Evidence of 1 vs. 2 vs. 3 Doses

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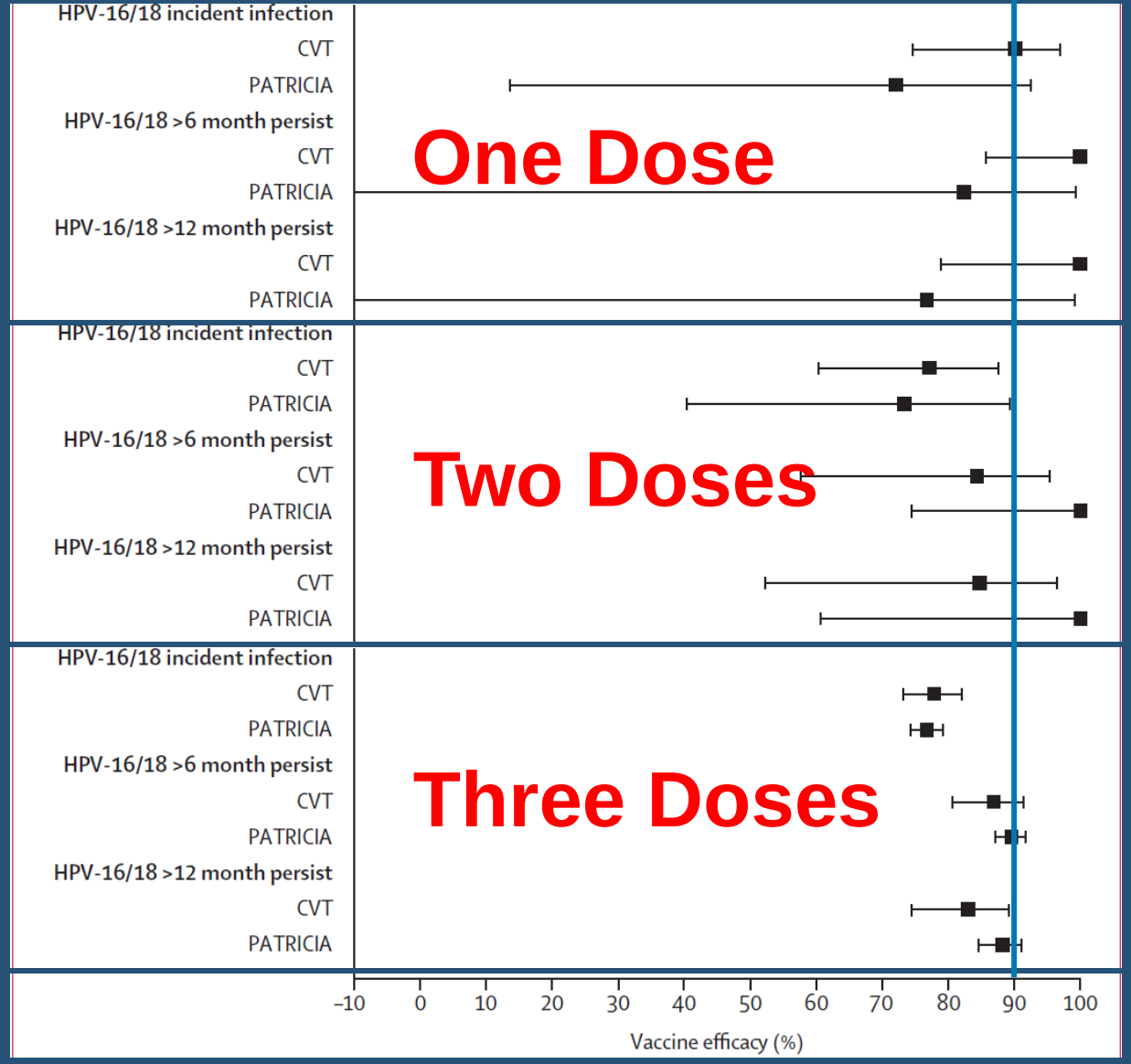
Disclosures

- I have received cervical screening tests and diagnostics for research at a reduced or no cost from Roche, Becton Dickinson, Cepheid, and Arbor Vita Corporation.

