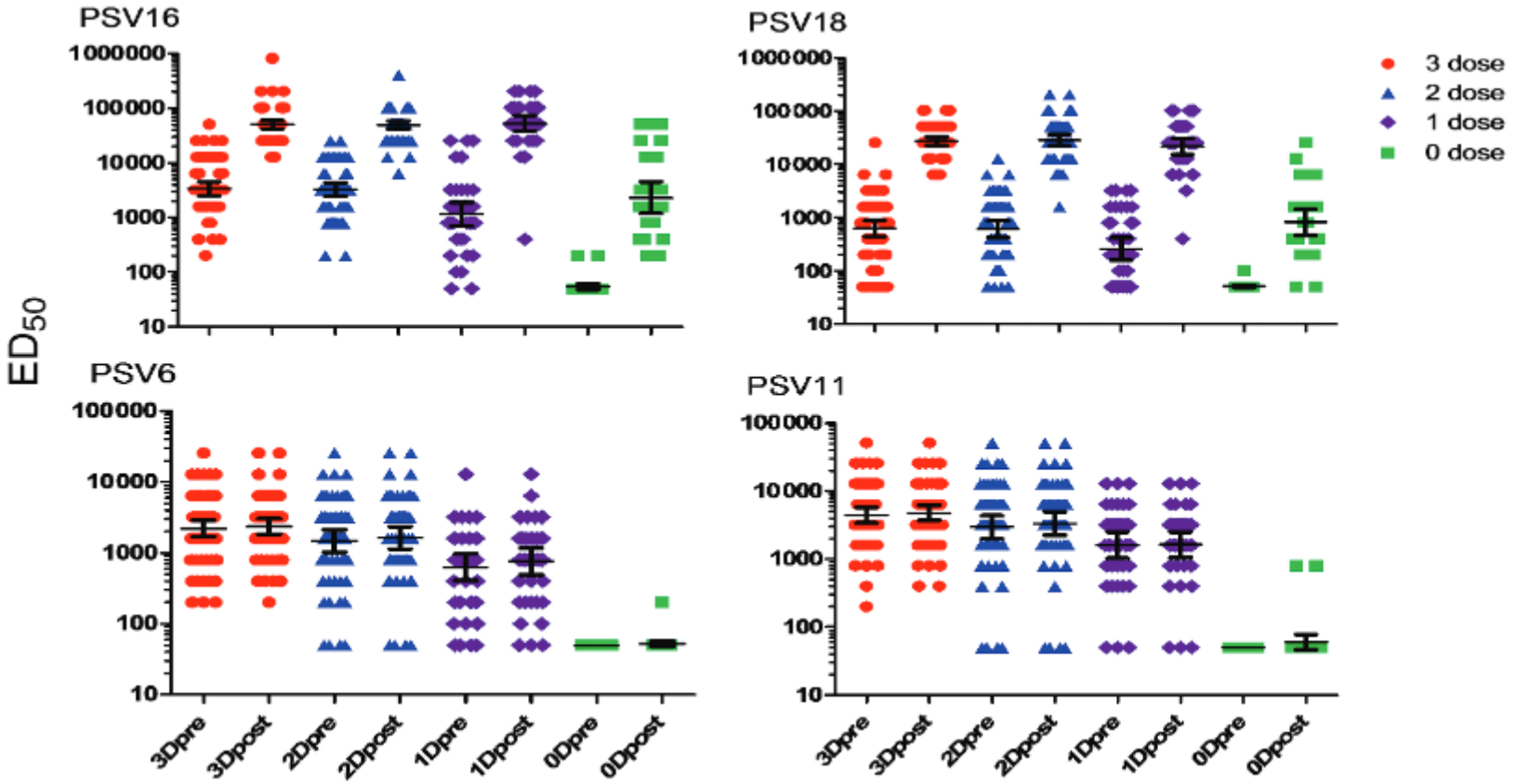
HPV Type	Dosing Group	Age	Sex	N	Antibody Titers, GMT (95% CI)	
					6 years after first dose, pre-2vHPV booster	1 month after 2vHPV booster
16	**0**	16-19	F	32	53 (46, 66)	2477 (1277, 4642)
16	**1**	9-11	F	40	1215 (710, 1861)	9621 (7439, 12769)
16	**2**	10	F	59	3187 (2435, 4265)	8907 (8036, 10664)
16	**3**	11	F	66	3408 (2547, 4362)	9139 (7831, 10664)
18	**0**	16-19	F	32	53 (50, 61)	811 (464, 1417)
18	**1**	9-11	F	40	253 (169, 414)	10544 (8309, 14485)
18	**2**	10	F	59	620 (453, 868)	6048 (4894, 7474)
18	**3**	11	F	66	679 (474, 929)	5890 (4894, 7089)

1. Dosing group refers to number of doses received before booster
2. Titers presented in ED50

EXTENDED INTERVAL

6 Toh et al 2017

Neutralizing antibody titers before and one month 2vHPV booster, ED50



START CENTER

SINGLE DOSE

1 LaMontagne et al 2014

Study Characteristics

- Cross-sectional study of immunogenicity after 1, 2, or 3 doses of 2vHPV
- Comparator groups: 1, 2, or 3 doses based on vaccine registry data
- Girls age 10-11 in Uganda
- Study group samples ranged from n = 36-195

Immunogenicity Data

- Antibody titers (GMT) reported 33-38 months after first dose
- Data available for HPV16, 18
- Assay: ELISA, performed by HPV Immunology Laboratory of the National Cancer Institute (Fredrick, Maryland, USA), reported as EU/ml

