Multicentric cohort study to compare efficacy of a single dose of 4-HPV vaccine compared to two & three doses in 10-18 yr old females in India

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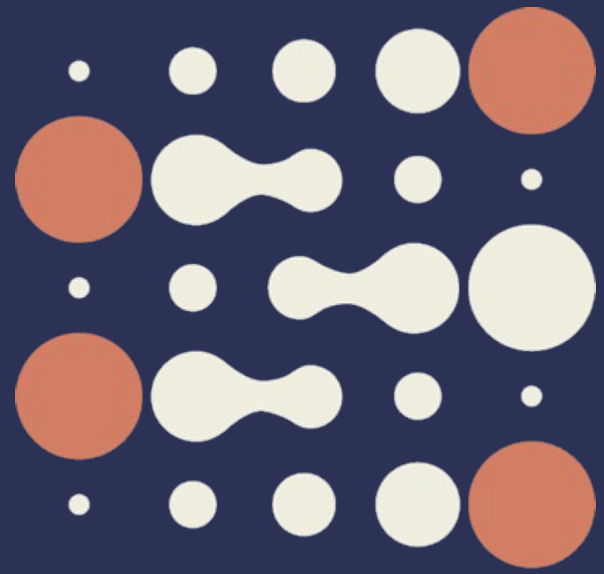


Lancet Oncol 2021; 22: 1518–29; further updated

Study designed as a cluster RCT to compare 2 vs. 3 doses of 4-HPV vaccine in 10-18 year old unmarried girls initiated in Sept 2009

Study arm to receive 2 doses of 4-HPV at 0 & 6 months
(Recruitment planned:10,000; Recruited: 9188)

Comparison arm to receive 3 doses of 4-HPV at 0, 2 & 6 months
(Recruitment planned: 10,000; Recruited:8541)

*Loss of randomization due to order issued on **8 April 2010** by Ministry of Health to stop HPV vaccination in research studies with immediate effect*

Recipients of 3 doses as per protocol (N= 4,348)

Recipients of 2 doses as per protocol (N= 4,980)

Recipients of 2 doses by default at 0 & 2 months (N= 3,452)

Recipients of a single dose by default (N= 4,949)