	Gardasil (qHPV)	Cervarix (bHPV)	Gardasil-9 (nHPV)
Manufacturer	Merck	GSK	Merck
Types and Virus-Like Particle (VLP) Dosing	40 µg HPV16; 20 mg HPV18; 20 µg HPV6; 40 µg HPV11	20 µg HPV16; 20 µg HPV18	60 µg HPV16; 40 µg HPV18; 30 µg HPV6; 40 µg HPV11; 20 µg HPV31; 20 µg HPV33; 20 µg HPV45; 20 µg HPV52; 20 µg HPV58
Recombinant Protein Expression System	*Saccharomyces cerevisiae* (bread yeast)	baculovirus (insect) cell	*Saccharomyces cerevisiae* (bread yeast)
Recommended Schedule	0, 2, and 6 months	0, 1, and 6 months	0, 2, and 6 months
Adjuvant	225 µg amorphous aluminum hydroxyphosphate sulfate	500 µg aluminum hydroxide and 50 µg 3-O-desacyl-4' monophosphoryl lipid A (MPL), a detoxified derivative of the lipopolysaccharide (LPS) of the gram-negative bacterium *Salmonella minnesota* R595 strain	500 µg amorphous aluminum hydroxyphosphate sulfate
Projected Prevention Benefits	70% Cervical Cancer; 90% Warts	70-80% Cervical Cancer	90% Cervical Cancer; 90% Warts

Study/Study Location: CVT (Costa Rica) and PATRICIA (Multiple)
Vaccine: Cervarix
Baseline Age: 18-25 and 15-25 years
Design for 1 vs. 2 vs. 3 Doses: Prospective (Observational)
Outcome: Incident and incident persist HPV infection
Observation Time: Median ~ 4 Years



