Vaccinazione e screening: i punti centrali.

La cross-protection ed il type replacement

Workshop precongressuale, Mercoledì 20 Maggio 2015.

International Agency for Research on Cancer
Lyon, France

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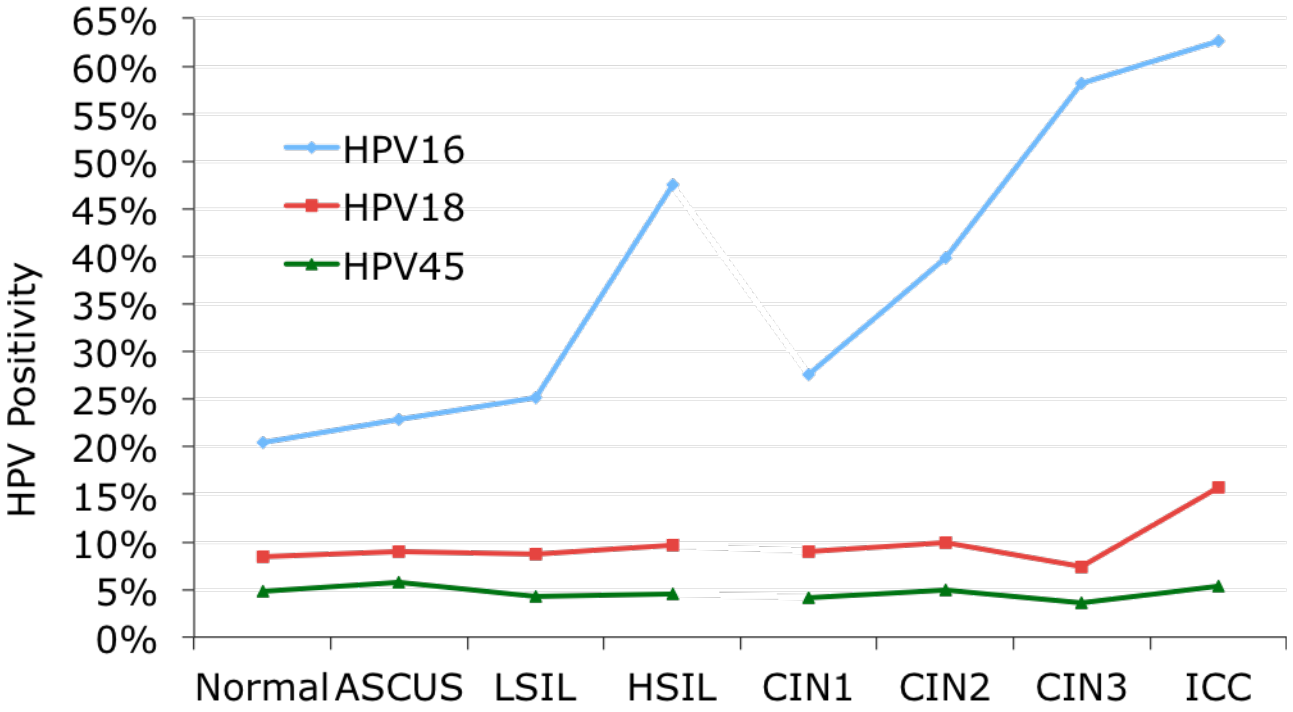
Outline

- **HPV enrichment across lesions.**
  - Relevant to assess the overall impact of direct and cross protection.
  - Relevant to interpret possible type-replacement in lesions/cancers

- **Cross-protection.**
  - Type of vaccines, duration, level, and type of protection.

- **Type replacement.**
  - Competition for ecological niches
  - Competing causal risks for lesions / cancers

HPV-type enrichment



Meta-analysis 423 studies.

260K normal cytology
103K cervical abnorm.

HPV16/18/45 increase in prevalence in direct proportion to the severity of the lesion

	Normal	CIN1	CIN2	CIN3	ICC	ICC/Normal ratio	ICC/CIN3 ratio
HPV 16	20.4 ± 3.6	27.6 ± 4.3	39.8 ± 5.0	58.2 ± 4.1	62.6 ± 2.2	**3.07**	**1.08**
HPV 18	8.4 ± 1.1	9.0 ± 1.7	10.0 ± 1.0	7.4 ± 1.2	15.7 ± 2.9	**1.87**	**2.11**
HPV 45	4.8 ± 0.9	4.2 ± 1.3	5.0 ± 1.7	3.6 ± 1.0	5.3 ± 0.7	**1.10**	**1.47**

