Schedules and strategies for HPV immunization: Burden of HPV-related diseases and vaccine clinical data

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On behalf of the Ad-hoc Expert Consultation of August 2016
SAGE meeting, 18–20 October 2016

Content

- Burden of HPV-diseases
  - Cervical and non-cervical cancers and relative contribution of HPV types
  - Anogenital warts (AGW)
- Data from vaccine clinical trials
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HPV-related disease burden

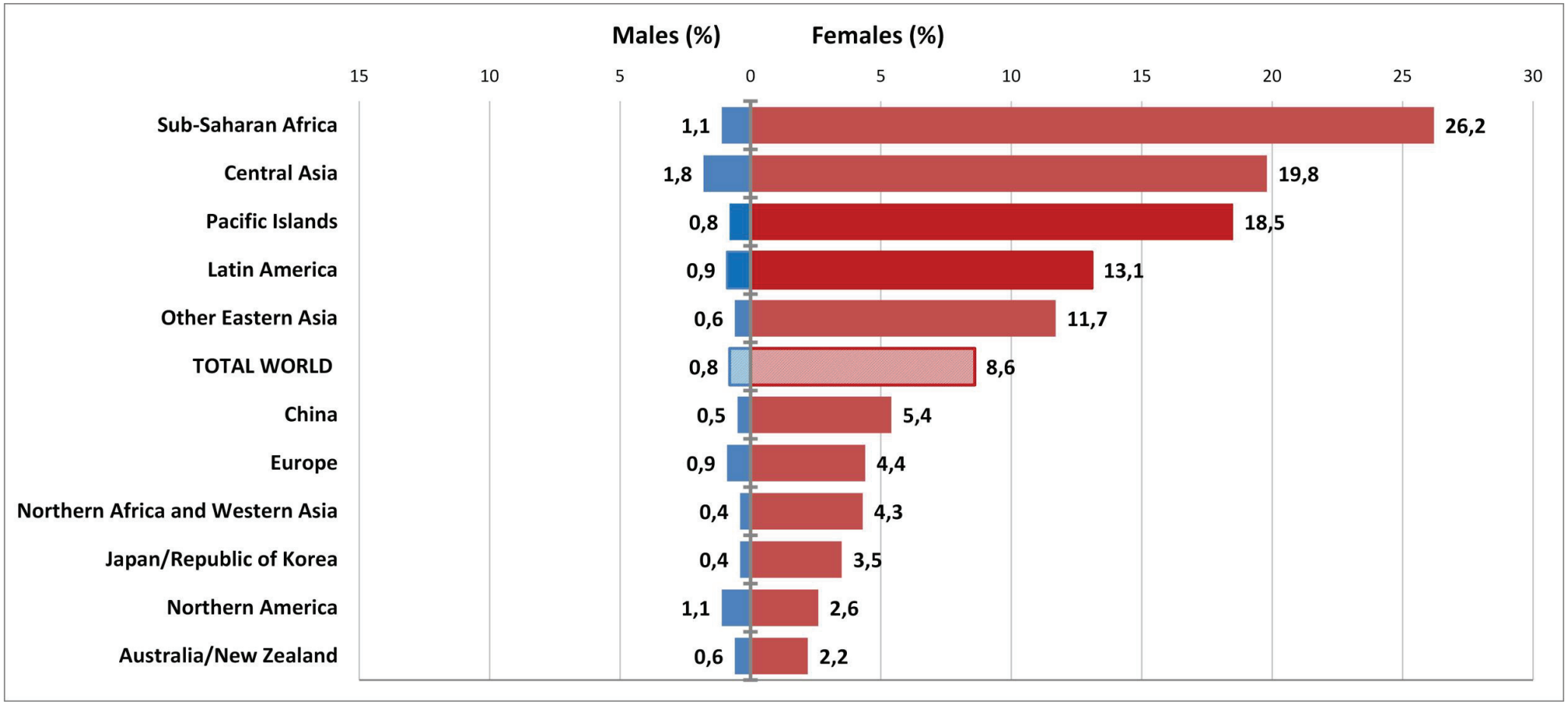
Estimated cancer cases attributable to HPV, by anatomical site—World, 2012

Anatomical cancer sites	Total incident cases	Total incident cases attributable to HPV	AF	By sex	
				Females	Males
Cervix uteri	530,000	530,000	100.0%	530,000	0
Vulva	34,000	8,500	24.9%	8,500	0
Vagina	15,000	12,000	78.0%	12,000	0
Anus	40,000	35,000	88.0%	18,000	17,000
Penis	26,000	13,000	51.0%	0	13,000
Oropharynx	96,000	29,000	30.8%	5,500	24,000
Oral cavity	200,000	4,900	2.5%	1,700	3,200
Larynx	160,000	3,800	2.4%	450	3,300
Other pharynx	78,000	0	0.0%	-	-
Total	1,200,000	630,000	54.0	570,000	61,000