SINGLE DOSE

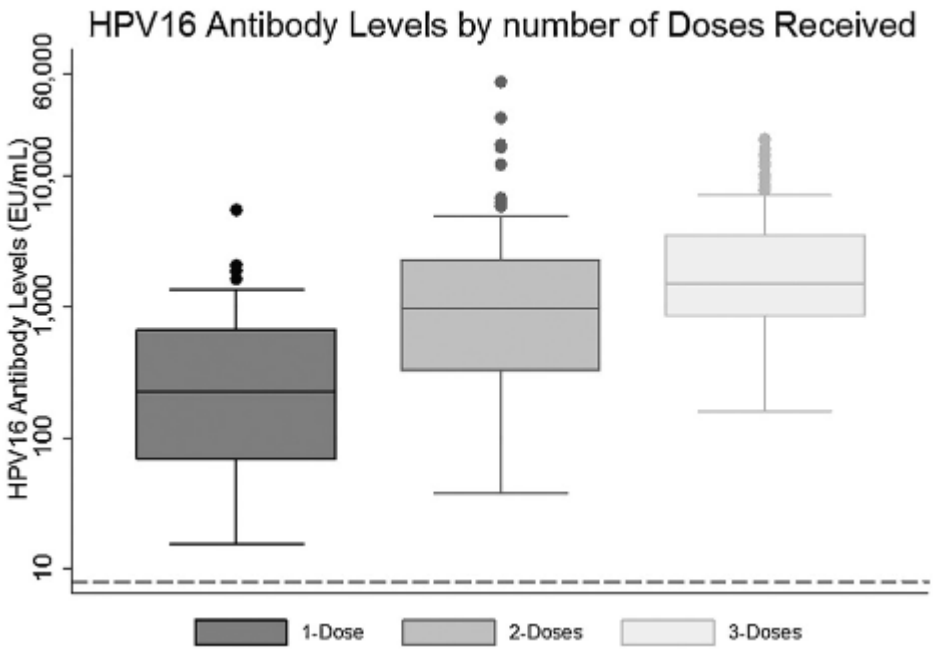
1 LaMontagne et al 2014

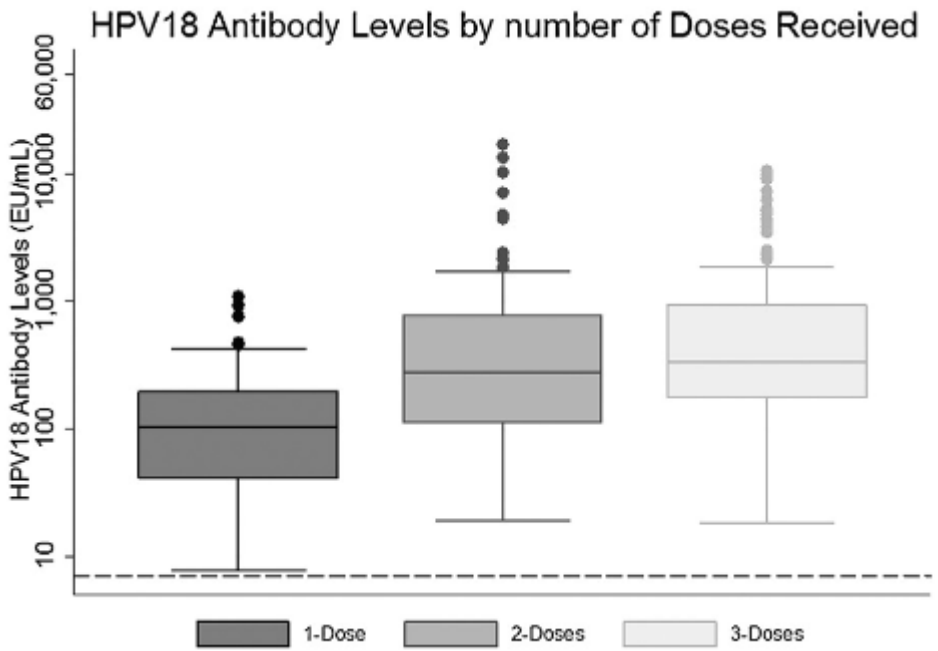
HPV Type	Dosing Group	Age	Sex	N	Antibody Titers 33-39m after First Dose, GMT (95% CI)
16	**1**	11	F	36	230 (139, 379)
16	**2**	10-11	F	145	808 (632, 1034)
16	**3**	10-11	F	195	1608 (1382, 1871)
18	**1**	11	F	36	87 (55, 137)
18	**2**	10-11	F	145	270 (213, 343)
18	**3**	10-11	F	195	396 (331, 472)

1. Titers presented in EU/ml

SINGLE DOSE

1 LaMontagne et al 2014





1. Antibody levels measured among seropositive patients only.
2. Dashed lines represent seropositivity thresholds (8 EU/mL for HPV16 and 7 EU/mL for HPV18)

SINGLE DOSE

2 Hurt et al 2016

Study Characteristics

- Retrospective cohort analysis of female service members receiving one, two, or three doses of 4vHPV
- Women age 17-26
- Study group samples ranged from n = 411-1260

Immunogenicity Data

- Seroconversion rates measured 4-6 years after last dose of 4vHPV
- Data available for HPV types 6, 11, 16, 18 and disaggregated by age
- Assay: ELISA, performed by Johns Hopkins University

SINGLE DOSE

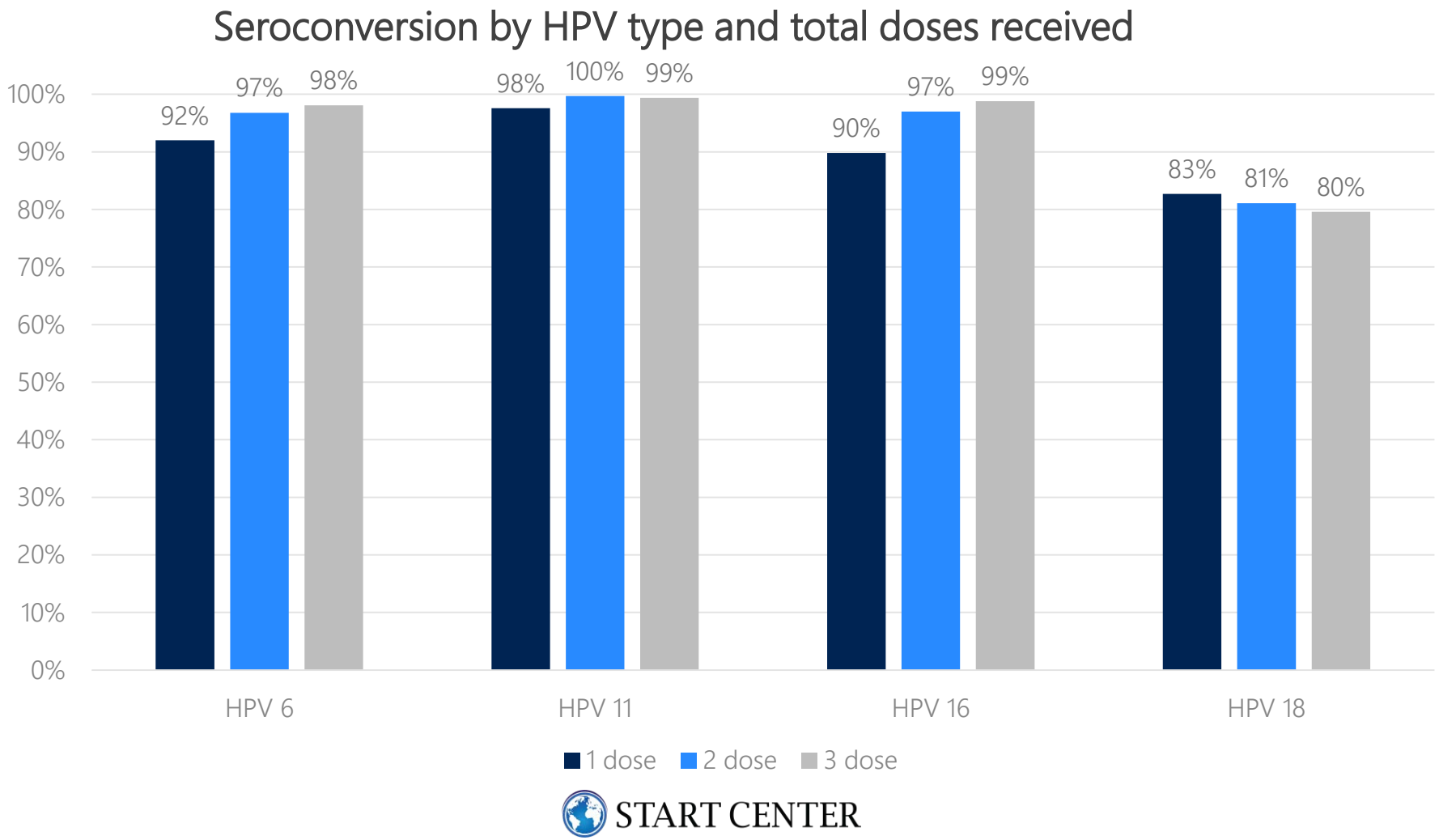
2 Hurt et al 2016

Total number of doses	Age	Sex	N	Seroconversion Rate, (95% CI)			
				HPV 6	HPV 11	HPV 16	HPV 18
1	17-26	F	411	92.0% (87.5%, 95.0%)	97.6% (94.7%, 99.0%)	89.8% (85.5%, 92.9%)	82.7% (78.4%, 86.3%)
2	17-26	F	420	96.8% (93.8%, 98.5%)	99.7% (97.9%-100.0%)	97.0% (94.4%, 98.5%)	81.1% (76.7%, 84.8%)
3	17-26	F	1260	98.1% (96.9%, 98.9%)	99.4% (98.6%, 99.8%)	98.8% (97.9%, 99.4%)	79.6% (77.1%, 81.9%)

1. Post-hoc analysis 4-6 years after last vaccine; groups based on total vaccine doses received; no set vaccine schedule (ie observational study)
2. Seroconversion thresholds not provided by author

SINGLE DOSE

2 Hurt et al 2016



START CENTER

SINGLE DOSE

3 Sankaranarayanan et al 2016

Study Characteristics

- Randomized trial comparing immunogenicity after 2D, 3D of 4vHPV; after trial suspension, 4 comparison groups by default
- Unmarried girls in India age 10-18
- Dose schedule: (0), (0,2), (0,6), (0,2,6)
- Study group samples ranged from n = 3452-4950

Immunogenicity Data

- Antibody GMT measured 18m post first dose of 4vHPV
- Data available for HPV types 6, 16, 18
- Assay: PBNA, performed by Rajiv Gandhi Centre for Biotechnology (RGCB; Thiruvananthapuram, India), units not reported

SINGLE DOSE

3 Sankaranarayanan et al 2016

Dosing Group	Age	Sex	N	Antibody Titers 18m after First Dose, GMT		
				HPV 6	HPV 16	HPV 18
(0)	10-18	F	4950	1059	532	143
(0,2)	10-18	F	3452	4208	2782	532
(0,6)	10-18	F	4979	11841	10315	1135
(0,2,6)	10-18	F	4348	17910	9628	1971