Guan et al IJC. 2012

Direct protection

VACCINE TYPE	ENDPOINT	Per-protocol cohort	Intention-to-treat cohort
2-valent (HPV16 and 18)	HPV16*	90.8% (82.4–95.6%)	84·1% (73·5 to 91·1)
	HPV18*	100% (94.2–100%)	74·0% (49·1 to 8·8)
	CIN2+	99.0% (94.2–100%)	60.7% (49.6–69.5%)
4-valent (HPV6, 11, 16, and 18)	HPV16*	96.6% (79.2 99.9)	91.6% (73.3–98.4%)
	HPV18*	90.6% (35.6 99.8)	91.6% (43.3–99.8%)
	CIN2	100% (88.7–100%)	53.0% (35.5–59.9%)
	External lesions	97.1% (92.4–99.2%)	79.3% (72.7–84.5%)
9-valent (risk reduction *vs.* 4-valent)	HPV31, 33, 45, 52, or 58	96.0 (94.4 to 97.2)	
	HPV6, 11, 16, or 18	26.4 (−4.3 to 47.5)	

*≥6-month HPV DNA persistence

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Adapted from: Lehtinen & Dillner. Nat. Rev. Clin. Oncol. 2013 . Joura et al, NEJM, 2015

Cross protection

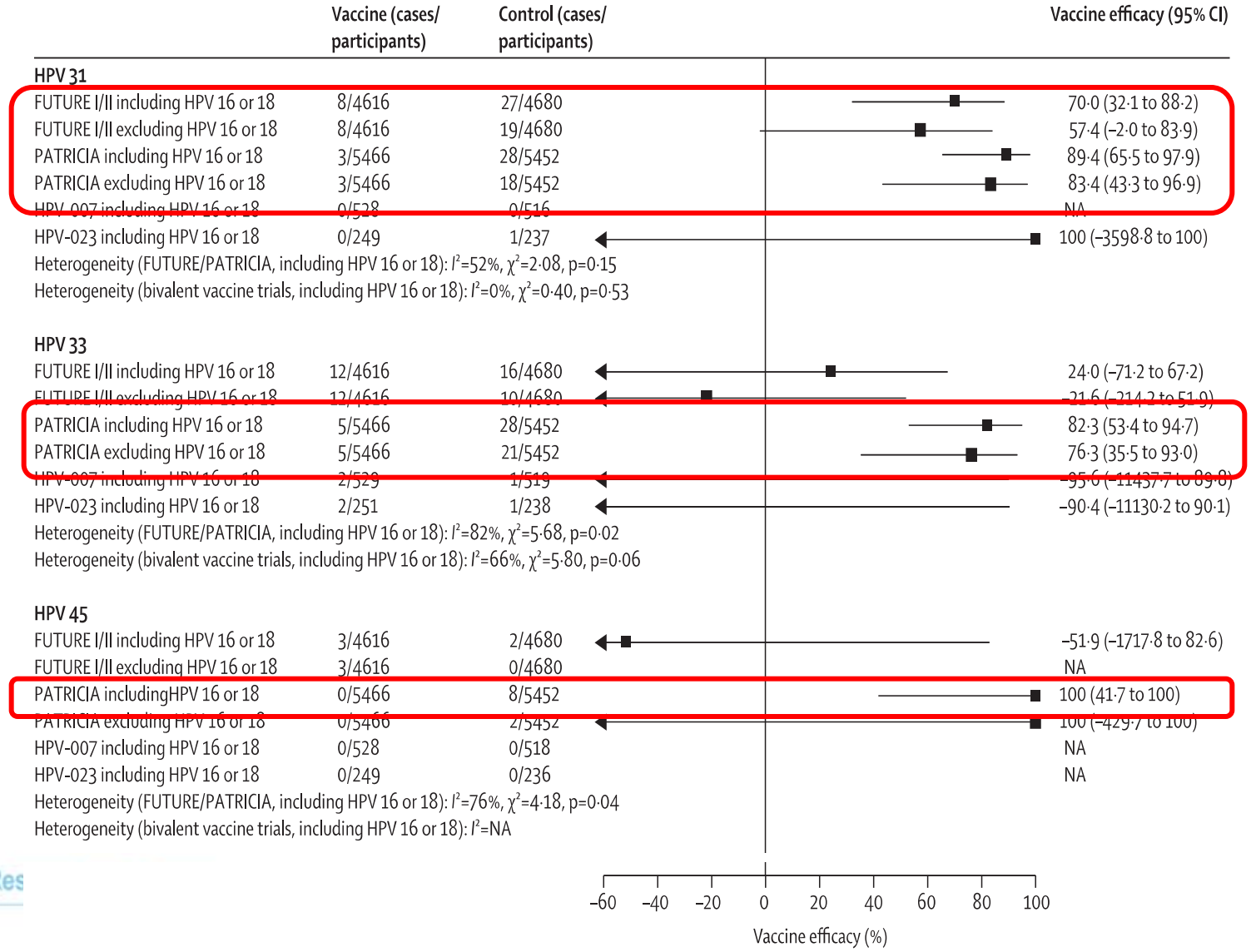
Efficacy *vs.*

CIN2+

4-val.: HPV 31

2-val.: HPV 31, 33, and 45.