84%

Ferlay et al, 2013; Plummer et al, 2016

Estimated cancer cases attributable to HPV, by regions—World, 2012



Ferlay et al, 2013; Plummer et al, 2016

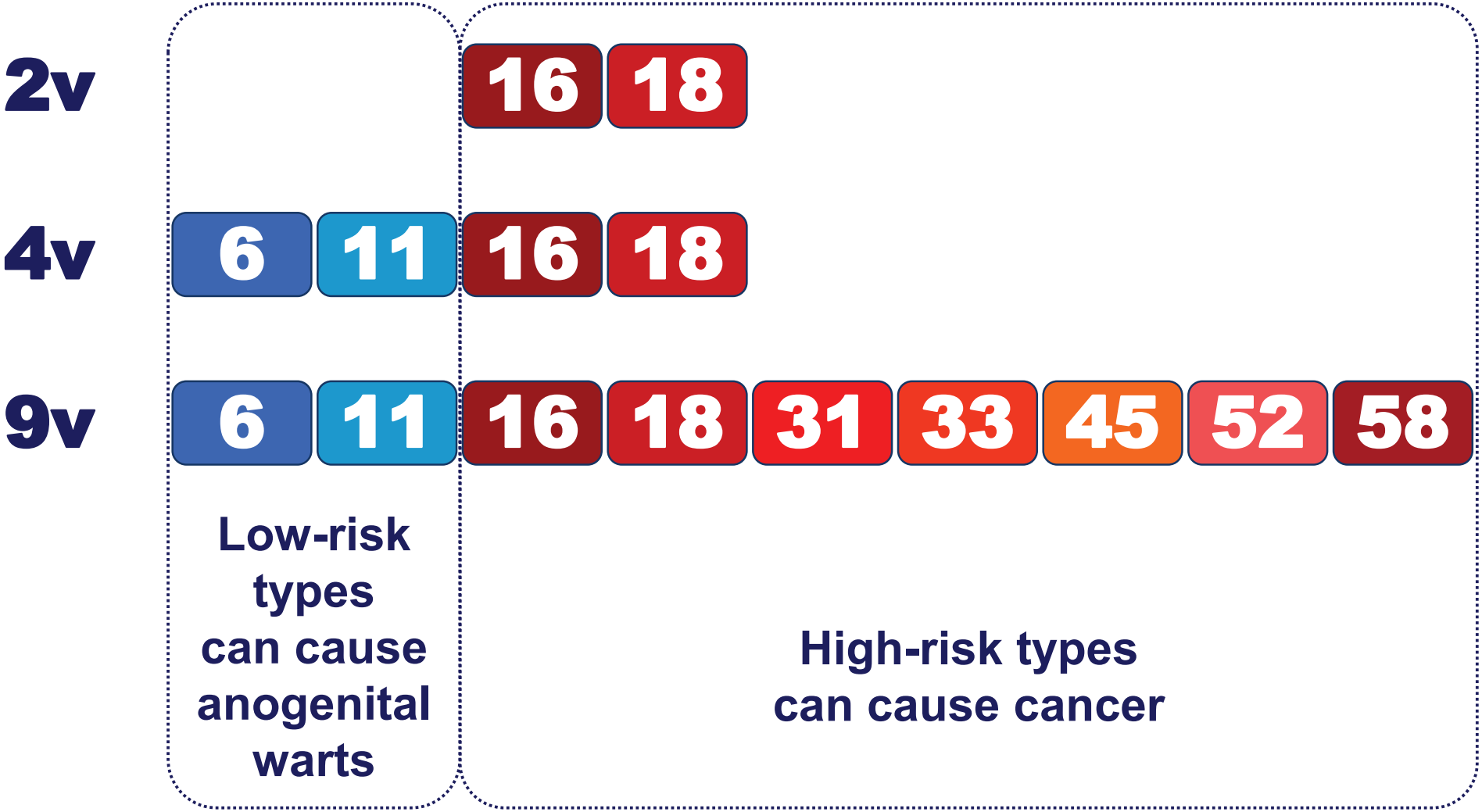
International Agency for Research on Cancer
World Health Organization

Estimated cancer cases attributable to HPV, by country income and vaccine introduction—World, 2012

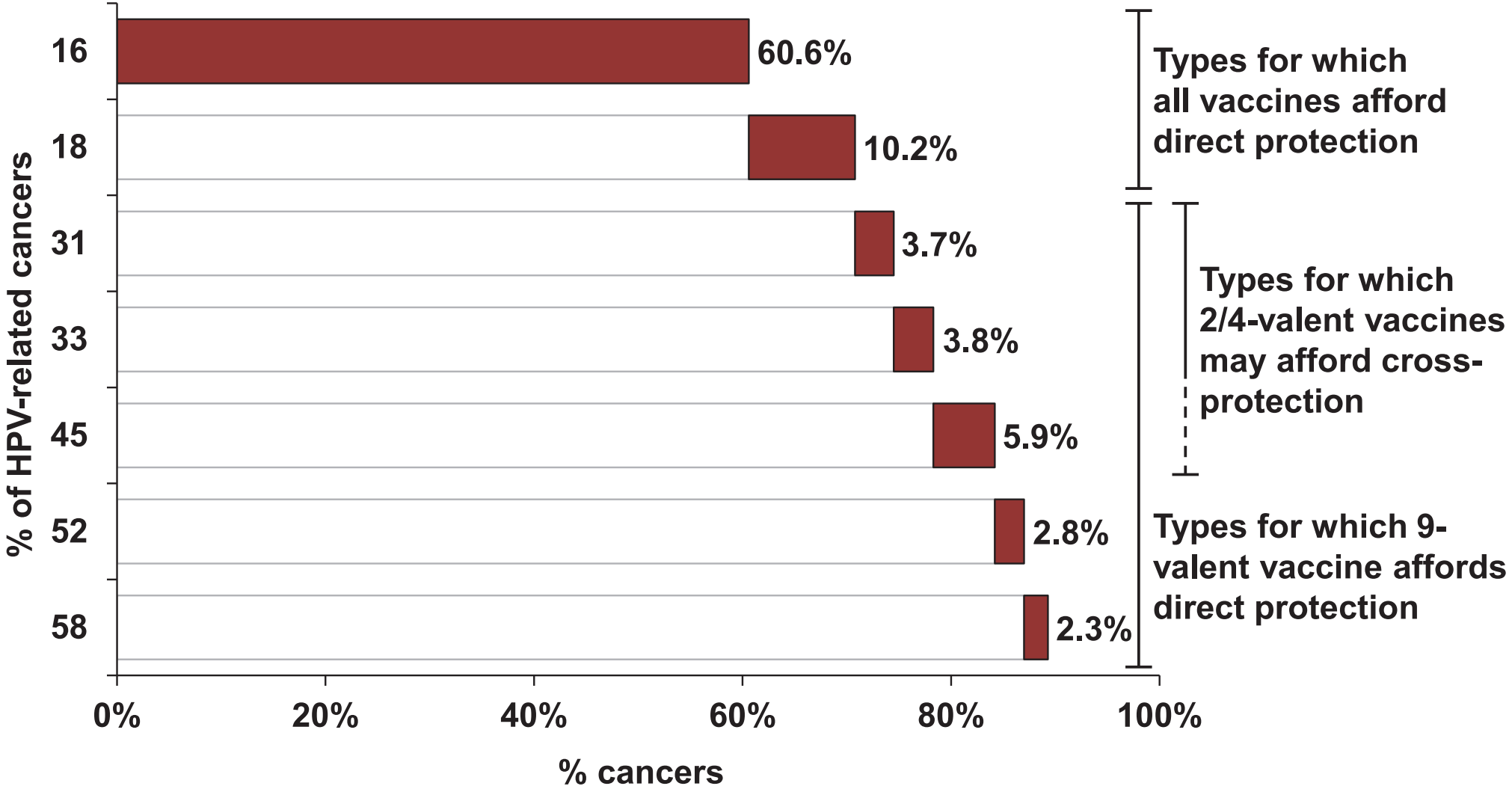
WB country income classification	Cervical cancer cases		
	Total	In countries that have introduced the HPV vaccine by 6/2016	In countries that have NOT introduced the HPV vaccine by 6/2016
- Low	59,804	5,281	54,523
- Lower middle	231,462	1,340	230,122
- Upper middle	169,448	74,329	95,119
- High	59,698	50,683	9,015
Total	525,368	136,589	388,779