Unvaccinated cohorts recruited post-hoc

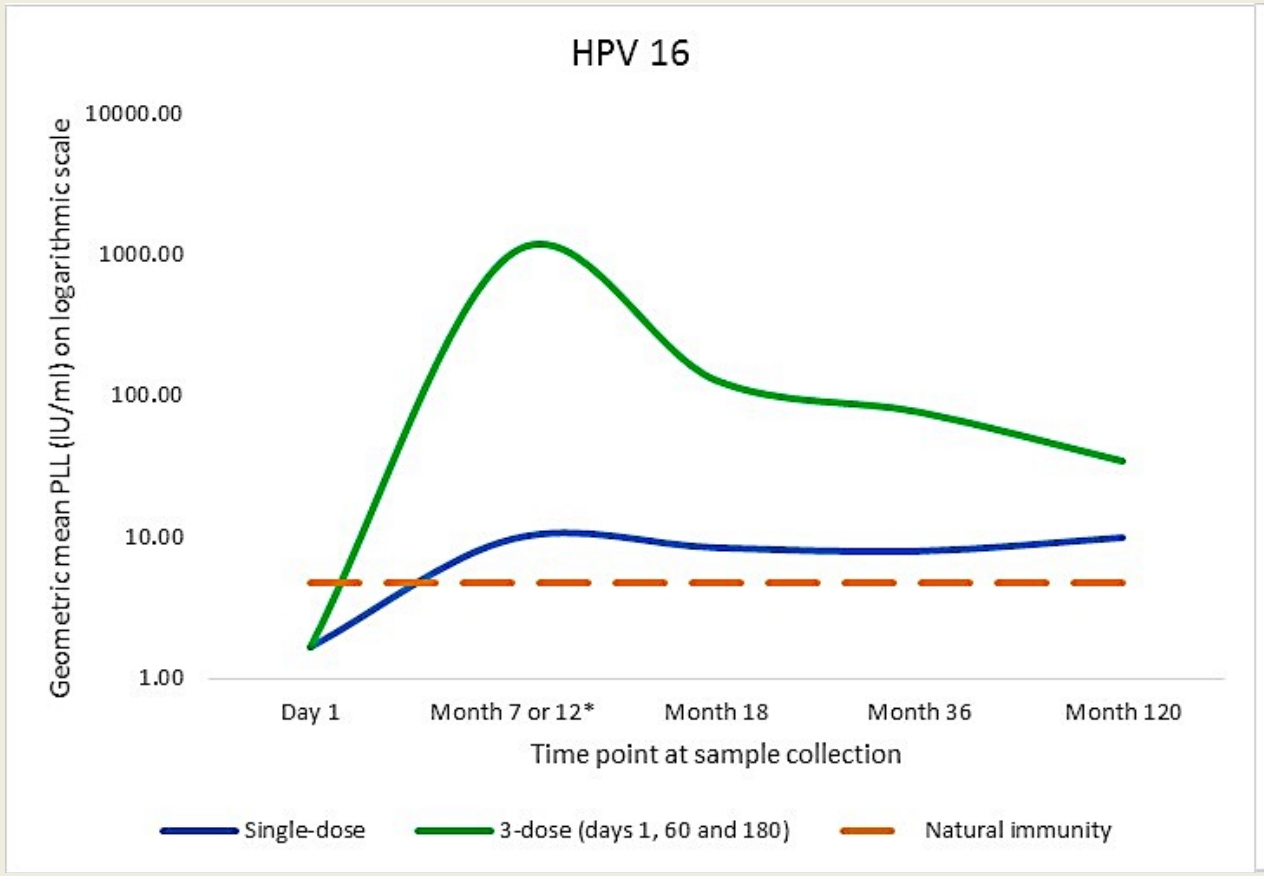
- Yearly follow up
- Cervical specimen collection for HPV genotyping (Luminex™ assay) for 21 HPV types starting at 18 months after marriage or 6 months after first pregnancy yearly x 4 such