HPV16/18/45/ 31/33 are responsible for ~90% of all cervical cancers.



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Malagon et al, Lancet Infect Dis 2012

Cross-protection: Doses & Duration

- **Direct protection (*vs.* HPV16/18).**
  - 3-doses regimen, 4-years vaccine ATP efficacy = 84% (77% - 89%)
  - 2-doses regimen, 4-years vaccine ATP efficacy = 81% (53% - 94%)
  - 1-dose regimen, 4-years vaccine ATP efficacy = 100% (79% - 100%)

  Evidence from Costa Rica trial

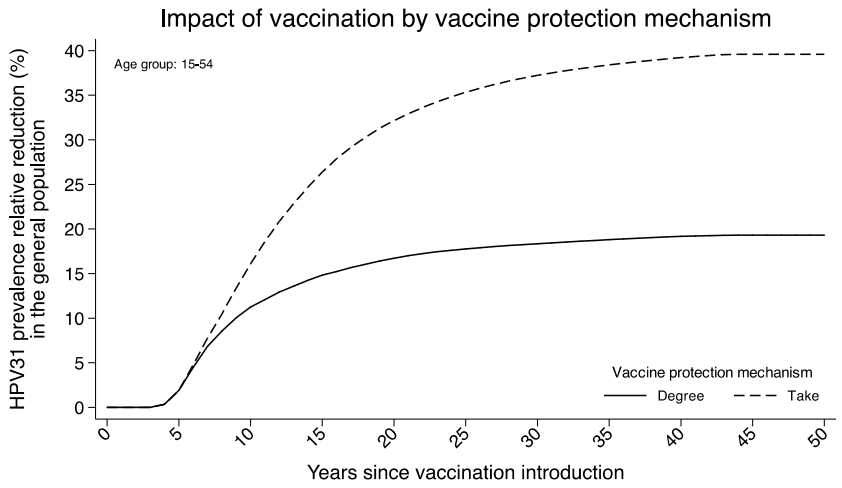
- **Indirect protection (*vs.* non-HPV16/18).**
  - Preliminary (unpublished) data suggest that cross-protection decreases over time with fewer-than-3 -doses regimens.

- **Vaccination registries *vs.* clinical trials.**
  - Women routinely vaccinated with < 3 doses are older the others → misclassification of prevalent infections as “failure”