1. No units provided by manuscript
2. (0) and (0,2) schedules by default due to study suspension

SINGLE DOSE

3 Sankaranarayanan et al 2016

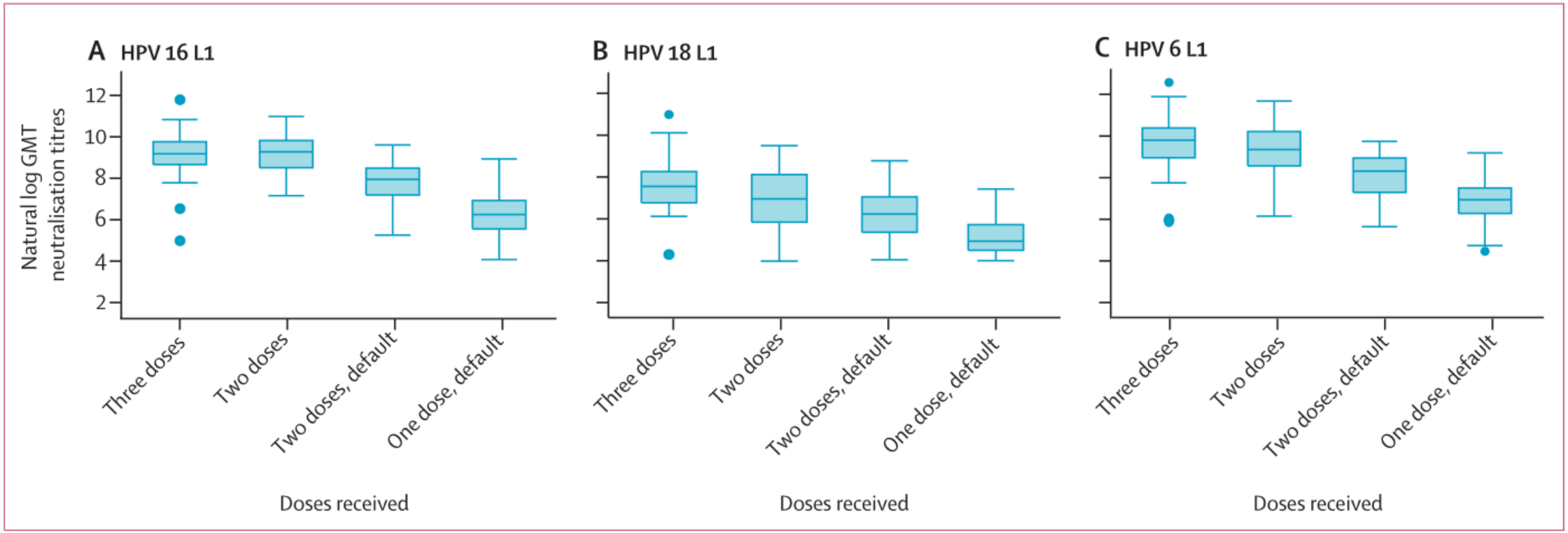
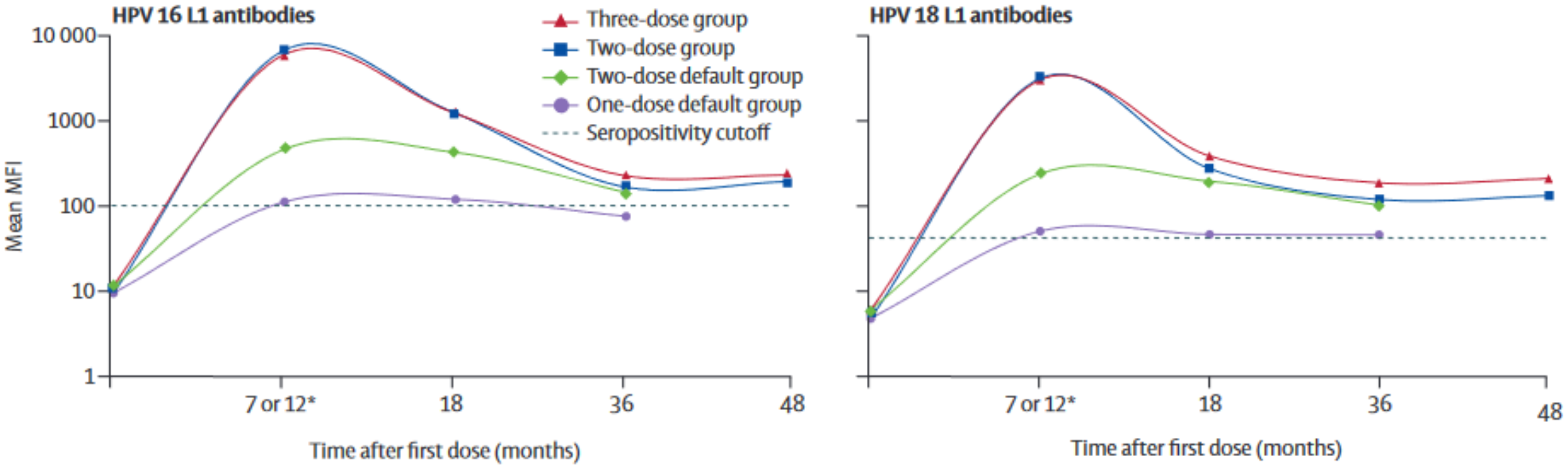


Figure 4: **Box plots of neutralisation titres of HPV types 16 (A), 18 (B), and 6 (C) L1 antibodies at 18 months after the first dose**
Samples without neutralising activity were not included in the GMT analyses. GMT=geometric mean neutralisation titre.

SINGLE DOSE

3 Sankaranarayanan et al 2016



1. Dashed lines show the threshold (cutoff) values for seroconversion. MFI values for month 7 were used for the three-dose and two-dose vaccine groups, whereas MFI values for month 12 were used for the two-dose default and one-dose default groups.

SINGLE DOSE

4 **Safaeian et al 2018**

Study Characteristics

- Randomized trial comparing immunogenicity alternate dosing schedules for 2vHPV
- Costa Rican women age 18-25
- Dose schedules: (0), (0,1), (0,6), (0,1,6)
- Study group samples ranged from n = 79-2043

Immunogenicity Data

- Antibody GMT measured 84m post first dose of 2vHPV
- Data available for HPV types 16, 18
- Assay: ELISA, performed at the NCI HPV Immunology Laboratory; EU/mL