Ferlay et al, 2013; World Bank Group, 2016; GAVI, 2016; WHO/IVB, 2016

HPV types directly targeted by vaccines



Relative contribution of different viral types to cervical cancer—World, 2012



Serrano et al, 2015

Relative contribution of selected high-risk HPV types to cervical and non-cervical HPV-related cancers—World, 2012

Anatomical cancer site	Cancers attributable to HPV	Estimated number of cancers attributable to (% [by row])		
		HPV 16/18 [A]	HPV 16/18/ 31/33/45/52/58 [B]	Difference [B-A]
Cervix uteri	530,000 (100%)	370,000 (71%)	470,000 (90%)	100,000 (19%)
All other sites	110,000 (100%)	84,800 (80%)	95,300 (90%)	10,500 (10%)
Total	640,000 (100%)	454,800 (71%)	565,300 (90%)	110,500 (17%)

Alemany et al, 2016; Castellsagué et al, 2016; Plummer et al, 2016; Serrano et al, 2015

Burden of anogenital warts

(Per 10,000 persons)	Both sexes	Men	Women
Incidence			
- HIV-negative persons of all ages	9–79	8–56	8–10
- HIV-negative persons aged ≤30 Years	23–79	13–56	32–103
- HIV-positive persons	139	N/A	N/A
Prevalence			
- All settings and ages	2–1,700	1–1,370	2–1,000
- High detection and prevalence settings omitted	2–110	1–130	2–90
- HIV-positive persons	160–1,700	730–3,100	280–370

Buckley et al, 2016

Considerations on AGW burden

- Higher incidence/prevalence for studies that included data from settings (overall, very low quality of evidence) where:
  - AGW detection is more likely (e.g. settings where genital examinations are routine), and/or
  - attending population at greater risk (e.g. sexually transmitted infection clinics, high HIV prevalence)
- Impact on quality of life is difficult to relate to cancer burden
  - In 14 studies, main impact was anxiety and depression
  - Only 1 study compared health status in people with AGW and with cancerous or non-cancerous HPV-related disease, with cancerous causing most marked reduction in health status

Buckley et al, 2016

Data from vaccine clinical trials

Formulation of licensed HPV vaccines

Characteristic	Bivalent 2vHPV	Quadrivalent 4vHPV	9-valent 9vHPV
Trade name and manufacturer	Cervarix™, GSK	Gardasil™, Merck	Gardasil9™, Merck
Virus-like particle types (VLP)	16 18	6 11 16 18	6 11 16 18 31 33 45 52 58
L1 protein dose	20/20 µg	20/40/40/20 µg	30/40/60/40 µg 20/20/20/20/20 µg
System for VLP L1 expression	*Trichoplusia ni* (Hi-5) insect cell line infected with L1 recombinant baculovirus	*Saccharomyces cerevisiae* (bread yeast) expressing L1	Same as 4v vaccine
Adjuvant	ASO4 (500 µg aluminium hydroxide, 50 µg 3-O-deacylated-4'-monophosphoryl lipid A)	AAHS (225 µg amorphous aluminium hydroxyphosphate sulfate)	500 µg AAHS

Adapted from Herrero et al, 2015, & Stanley, 2016.

Efficacy of 2/4-valent HPV vaccines against cervical endpoints associated with HPV 16/18

Endpoint	Vaccine efficacy (95% CI)	
	2vHPV [a]	4vHPV [b]
CIN2+	95% (88–98%)	98% (93–100%)
CIN3+	92% (67–99%)	97% (89–100%)
AIS	100% (-9–100%)	100% (31–100%)