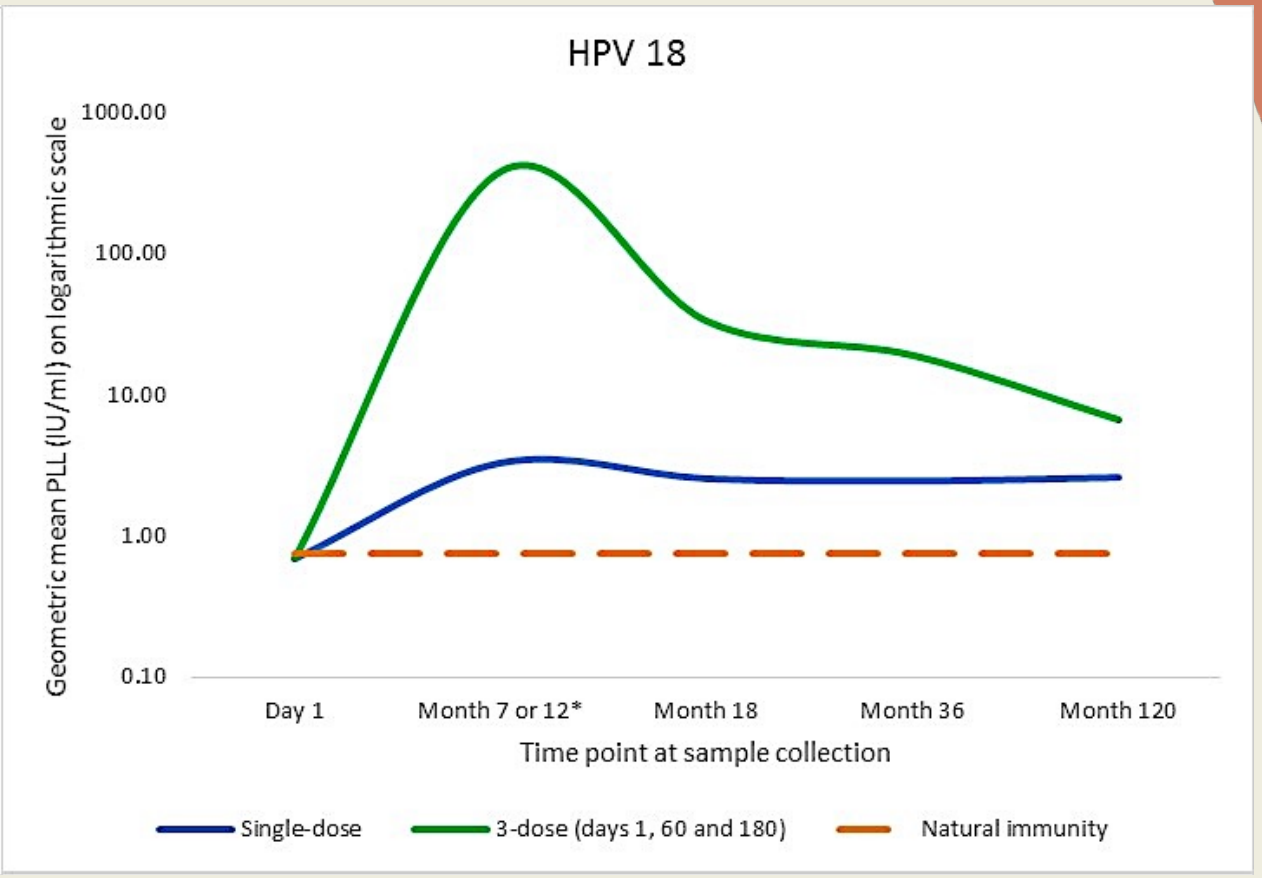
Age & site-matched first unvaccinated control group recruited during 2013-2015 (N= 1,541)

- Screening for cervical cancer using Hybrid Capture II™ (HC II) for married participants at 25 & 30 years of age
- HC II positive women tested for HPV 16/18/45 only using PS genotyping test (test used for triaging of HPV positives)
- HC II positive women undergo colposcopy (& biopsy)

Age & site-matched second unvaccinated control group (screening-only) recruited during 2017-2019 (N= 3,631)

Evolution of total Ab response against HPV 16 & 18 over time in the recipients of 1-dose vs. 3-doses (M9ELISA)