SINGLE DOSE

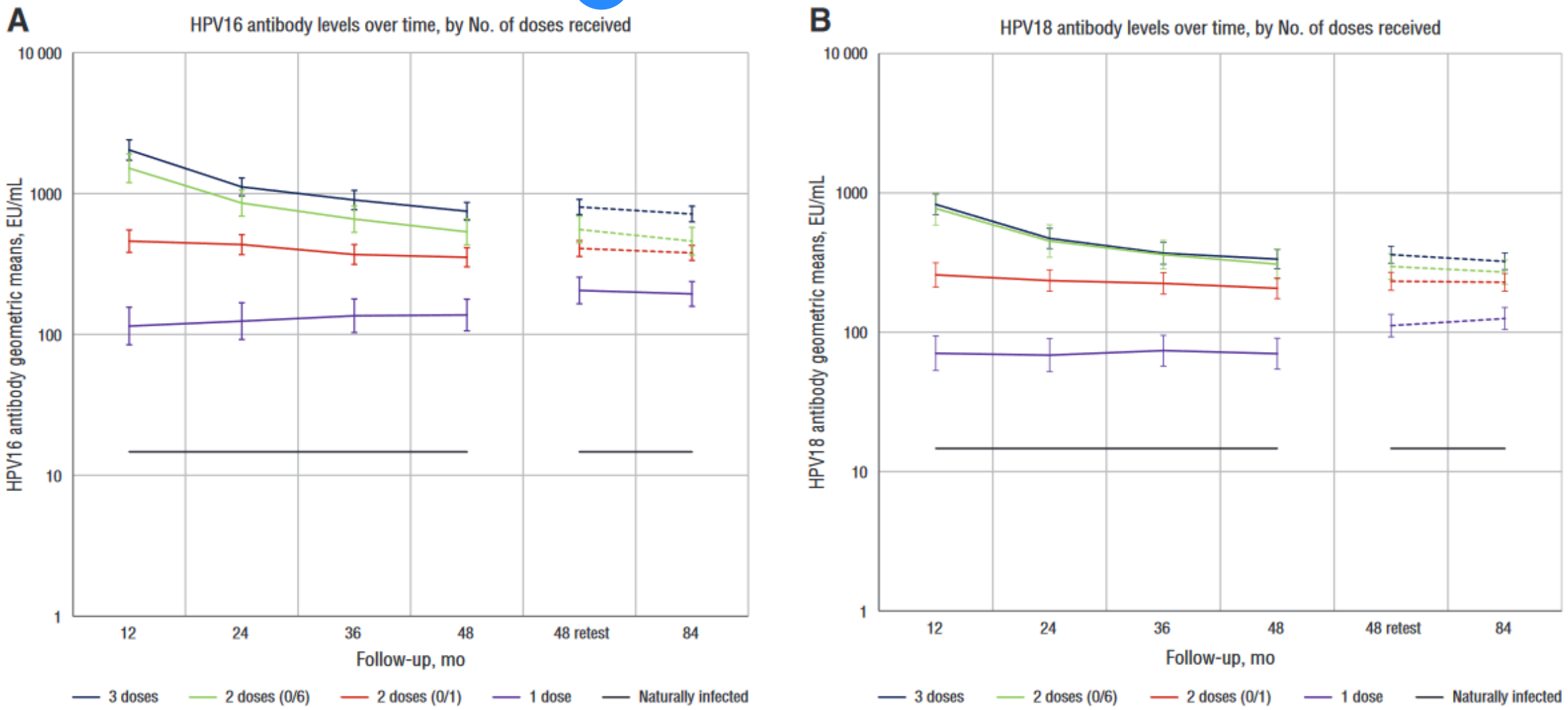
4 Safaeian et al 2018

HPV Type	Dosing Group	Age	Sex	N	Antibody Titers by Time after First Dose, GMT (95% CI)	
					48m	84m
16	**(0)**	18-25	F	134	205 (165, 255)	194 (158, 237)
16	**(0,1)**	18-25	F	193	407 (356, 464)	379 (335, 429)
16	**(0,6)**	18-25	F	79	555 (447, 690)	460 (367, 576)
16	**(0,2,6)**	18-25	F	2043	803 (708, 909)	716 (630, 814)
18	**(0)**	18-25	F	134	112 (93, 134)	125 (105, 150)
18	**(0,1)**	18-25	F	193	232 (200, 269)	228 (198, 264)
18	**(0,6)**	18-25	F	79	296 (240, 366)	270 (221, 330)
18	**(0,2,6)**	18-25	F	2043	360 (313, 414)	322 (281, 369)

1. Titer presented in EU/mL

SINGLE DOSE

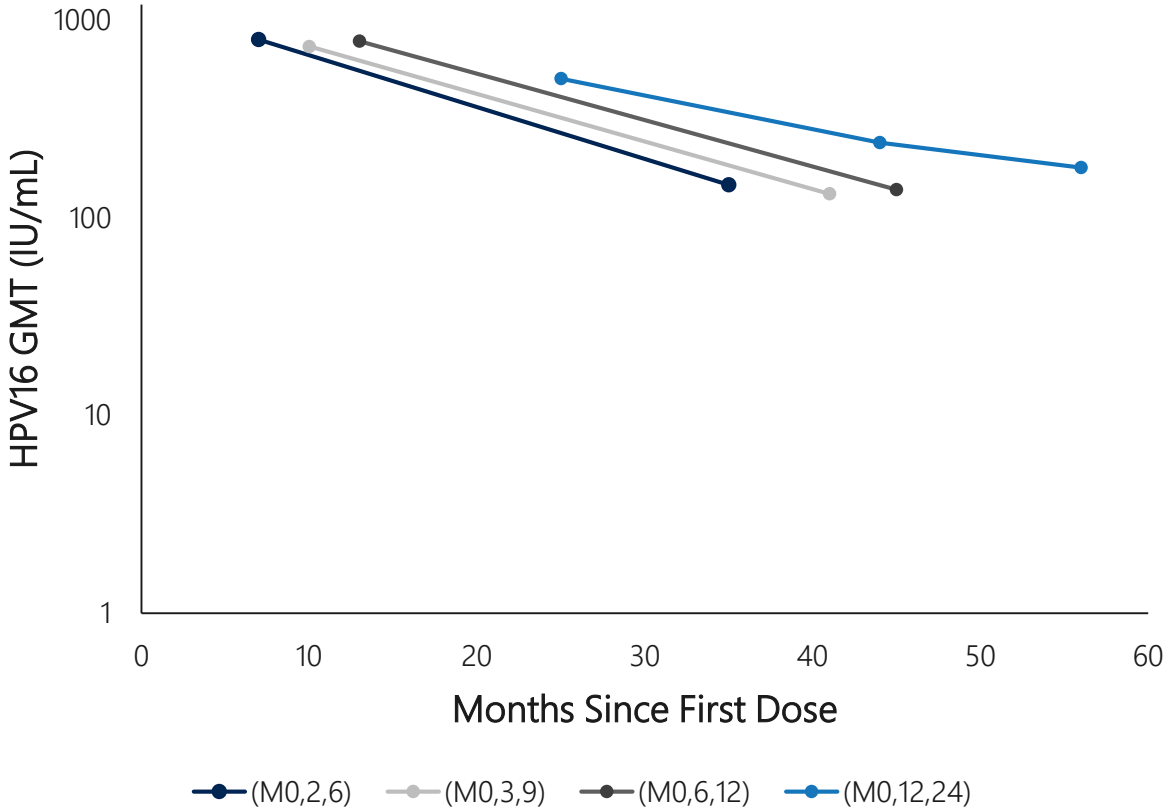
4 Safaeian et al 2018

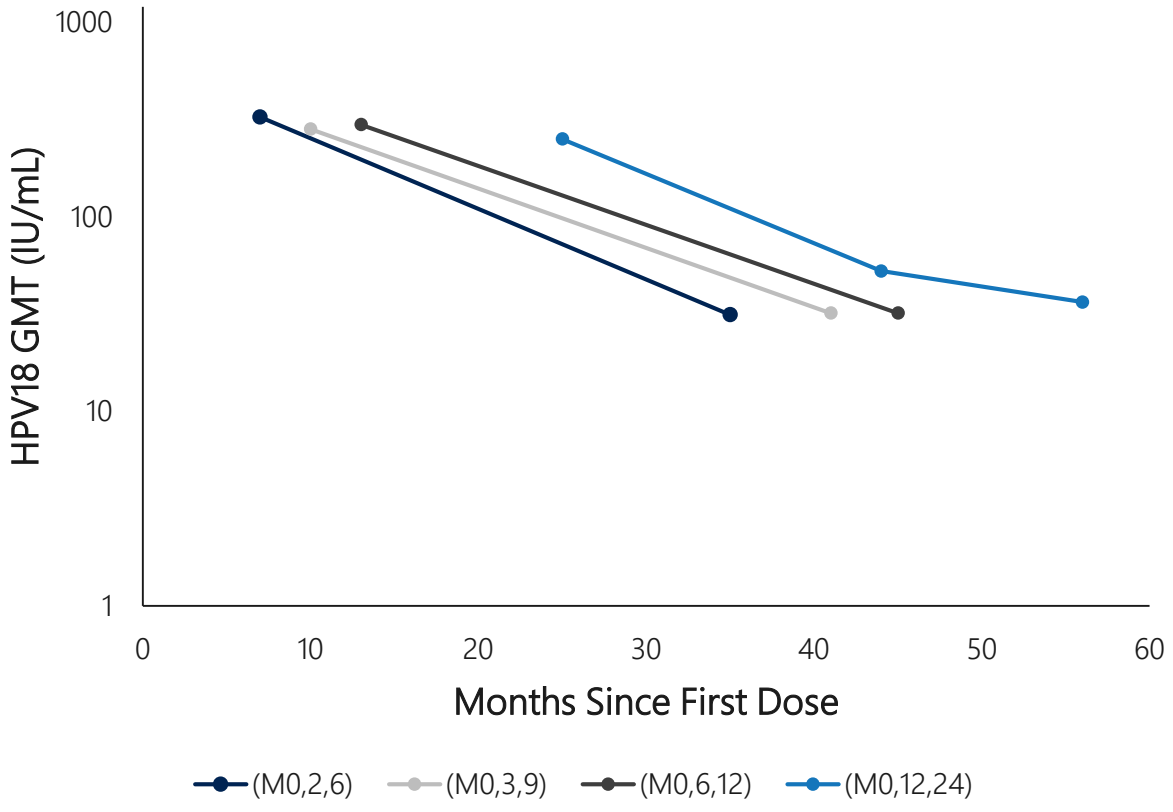


APPENDIX B: ANCILLARY INVESTIGATION OF 3-DOSE EXTENDED INTERVAL

4vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

4vHPV Delivered at (M0,12, 24) Demonstrates Comparable Immune Response Compared to Standard Schedule