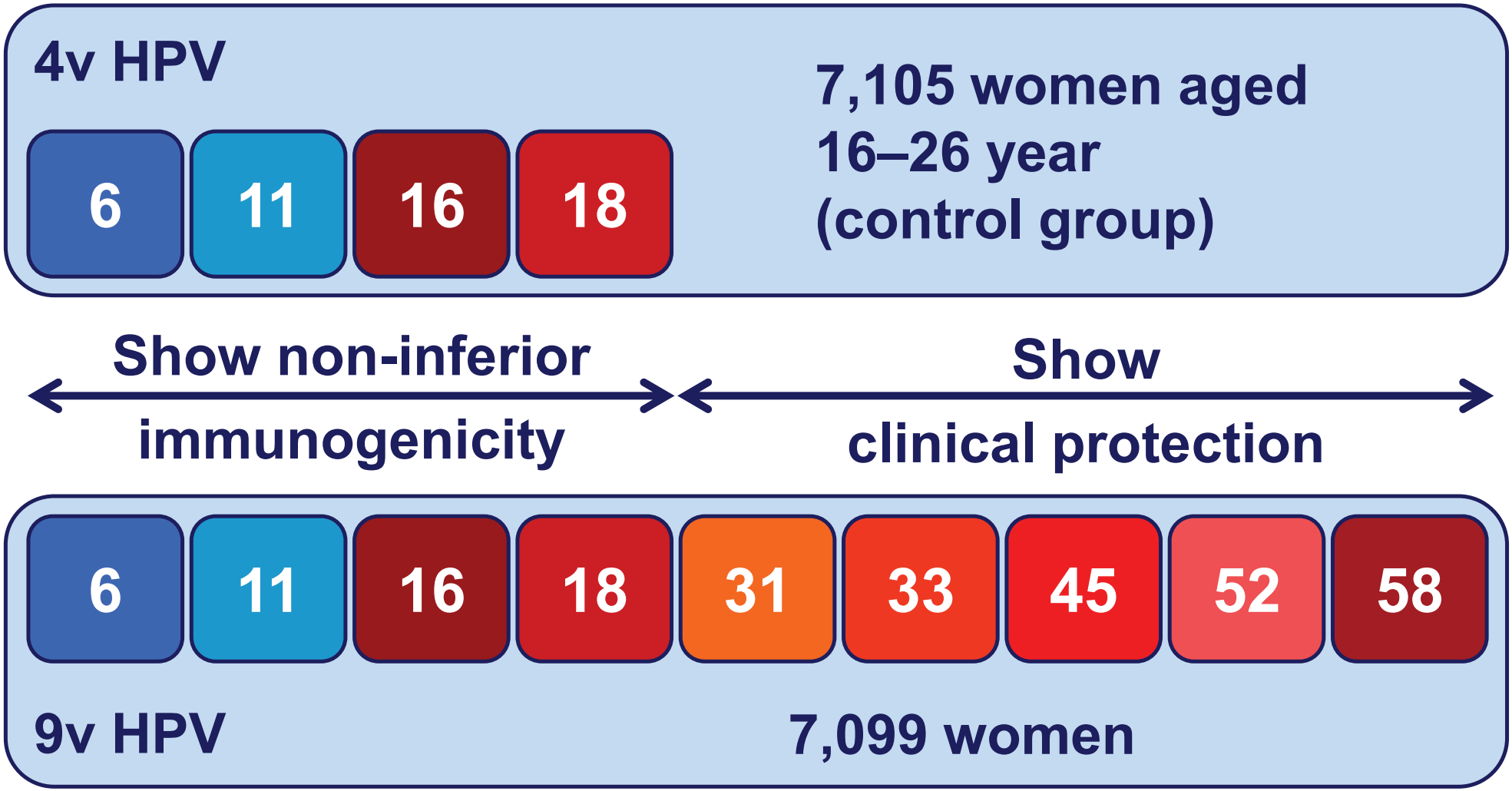
* Per-protocol analysis.

Note: Only for illustrative purpose because trials are not directly comparable.

a) Lehtinen et al, 2012

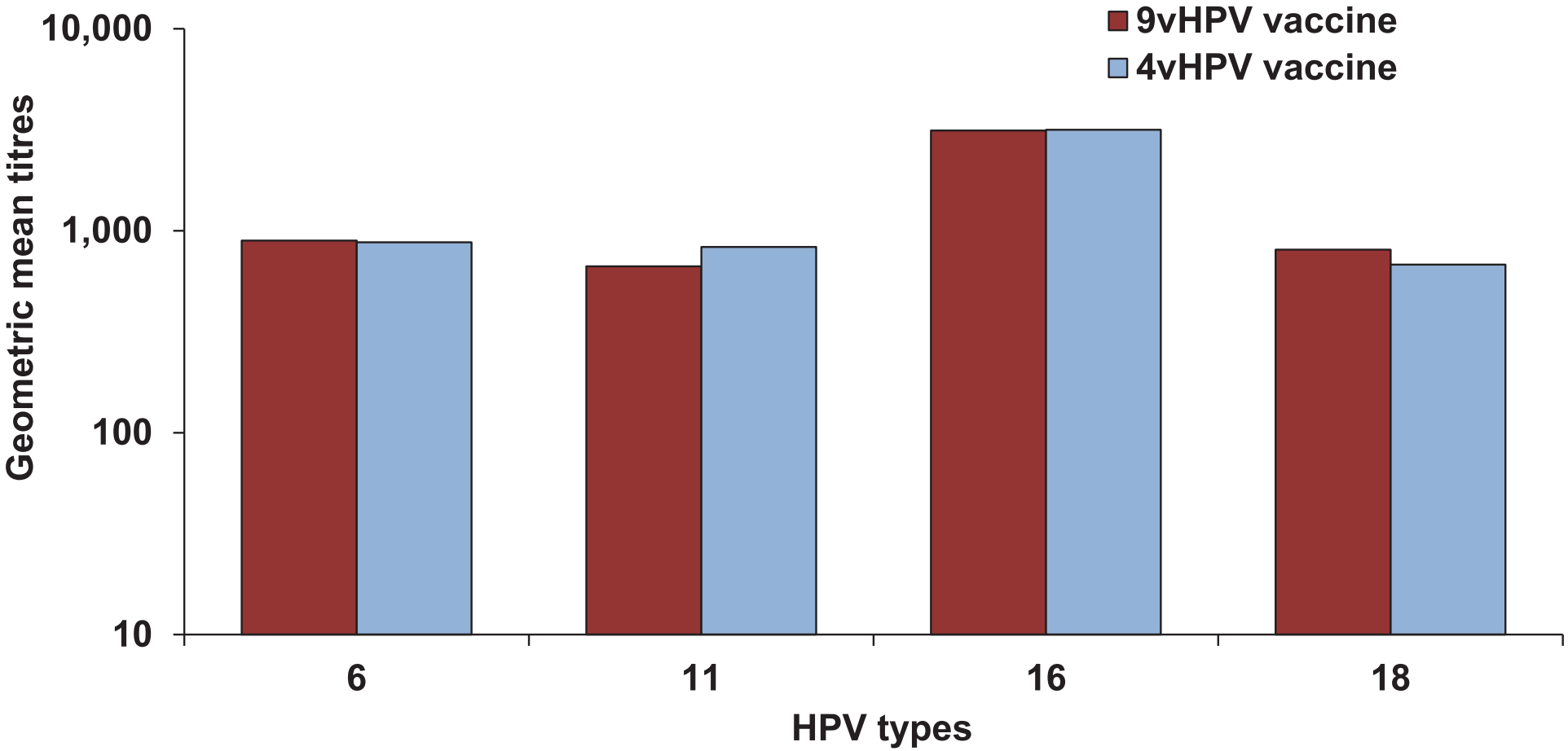
b) Kjaer et al, 2009 (efficacy against HPV 6/11/16/18)