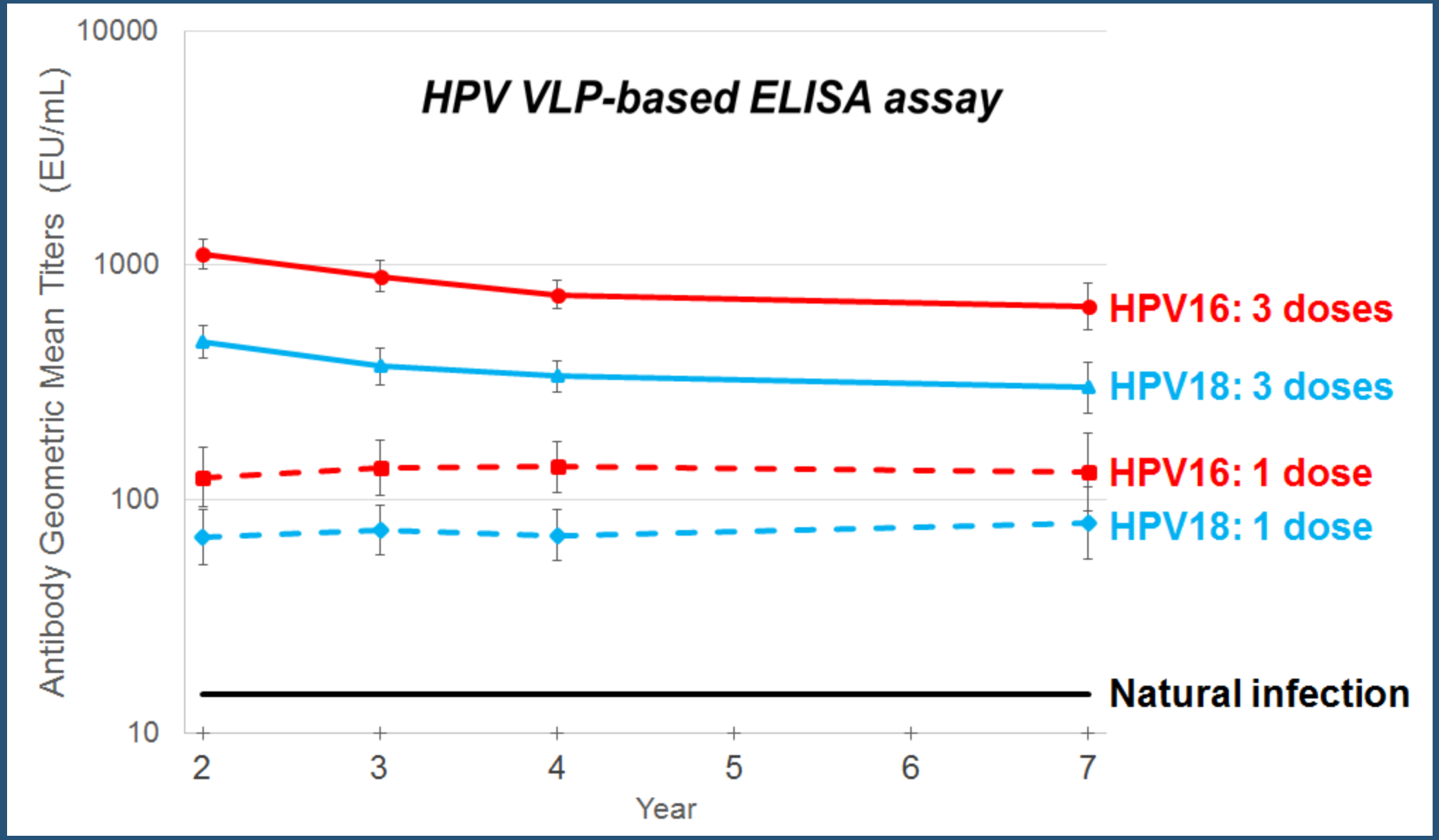
Kreimer *et al.*, *Lancet*, 2015

Study/Study Location: Costa Rica Vaccine Trial
Vaccine: Cervarix
Baseline Age: 18-25 Years
Design for 1 vs. 2 vs. 3 Doses: Observational
Outcome: Incident Infection
Observation Time: Median of 6.9 Years

	3 Doses		2 Doses (0/6)			2 Doses (0/1)			1 Dose		
	Events/ Women	%	Events/ Women	%	P*	Events/ Women	%	P*	Events/ Women	%	P*
HPV16 and 18	88/2036	4.3	3/78	3.8	1.0	7/192	3.6	0.85	2/133	1.5	0.17
HPV31, 33, and 45	164/2043	8.0	7/79	8.9	0.68	29/193	15.0	0.002	11/133	8.2	0.87
Other Carcinogenic**	891/2043	43.6	35/79	44.3	0.91	89/193	46.1	0.54	53/134	39.6	0.37
Non-Carcinogenic	943/2043	46.2	42/79	53.2	0.25	111/193	57.5	0.003	59/134	44.0	0.66

* vs. 3 doses
**HPV35, 39, 51, 52, 56, 58, and 59

Safaeian *et al.*, *JNCI*, 2017


HPV VLP-based ELISA assay
Antibody Geometric Mean Titers (EU/mL)
10000
1000
100
10
2
3
4
5
6
7
Year
HPV16: 3 doses
HPV18: 3 doses
HPV16: 1 dose
HPV18: 1 dose
Natural infection

Study/Study Location: Scotland
Vaccine: Cervarix
Baseline Age: Variable

Design for 1 vs. 2 vs. 3 Doses:Observational
Outcome: Prevalent Infection
Observation Time: Variable (Age 20-21 Years)

	Number of doses	Number tested	HPV types 16 and 18		HPV types 31, 33, and 45		Other high-risk HPV types*	
			Number positive	Adjusted vaccine effectiveness† (95% CI)	Number positive	Adjusted vaccine effectiveness† (95% CI)	Number positive	Adjusted vaccine effectiveness† (95% CI)
12–13 years	3 doses	971	39	89·1% (85·1 to 92·3)	20	85·1% (77·3 to 90·9)	296	7·8% (–7·3 to 20·9)
14 years	3 doses	269	12	87·7% (78·9 to 93·5)	6	83·6% (66·2 to 93·6)	86	0·2% (–29·6 to 23·8)
15 years	3 doses	880	56	82·3% (76·8 to 86·7)	37	69·2% (57·2 to 78·5)	293	–4·8% (–22·3 to 10·3)
16 years	3 doses	1156	97	75·9% (70·2 to 80·8)	66	56·8% (44·0 to 67·1)	412	–17·1% (–34·3 to –2·0)
17 years	3 doses	422	59	58·1% (44·8 to 68·8)	24	57·9% (37·2 to 73·1)	141	–4·9% (–29·5 to 15·4)
≥18 years	3 doses	264	57	28·9% (4·5 to 47·8)	24	29·5% (–6·2 to 55·3)	75	16·9% (–9·0 to 37·2)
All ages‡ *	2 doses	391	76	39·0% (21·3 to 53·3)	32	40·3% (14·5 to 59·7)	146	–23·1% (–52·5 to 1·0)
All ages§ **	1 dose	223	50	27·6% (0·7 to 48)	30	–3·6% (–51·7 to 31·6)	81	–17·3% (–54·9 to 11·8)
All ages	Unvaccinated	4008	1116	..	504	..	1297	..