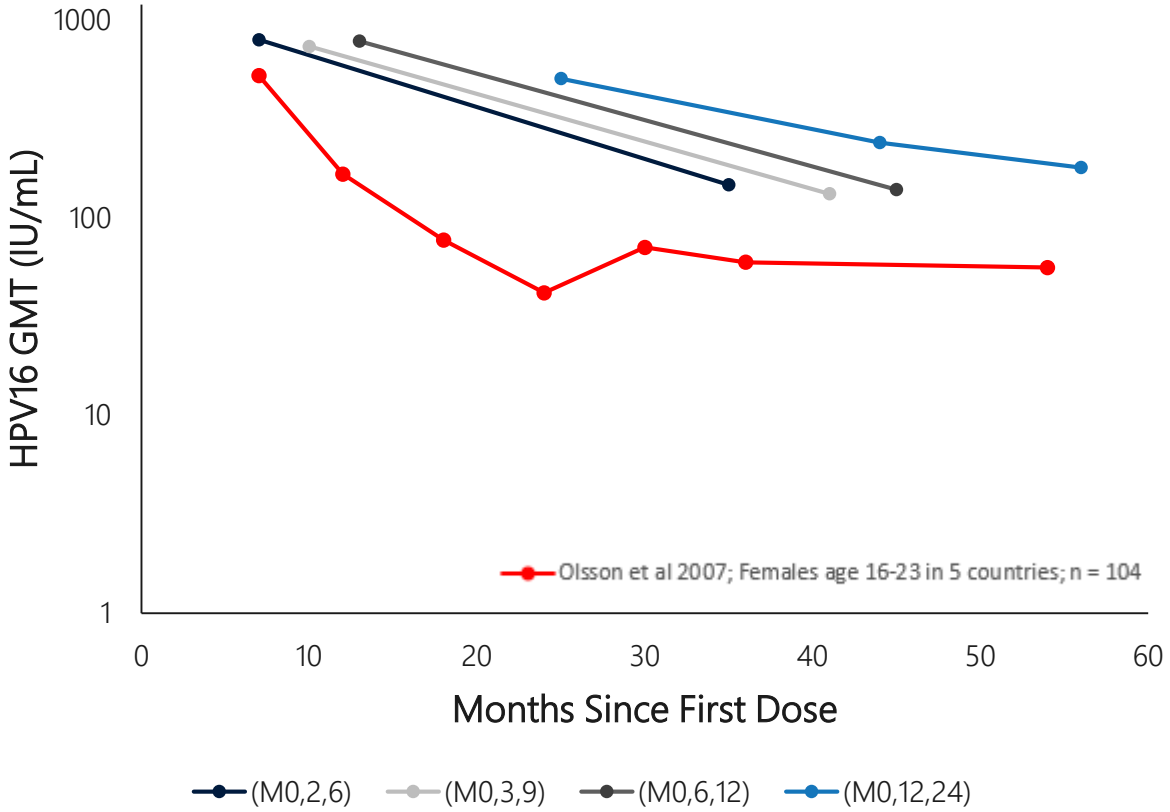


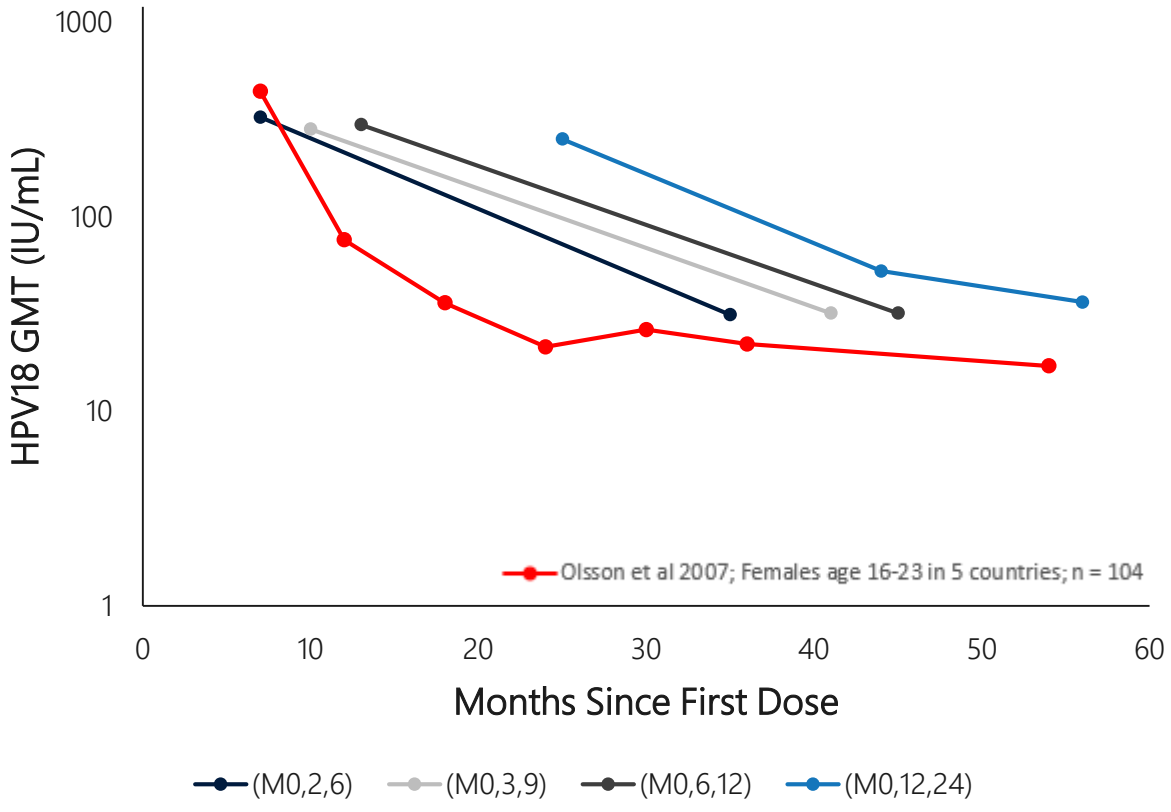


1. Graphs present GMT over time in Neuzil et al 2013 (girls age 11-13) compared to GMTs from standard (M0,2,6) schedules in relevant comparator studies. Comparator studies include Olsson et al 2007, Dobson et al 2013, Ferris et al 2017, and Ruiz-Sternberg et al 2018.

4vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

4vHPV Delivered at (M0,12, 24) Demonstrates Comparable Immune Response Compared to Standard Schedule