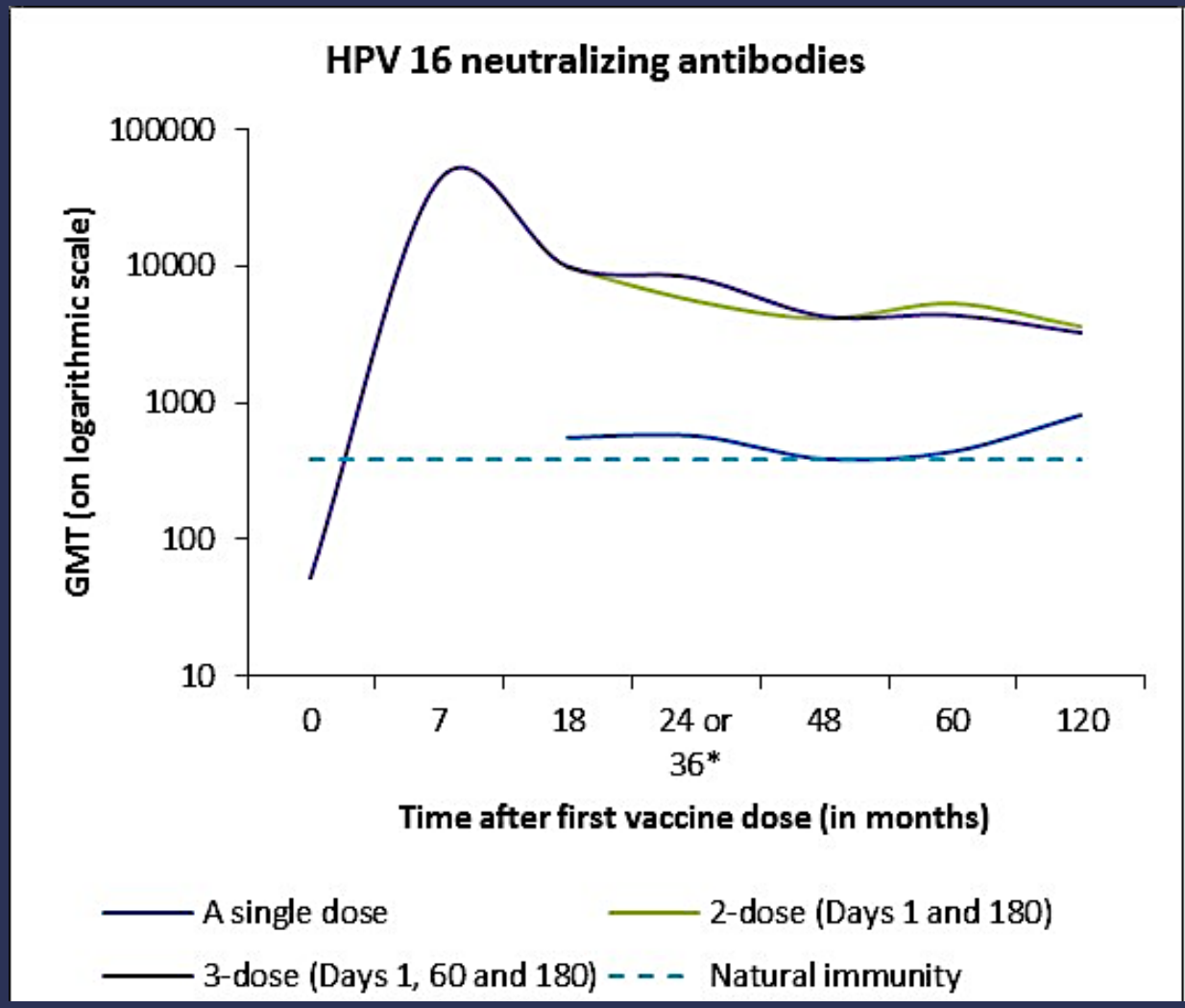


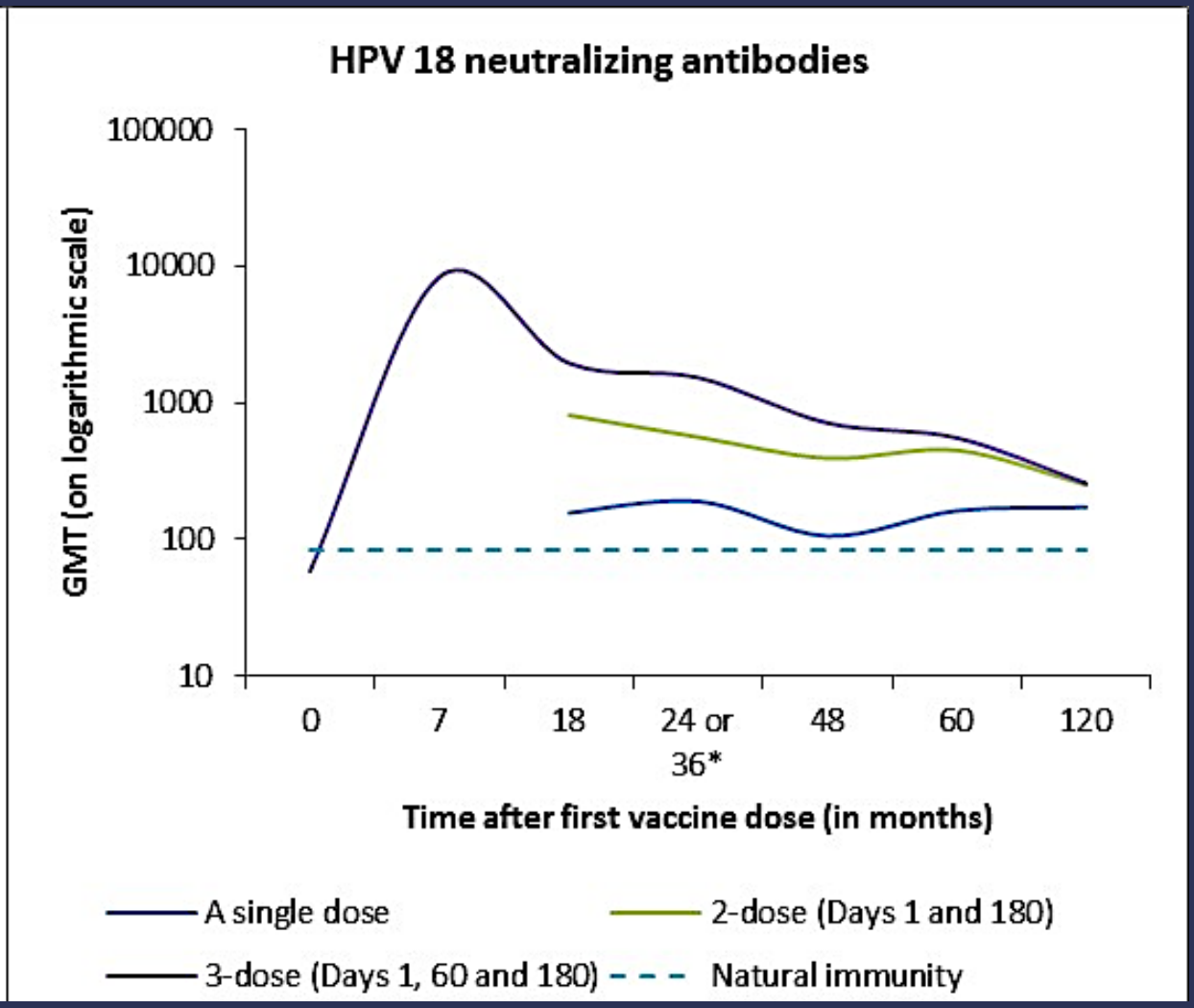
HPV 16: 96% of 1 dose recipients had detectable Ab at 10 yrs; Ab titre was 15X higher than natural immunity

HPV 18: 97% of 1 dose recipients had detectable Ab at 10 yrs; Ab titre was 10X higher than natural immunity

unpublished data

Evolution of Neutralizing Ab response against HPV 16 & 18 up to 10 years in the recipients of 1-dose vs. 2/3-doses (PBNA)





unpublished data

Cervical sample collection profile of the recruited women by dose groups (till March 2021)

	Single dose recipients	Two-dose recipients	Three-dose recipients	Unvaccinated participants
Participants by dose groups	4949	4980	4348	1484
Eligible for first sample collection	3665 (74%)	3286 (66%)	3041 (70%)	1484 (100%)
1st sample collected of the eligible	3105 (85%)	2373 (72%)	2234 (73%)	1479 (100%)
Eligible for the 2nd sample collection	2673	2273	2107	1479
2nd sample collected	2441 (91%)	1703 (75%)	1687 (80%)	1270 (86%)
Median time between marriage & first sample collection (median; IQR)	**1.3 yrs (1.0-1.8)**	**1.2 yrs (1.0-1.7)**	**1.2 Yrs (1.0-1.7)**	**2.8 Yrs (2.0-4.2)**
Time between consecutive sample collection (median; IQR)	**1.3 yrs (1.0-1.8)**	**1.2 yrs (1.0-1.7)**	**1.2 yrs (1.0-1.7)**	**1.3 Yrs (1.0-2.1)**