*28.1% are 18 years and older
**30.0% are 18 years and older

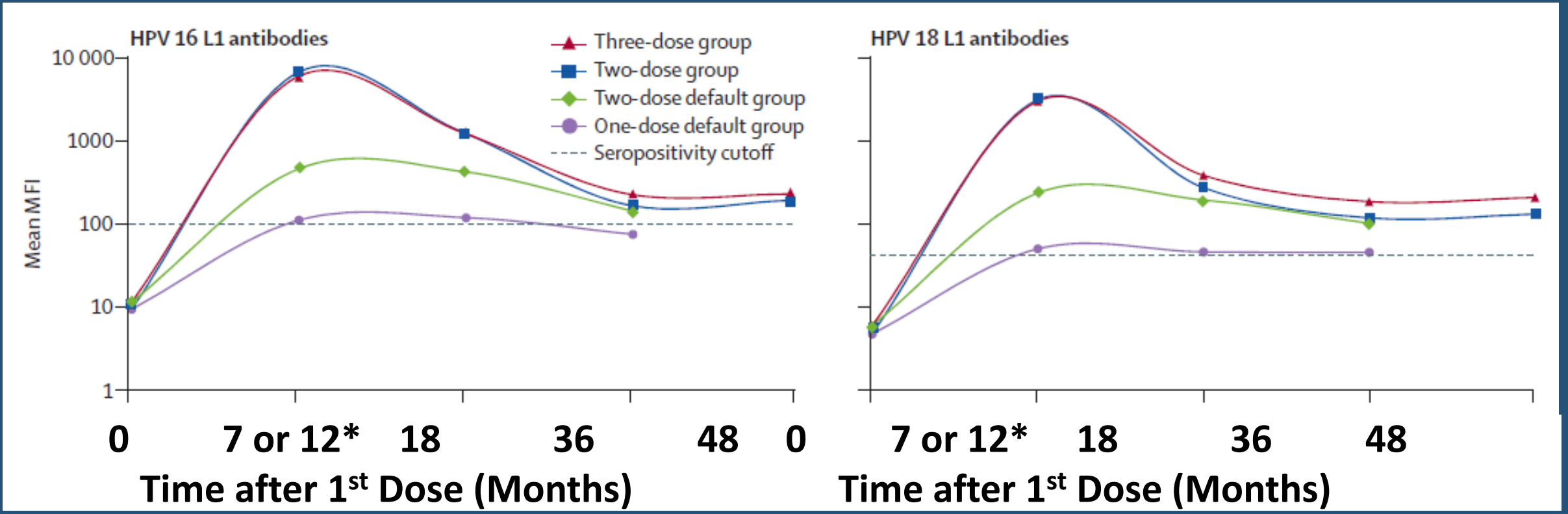
Kavanagh *et al*., *Lancet Infect Dis*, 2017

Study/Study Location: India
Vaccine: Gardasil
Baseline Age: 15-25 Years
Design for 1 vs. 2 vs. 3 Doses: RCT (3 vs. 2); Observational
Outcome: Incident Infection
Observation Time: Median of 4.7 Years

	3 Doses		2 Doses			2 Doses (Default)			1 Dose (Default)		
	Events/ Women	%	Events/ Women	%	P*	Events/ Women	%	P*	Events/ Women	%	P*
HPV16 and 18	2/536	0.4	4/526	0.8		9/717	1.3		10/870	1.1	
HPV31, 33, and 45	32/536	6.0	26/526	4.9		33/717	4.6		77/870	8.9	
Other HPV	74/536	13.8	48/526	9.1		68/717	9.5		118/870	13.6	