Clinical trial of 9-valent HPV vaccine: Primary objectives



Luxembourg et al, 2015; Joura et al, 2015

Immunogenicity of 4/9-valent HPV vaccines in women aged 16–26 years



GMT ratio 9v/4v (95% CI)	1.02 (0.99–1.06)	0.80 (0.77–0.83)	0.99 (0.96–1.03)	1.19 (1.14–1.23)

Per-protocol immunogenicity population (9v HPV vaccine, n=6,792; 4v HPV vaccine n=6,795)
Joura et al, 2015

Efficacy of 9-valent HPV vaccines against cervical endpoints associated with HPV 31/33/45/52/58

Endpoint	Vaccine efficacy (95% CI) 9vHPV
CIN2/3+	96% (80–100%)
High-grade cervical, vulvar, and vaginal disease	97% (81–100%)

* Per-protocol analysis.

Joura et al, 2015

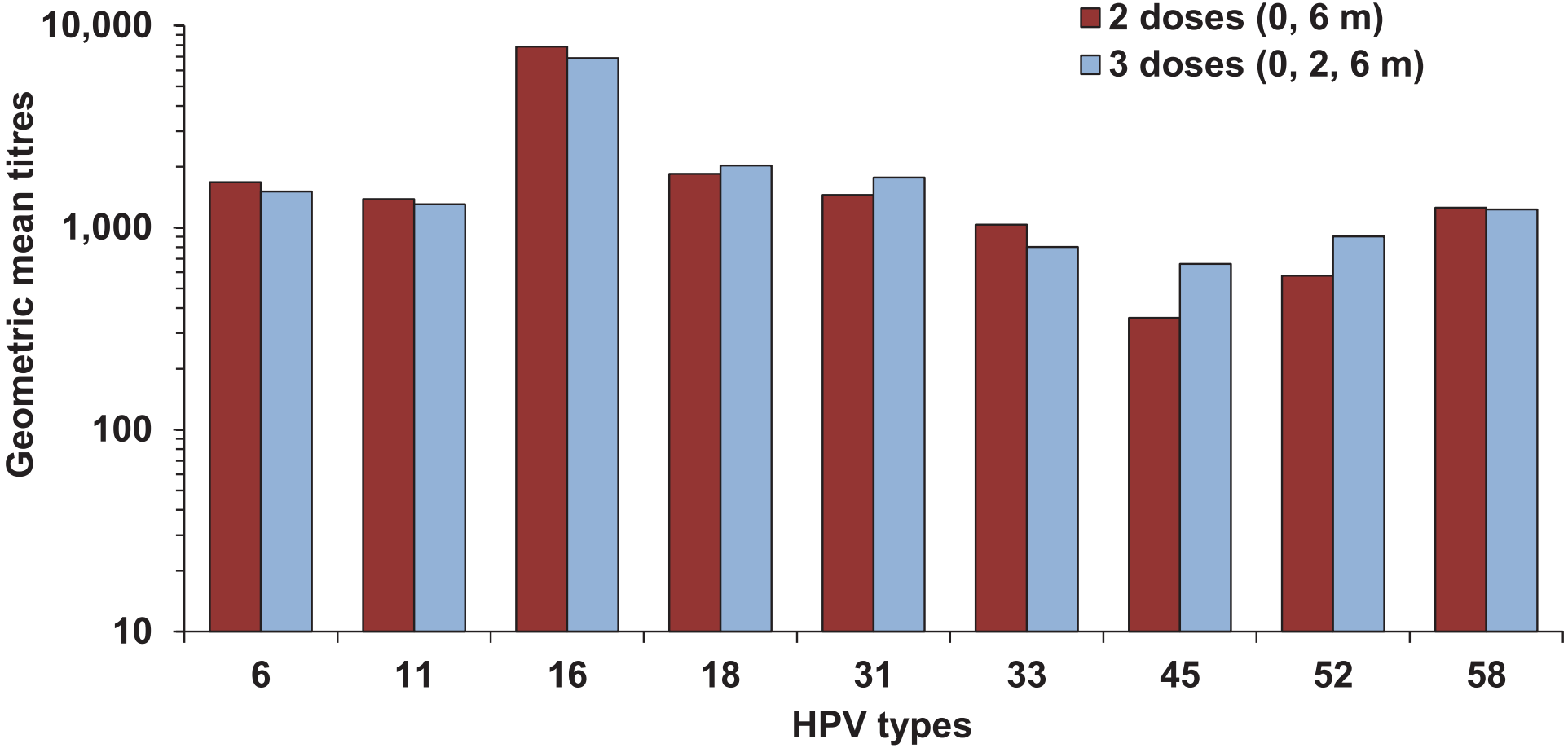
Available minimum follow-up period for immunogenicity and selected cervical endpoints of HPV vaccine clinical trials among young women

Endpoints related to vaccine HPV types	Available minimum follow-up period		
	2vHPV vaccine	4vHPV vaccine	9vHPV vaccine
Immunogenicity	9.4 years	9.9 years	5 years
≥6-month persistent cervical infection	9.4 years	9.9 years	5.5 years
Cervical intraepithelial neoplasia grade 1+	9.4 years	9.9 years	5.5 years

Note: Follow-up methodology varies by vaccine.