Analysis of incident HPV infections

Study Group	Women assessed (N)	Incident HPV 16/18 infection N (%; 95% CI)		Incident HPV 31/33/45 infection N (%; 95% CI)		Non-targeted HPV inf excluding 31, 33, 45 N (%; 95% CI)	
1- dose	**3,125**	98	(3.1; 2.6–3.8)	149	(4.8; 4.0–5.6)	537	(17.2; 15·9–18·6)
3- dose	2,193	65	(3.0; 2.3–3.8)	**91**	(4.1; 3.4–5.1)	440	(20.1; 18.4–21.8)
2- dose (D 1 & 180+)	2,337	61	(2.6; 2.0–3.3)	**96**	(4.1; 3.3–5.0)	442	(18.9; 17.3–20.6)
All vaccinated	9,962	303	(3.0; 2.7–3.4)	**404**	(4.1; 3.7–4.5)	1,748	(17.5; 16·8–18·3)
Unvaccinated	1,486	144	(9.7; 8.2–11.3)	156	(10.5; 9.0–12.2)	430	(28.9; 26.6–31.3)

Lancet Oncol 2021; 22: 1518–29 (further updated)

Analysis of persistent HPV infections (N=8.900)

Study Group	Women assessed (N)	Persistent HPV 16/18 infection N (%; 95% CI)		Persistent HPV 31/33/45 infection N (%; 95% CI)		Non-targeted HPV inf excluding 31, 33, 45 N (%; 95% CI)	
1- dose	2454	2	(0.1; 0.0–0.3)	15	(0.6; 0.3–1.0)	85	(3.5; 2.8–4.3)
3- dose	1460	2	(0.1; 0.0–0.4)	12	(0.7; 0.4–1.3)	65	(3.9; 3.1–5.0)
2- dose (D 1 & 180+)	1451	2	(0.1; 0.0–0.4)	14	(0.8; 0.5–1.4)	66	(3·9; 3.0–5.0)
All vaccinated	7,632	10	(0.1; 0.0–0.2)	44	(0.6; 0.4–0.8)	277	(3.6; 3.2–4.1)
Unvaccinated	1268	34	(2.7; 1.9–3.7)	17	(1.3; 0.8–2.1)	78	(6.2; 4.9–7.6)

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Vaccine efficacy (Adjusted) against Incident & Persistent HPV 16/18 infections

Endpoint	3-dose (Days 1, 60 and 180)		2-dose (Days 1 and 180)		Single dose	
Persistence	93.3%		93.1%		95.4%	
95%CI	(77.5 to	99.7)	(77.3 to	99.8)	(85.0 to	99.9)
Incidence	66.4%		67.7%		63.5%	
95%CI	(53.6 to	76.3)	(55.2 to	77.2)	(51.2 to	73.1)

Adjusted for background HPV infection frequency, time between date of marriage and first cervical specimen collection, and number of cervical specimens per participant

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Outcomes of cervical cancer screening

Study Group	Women screened (N)	Screened +ve		CIN detected		CIN 2+ associated with HPV 16/18
		hrHPV	HPV 16/18	CIN 1	CIN 2+	
1- dose	1511	59 (3.9%)	2 (0.1%)	4	1	0
3- dose	1037	46 (4.4%)	1 (0.1%)	2	0	0
2- dose (D 1 & 180+)	1143	61 (5.3%)	4 (0.3%)	5	0	0
All vaccinated*	4.819	197 (4.1%)	7 (0.1)	12	1	0
Unvaccinated	4626	277 (6.0%)	63 (1.4%)	16	6	3

*Includes 2 dose (0, 60 days) group

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To conclude..

Systematic and rigorous evaluation of infection end-points in the IARC study has established the robust protection offered by a single dose against persistent infection

The long term protection is well-supported by immunogenicity data

Possibility of selection bias is extremely low in assigning participants to the three dose groups

The background risk of getting HPV infection was similar across the dose groups that make them highly comparable

Early data from screening outcomes is also quite encouraging