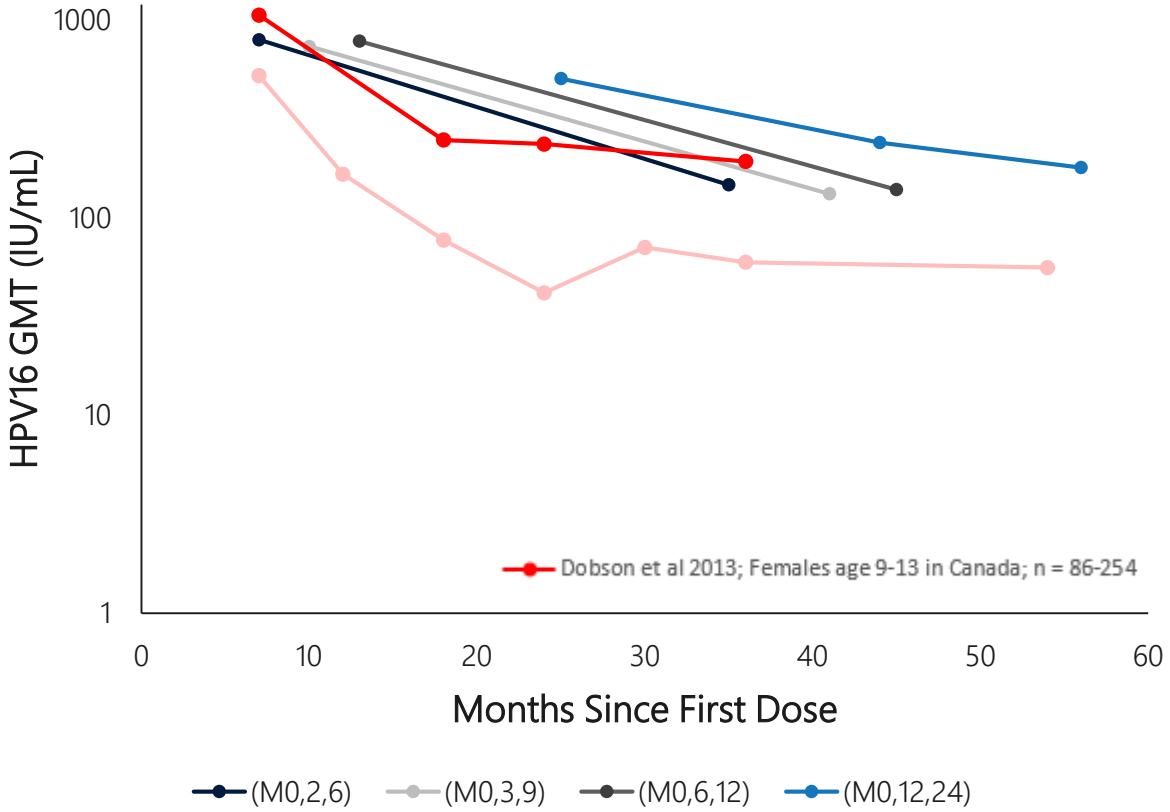


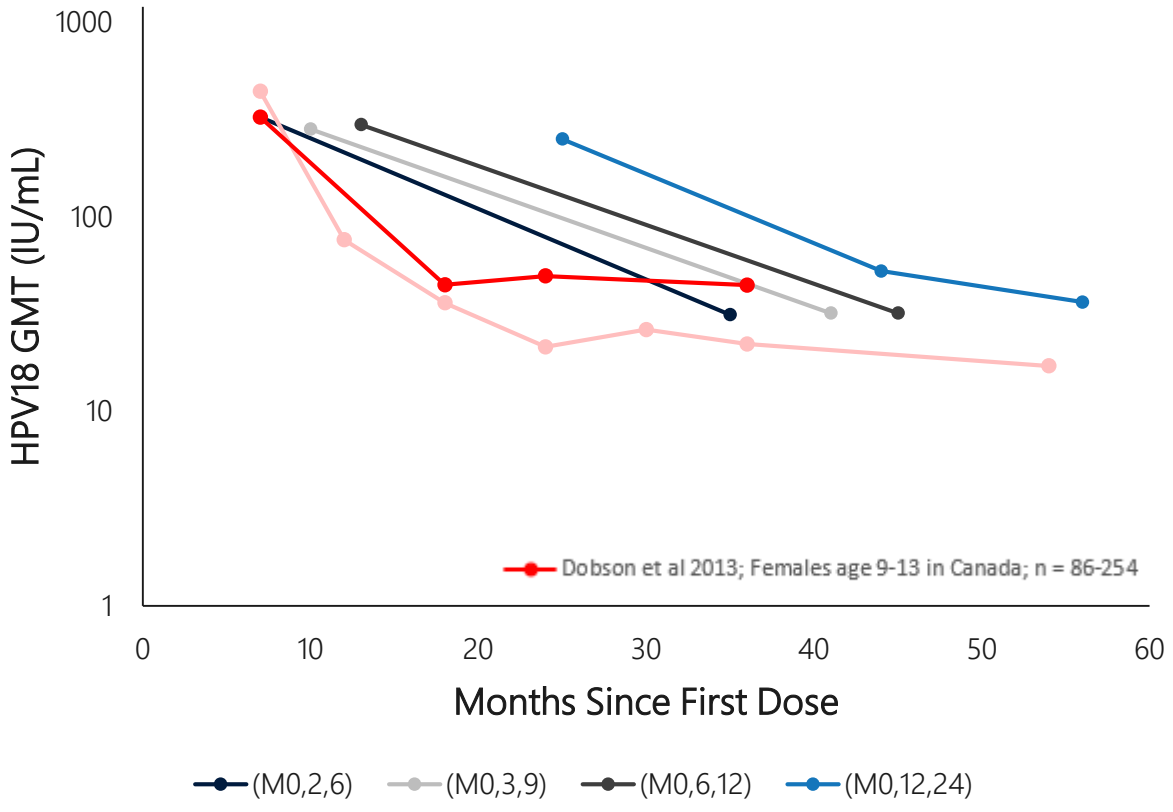


1. Graphs present GMT over time in Neuzil et al 2013 compared to GMTs from standard (M0,2,6) schedules in relevant comparator studies. Comparator studies include Olsson et al 2007, Dobson et al 2013, Ferris et al 2017, and Ruiz-Sternberg et al 2018.

4vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

4vHPV Delivered at (M0,12, 24) Demonstrates Comparable Immune Response Compared to Standard Schedule