2v: Naud et al, 2014; Skinner et al, 2016 // 4v: Kjaer et al, 2015; Das et al, 2016 //
9v: Joura, 2016; McKeage & Lyseng-Williamson, 2016;

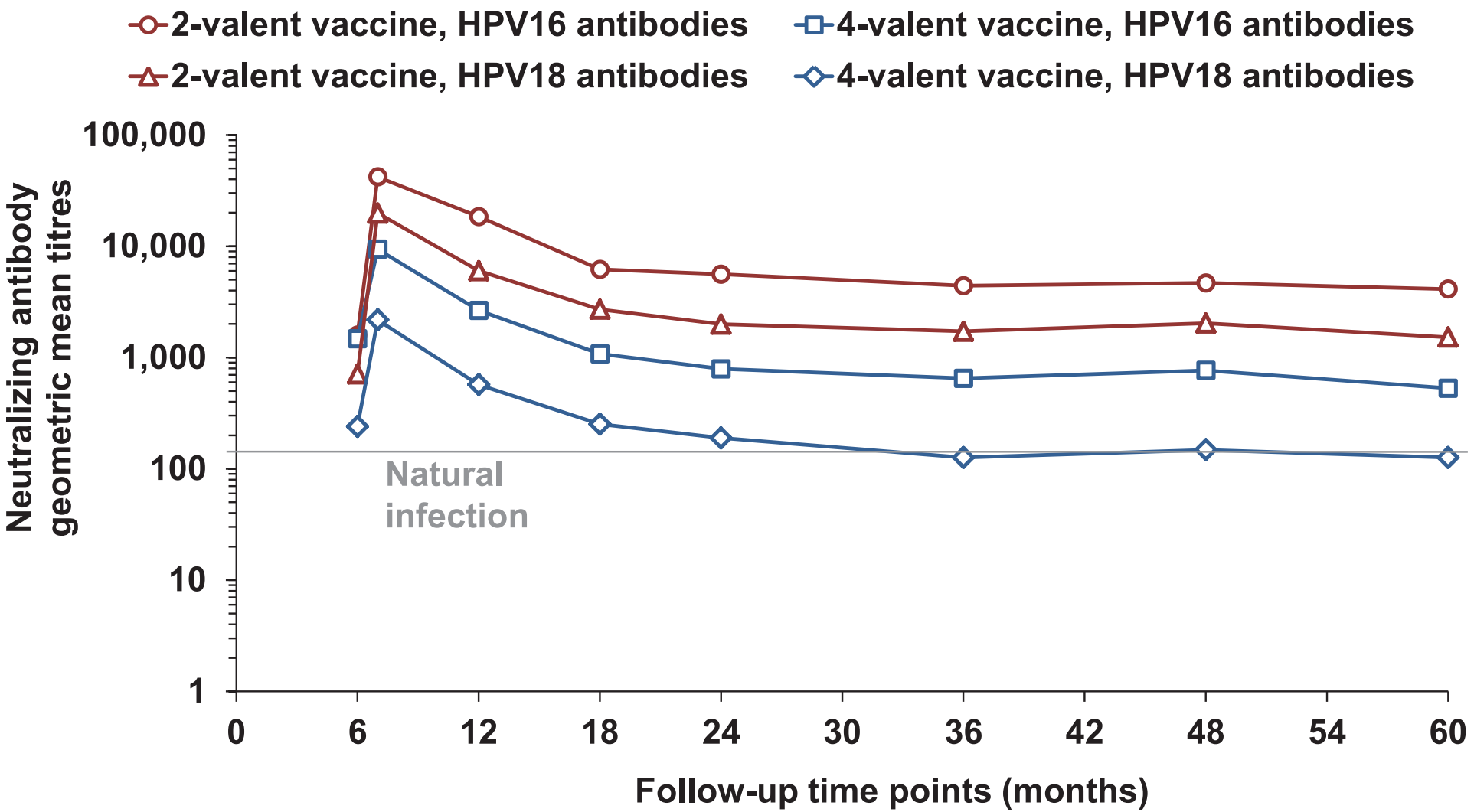
Immunogenicity of 2- and 3-doses of 9-valent HPV vaccine in girls aged 9–14 years



GMT ratio 2/3d	1.11	1.06	1.14	0.91	0.82	1.29	0.54	0.64	1.02
(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)