* vs. 3 doses

Sankaranarayanan *et al*., Lancet, 2016



*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

Sankaranarayanan *et al*., Lancet, 2016

Study/Study Location: Australia
Vaccine: Gardasil
Baseline Age: 11-27 Years
Design for 1 vs. 2 vs. 3 Doses: Case-Control Study
Outcome: CIN2+
Observation Time: Median ~ 3 Years

No of doses, by age in 2007	No (%) of controls	High grade cases		
		No (%)	Crude odds ratio† (95% CI)	Adjusted odds ratio‡ (95% CI)
11-14 years:				
0	619 (24.5)	4 (30.8)	reference	reference
1	171 (6.8)	3 (23.1)	2.72 (0.6 to 12.2)	2.54 (0.54 to 11.8)
2	325 (12.9)	0	-	-
3	1410 (55.8)	6 (46.2)	0.66 (0.19 to 2.34)	0.71 (0.19 to 2.66)
15-18 years:				
0	9918 (31.0)	101 (47.4)	reference	reference
1	2564 (8.0)	22 (10.3)	0.84 (0.53 to 1.34)	0.86 (0.54 to 1.37)
2	4195 (13.1)	31 (14.6)	0.73 (0.48 to 1.09)	0.77 (0.51 to 1.16)
3	15 367 (48.0)	59 (27.7)	0.38 (0.27 to 0.52)	0.43 (0.31 to 0.62)
19-22 years:				
0	20 896 (62.2)	306 (72.3)	reference	reference
1	4230 (12.6)	46 (10.9)	0.74 (0.54 to 1.01)	0.75 (0.55 to 1.02)
2	4254 (12.7)	42 (10.0)	0.67 (0.49 to 0.93)	0.68 (0.49 to 0.94)
3	4188 (12.5)	29 (6.9)	0.47 (0.32 to 0.69)	0.47 (0.32 to 0.70)

Crowe *et al.*, *BMJ*, 2014

A scientific evaluation of one or two doses of vaccine against HPV: ***the ESCUDDO study***

(Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano)

proyecto escuddo

Primary objectives

1. For each vaccine, evaluate the non-inferiority of 1 vs 2 doses in the prevention of new cervical HPV16/18 infections that persist 6+ months

2. For each vaccine, evaluate 1 dose of HPV vaccination compared to 0 vaccination doses (virologic endpoint)

Lowy DR et al, Lancet Oncol 2015

RCT

- Goal: assess non-inferiority of 1 to 2 doses of the vaccine
- Randomized into one of four arms:
  - 1 and 2 doses
  - GSK bivalent and Merck 9-valent HPV vaccines
- Girls only, aged 12 to 16 years
- N=5,000 per arm (20,000 total)
- Followed every six months for four years

Immunobridging studies to the 1DT

Goal: bridge finding from Costa Rica to other populations and VLP-based HPV vaccine formulations

- Tanzania
  - Outside collaborators: Debbie Watson-Jones, Charles Lacey
- Gambia
  - Outside collaborators: Ed Clarke, Margaret Stanley
- United States
  - Outside collaborators: Barbara Moscicki and Yi Zeng
- China (?)
  - Outside collaborators: You-Lin Qiao (CCAMS, China)

Potential for Impact

- Women at the greatest lifetime risk of cervical cancer are not being vaccinated
- Our data show that a single dose of the HPV vaccine continues to protect against HPV for at least 7 years
- Implementing the ESCUDDO study, a formal trial of 1 and 2 doses of the bivalent and nonavalent HPV vaccines
- Immunobridging studies will focus on regions that may have additional comorbidities to ensure findings are generalizable
- Intended to provide sufficient evidence to motivate policy change

Final Comments/Questions

- Given that we have >10 years of evidence of protection, is 5 years of follow-up sufficient evidence of protection to recommend a single dose?
- What level of protection (duration and efficacy) for a single dose that would make it more cost effective than two doses?
- What (lesser) level of protection of a single dose of Gardsil would make it more cost effective than Cervarix?
- What about HIV+ females?
- What about some company combining the 7 types targeted by Gardasil with the AS04 adjuvant to create a super vaccine?