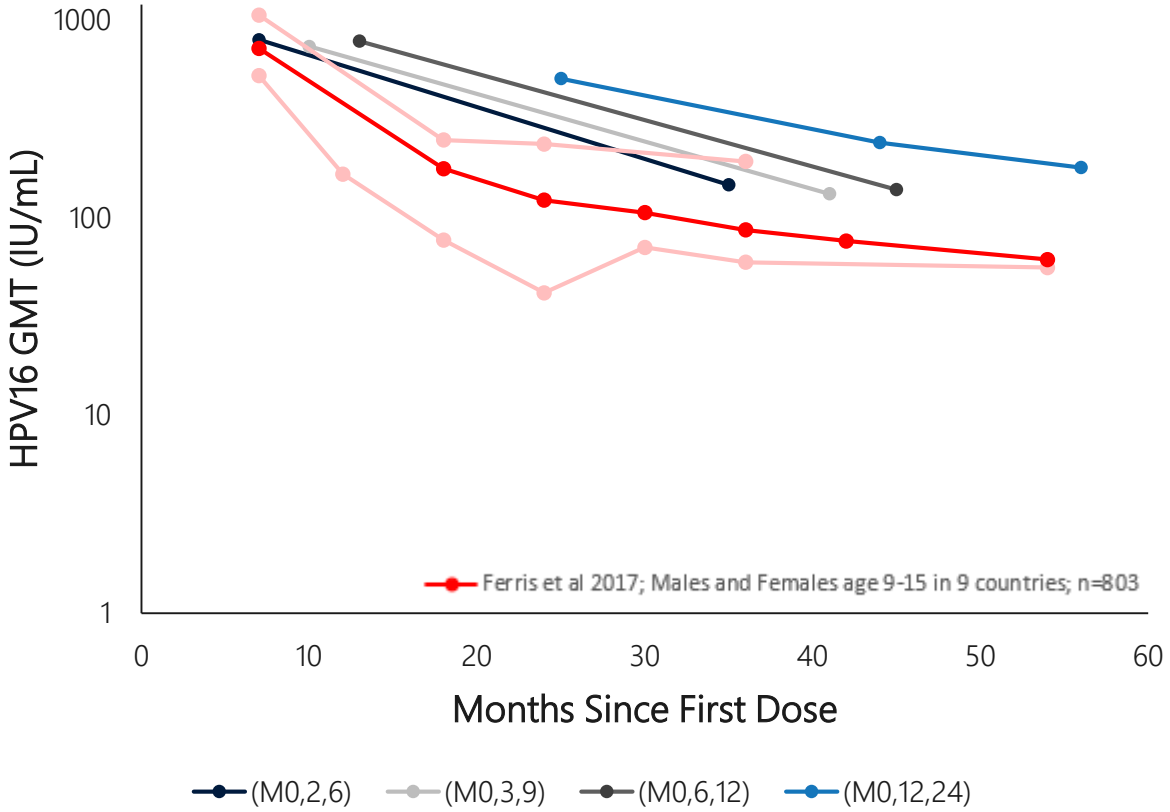


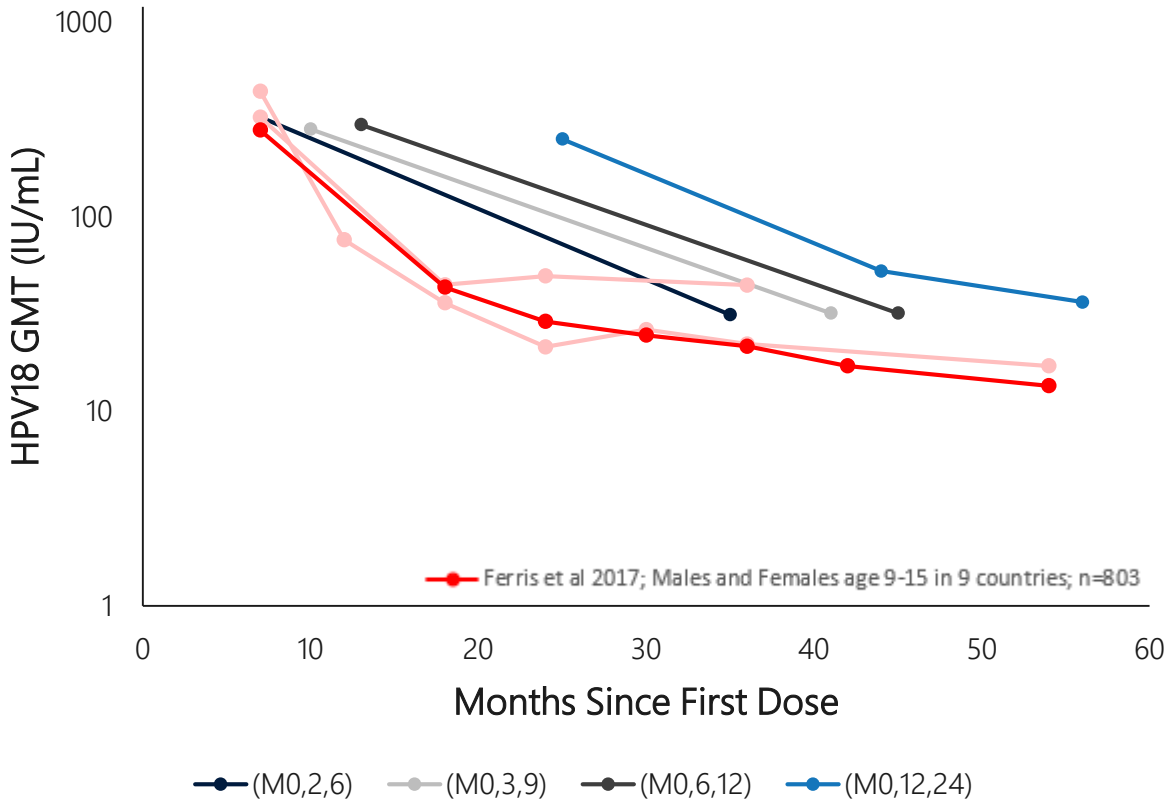


1. Graphs present GMT over time in Neuzil et al 2013 compared to GMTs from standard (M0,2,6) schedules in relevant comparator studies. Comparator studies include Olsson et al 2007, Dobson et al 2013, Ferris et al 2017, and Ruiz-Sternberg et al 2018.

4vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

4vHPV Delivered at (M0,12, 24) Demonstrates Comparable Immune Response Compared to Standard Schedule