Luxembourg A, US ACIP meeting of 24 February 2016

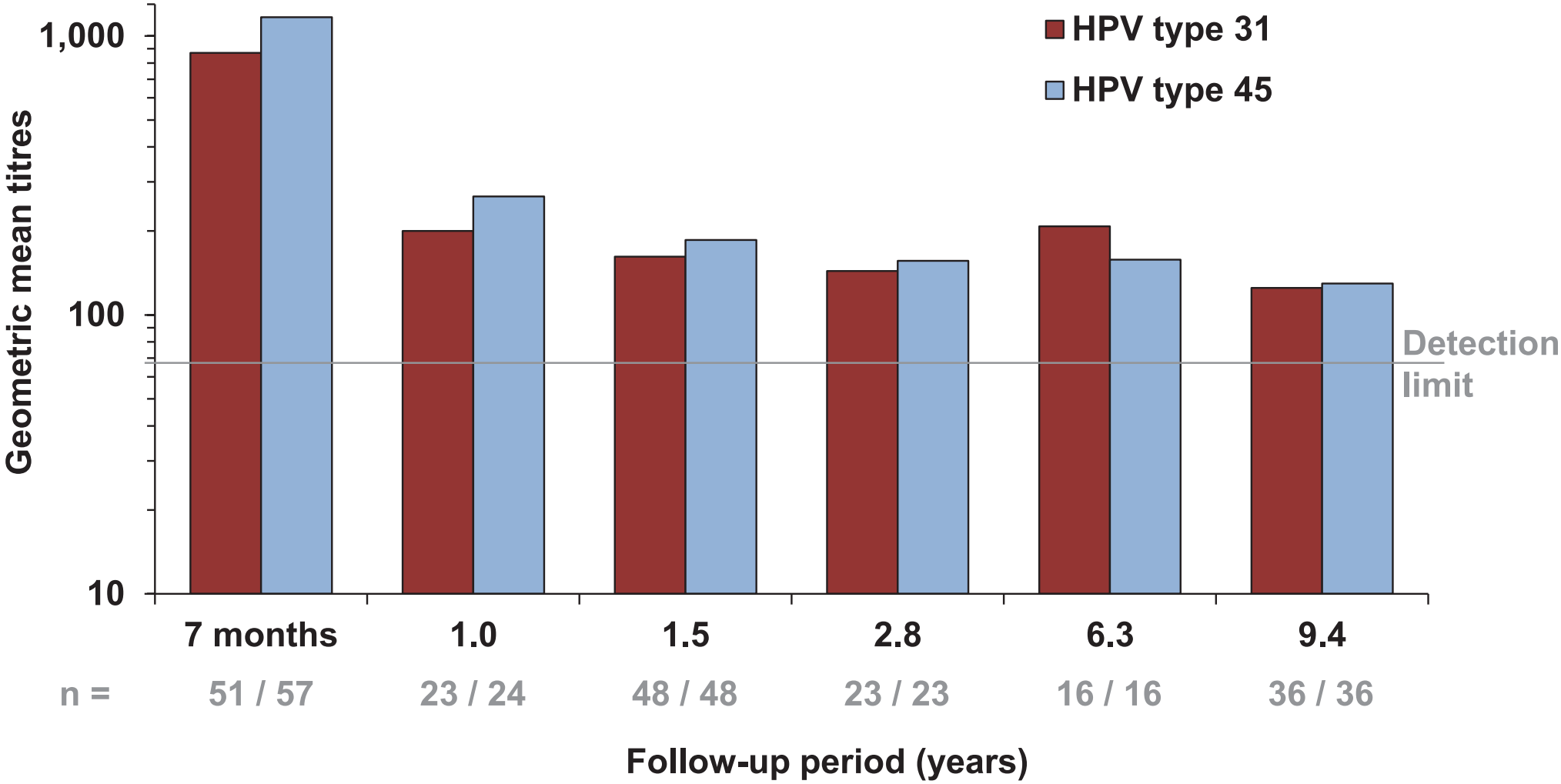
Comparative immunogenicity of 2/4-valent HPV vaccines for types 16/18 in women aged 18–26 years*



* Seronegative and DNA-negative for analyzed HPV types prior to vaccination, per-protocol analysis

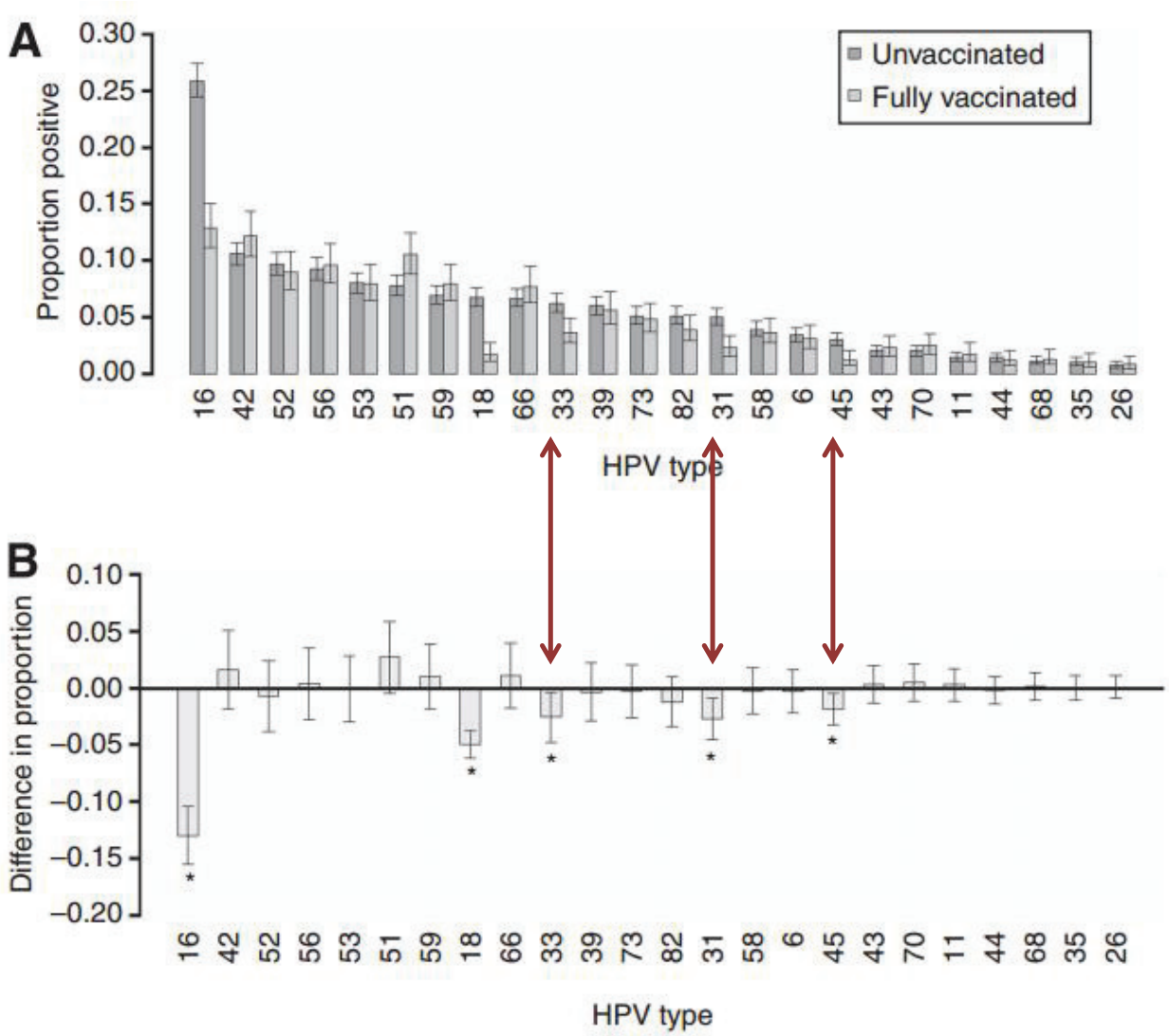
Einstein et al, 2014

Immunogenicity of 2-valent HPV vaccine for non-vaccine HPV types 31/45 in women aged 15–25 years



Moscicki et al, 2015

Difference in HPV infection by types among vaccinated and unvaccinated women attending cervical cancer screening—Scotland, 2009–2012*



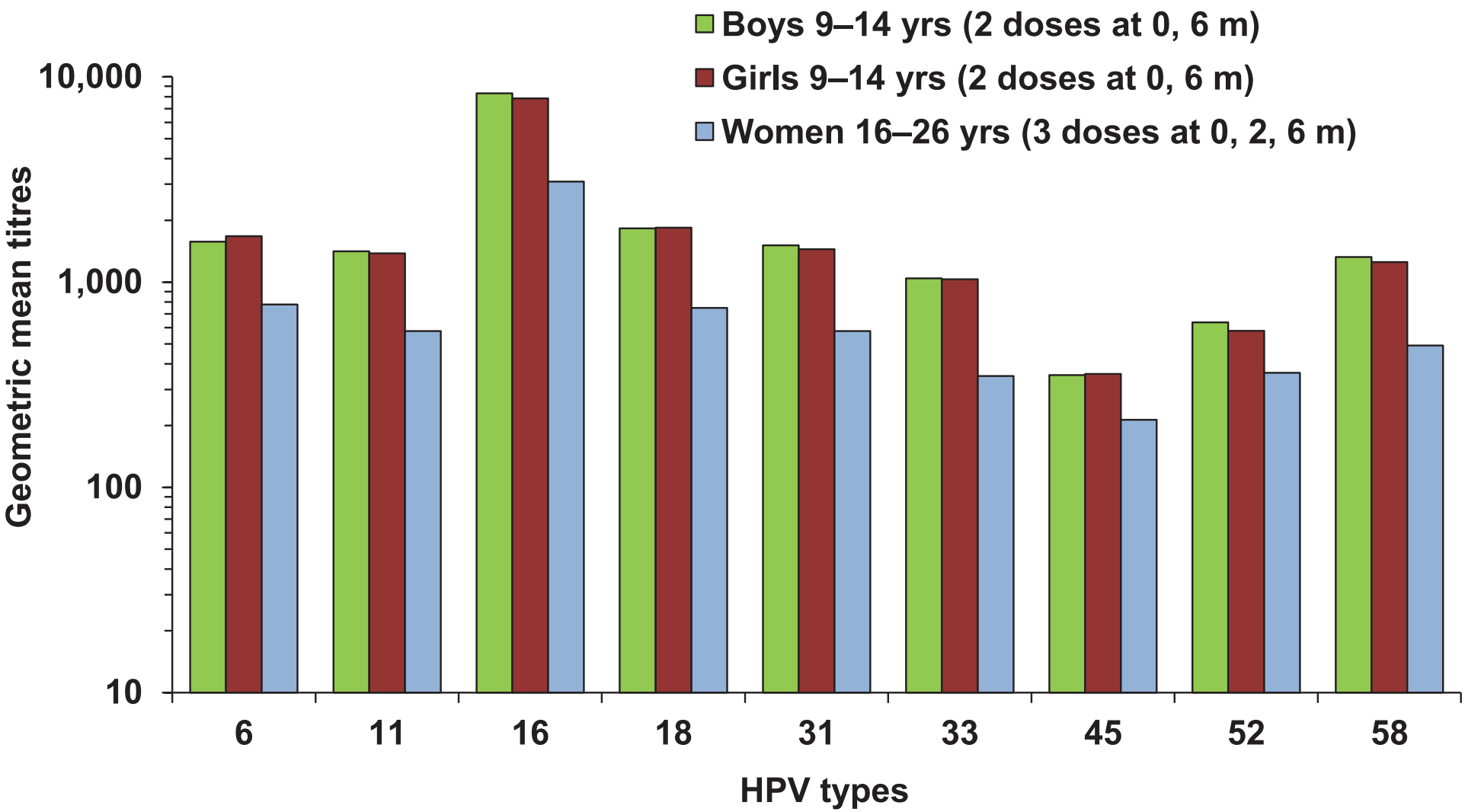
* Bivalent vaccine was prevalently used in Scotland during this period.

Kavanagh et al, 2015

Cross-protective efficacy of 2/4-valent HPV vaccines

- Systematic review and meta-analysis of 3 and 2 trials of the bi- and quadrivalent vaccines, respectively (Malagón et al, 2012)
  - Efficacy against infections and lesions associated with HPV 31/33/45 was usually higher for 2- than 4-valent vaccine
  - Differences were not all significant and might be attributable to differences in trial design
  - Efficacy against persistent infections with HPV 31/45 seemed to decrease in a trial of 2-valent vaccine with increased follow-up
- In the near future, post-introduction impact evaluations are expected to provide additional long-term data, including for endpoints such CIN3

Immunogenicity of 9-valent HPV vaccine in boys and girls aged 9–14 years vs. women aged 16–26 years



Luxembourg A, US ACIP meeting of 24 February 2016

Final considerations

- Overwhelmingly high cervical cancer burden (84% of all HPV-related cancers)
  - Mainly HPV 16/18, but also others types
  - All three vaccines highly efficacious
  - More data on cross-protection of 2/4v vaccines expected from post-introduction impact evaluations
- For non-cervical cancers, lower burden mainly by HPV16/18 and other types contained in vaccine much less relevant
- Still, significant uncertainties on AGW burden

Thank you