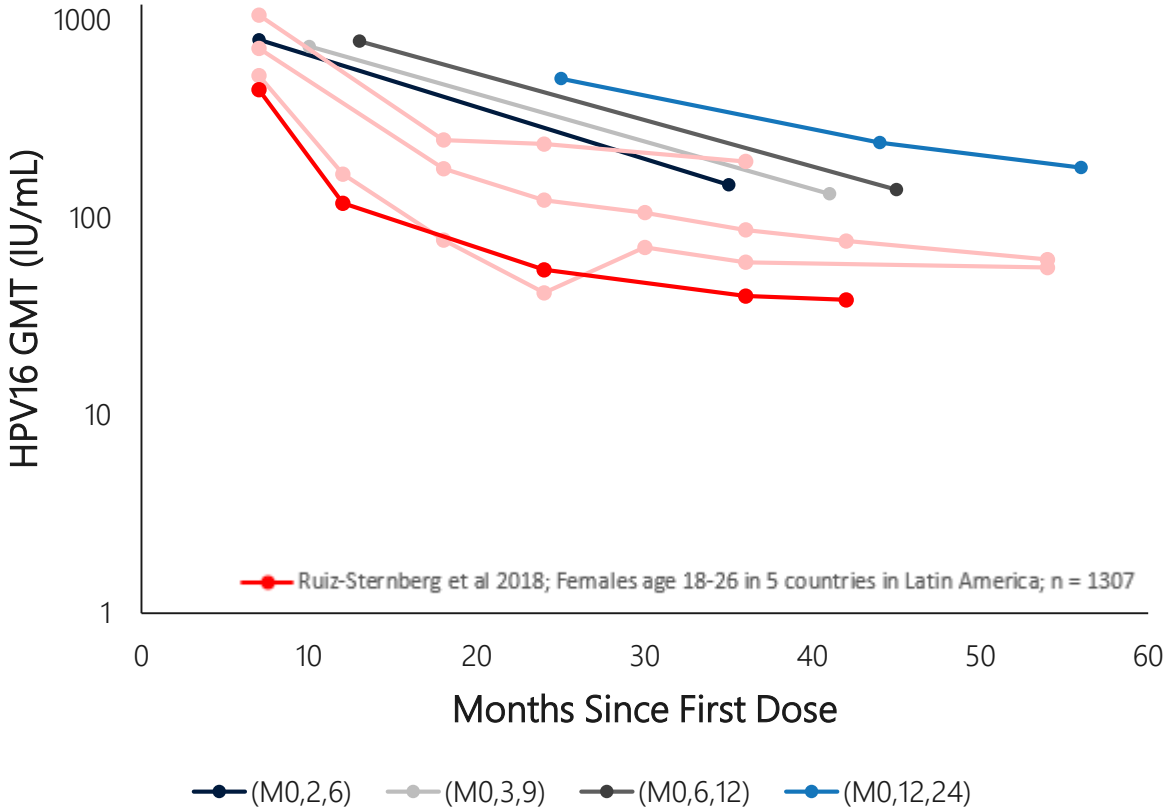


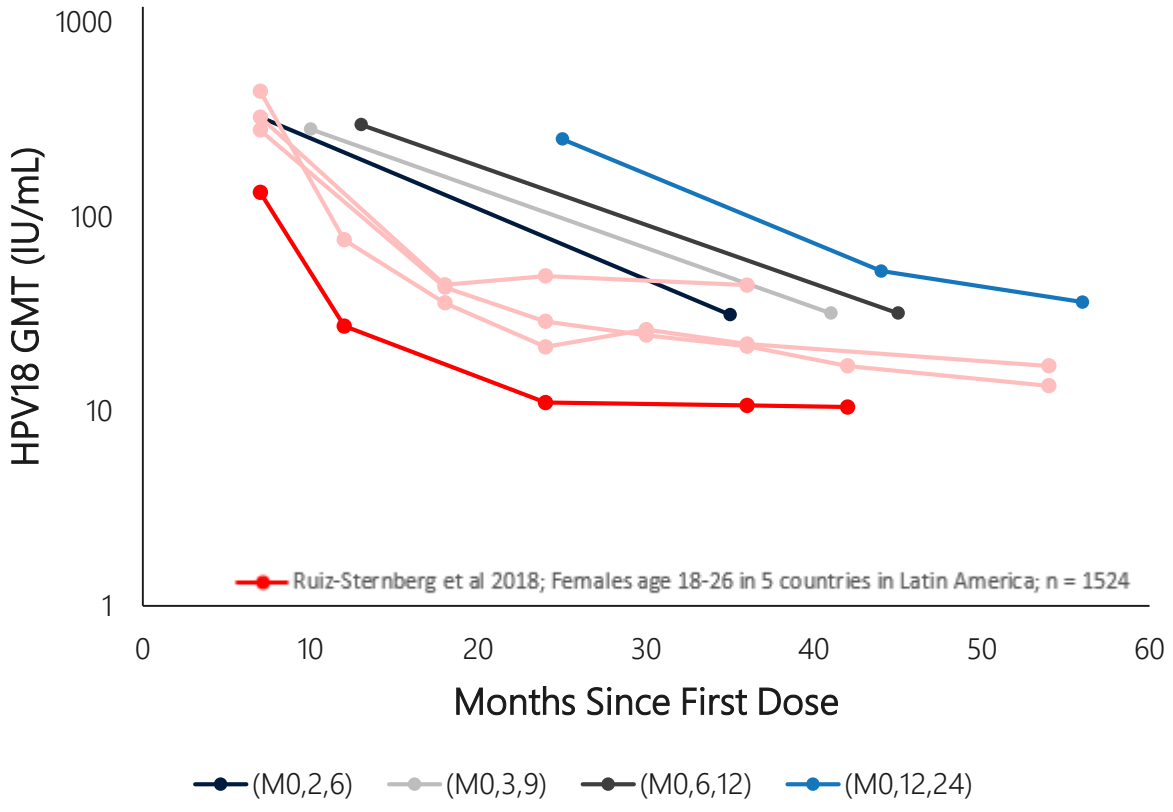


1. Graphs present GMT over time in Neuzil et al 2013 compared to GMTs from standard (M0,2,6) schedules in relevant comparator studies. Comparator studies include Olsson et al 2007, Dobson et al 2013, Ferris et al 2017, and Ruiz-Sternberg et al 2018.

4vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

4vHPV Delivered at (M0,12, 24) Demonstrates Comparable Immune Response Compared to Standard Schedule

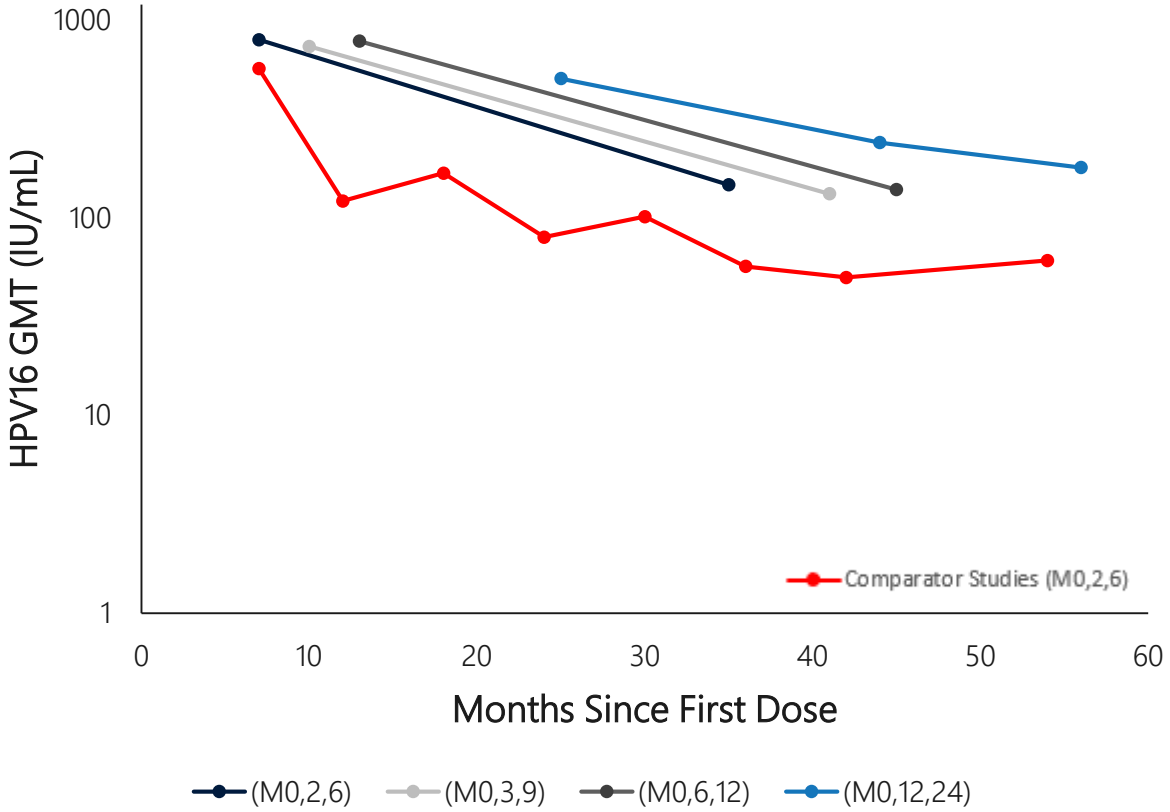


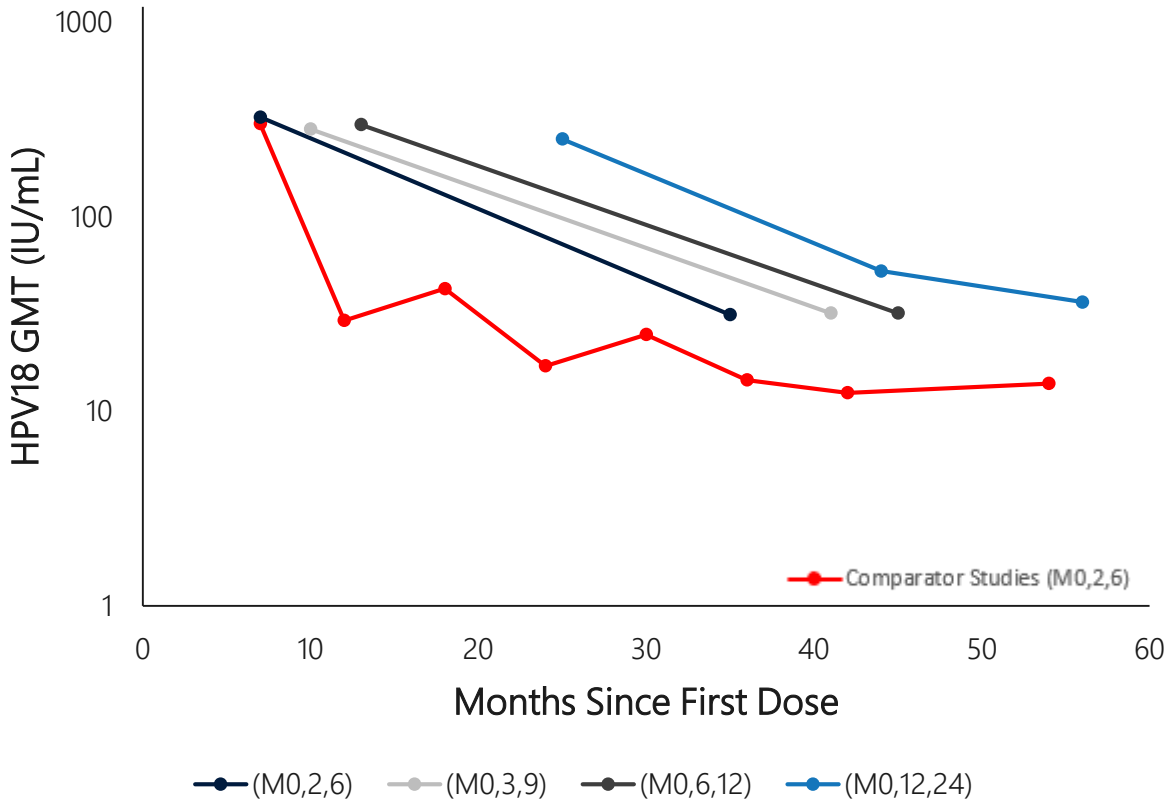


1. Graphs present GMT over time in Neuzil et al 2013 compared to GMTs from standard (M0,2,6) schedules in relevant comparator studies. Comparator studies include Olsson et al 2007, Dobson et al 2013, Ferris et al 2017, and Ruiz-Sternberg et al 2018.

4vHPV EXTENDED INTERVAL IMMUNOGENICITY COMPARISON

4vHPV Delivered at (M0,12, 24) Demonstrates Comparable Immune Response Compared to Standard Schedule





1. Graphs present GMT over time in Neuzil et al 2013 compared to aggregated GMTs from standard (M0,2,6) schedules in relevant comparator studies. Comparator studies include Olsson et al 2007, Dobson et al 2013, Ferris et al 2017, and Ruiz-Sternberg et al 2018.

COMPARATOR STUDIES: REFERENCES

START CENTER

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