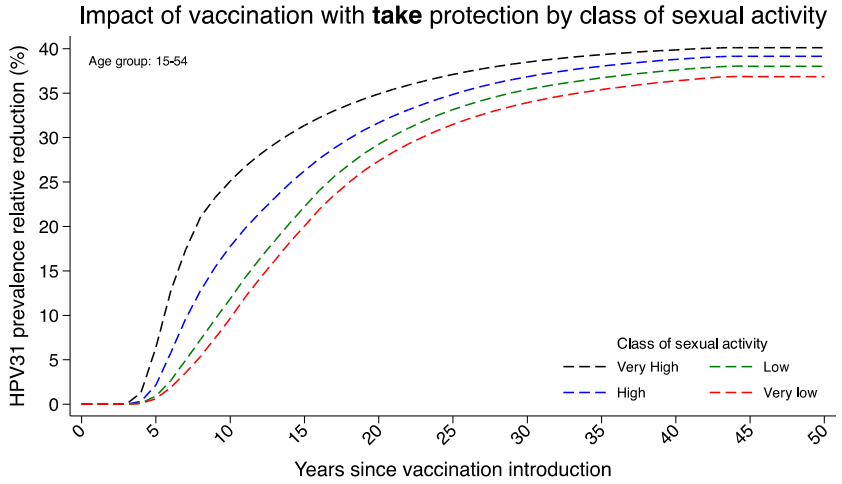
Kreimer et al, JNCI 2015

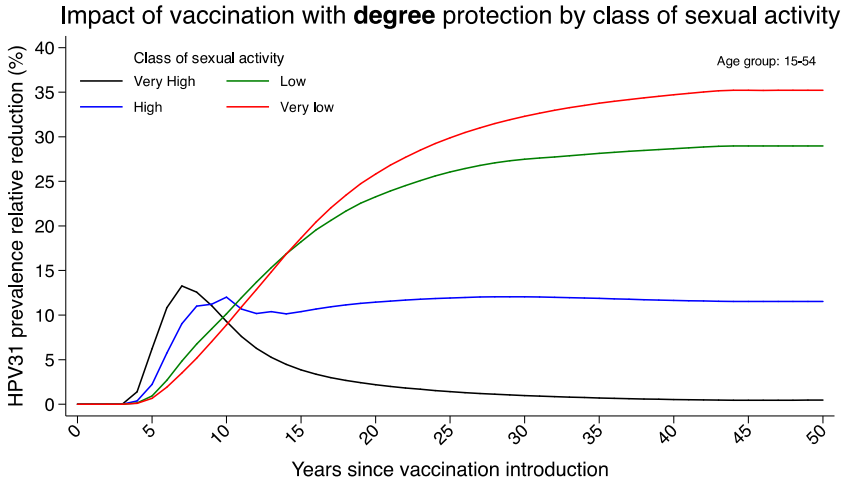
Mechanisms for protection

Girls-only coverage 50%



- **Take.** The fraction of women effectively vaccinated is fully protected
- **Degree.** The women vaccinated are all partially protected.





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Baussano et al, unpublished

Type replacement

- **Exposure replacement.** HPV types compete for the same ecological “niche”. Vaccination may alter an existing ecological equilibrium in favor of non-targeted types. Note it has been clearly shown only for bacterial diseases.

- **Outcome unmasking.** Multiple causal pathways converge towards the same outcome with different distributions of time to event (i.e. competing risks). Vaccination may unmask “weaker” carcinogenic HPV genotypes.

Ecological replacement

- **Consistency of absence of evidence.**

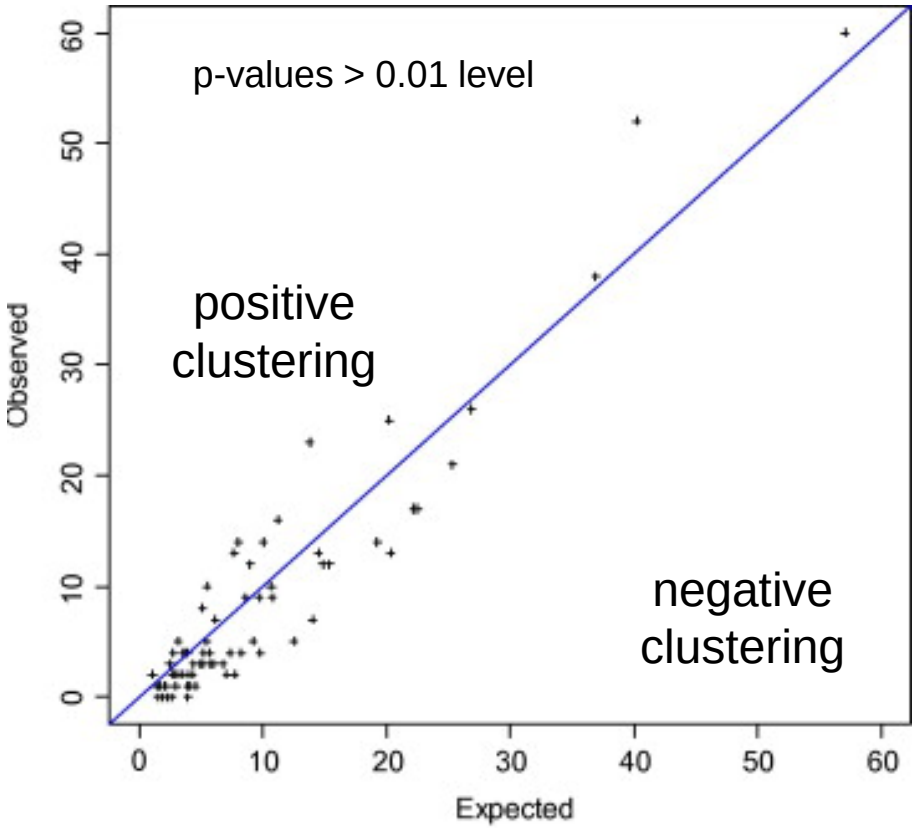
  Observational (cross-sectional & longitudinal) and experimental (vaccine & screening) studies have shown that there is no evidence of clustering.

- **Histological model.**

  One virus, One lesion. (van de Marel et al, Am J Surg Pathol 2015)

  Discrete population of squamo-columnar junction cells. (Herf et al, PNAS 2012)

Pair-wise Clustering in NTCC trial (13 HR HPV types) .



Carozzi et al, EJC 2012

Unmasking phenomenon

- **Competing risk for cervical cancer.**
  - "Slower" HR HPV types not targeted by the vaccines are not outcompeted any more by "faster" types in causing lesions/cancers.

- **Attribution of lesions to specific types.**
  - A. Hierarchical; B. Longer persistence; C. Proportional. Methods A & B are prone to misclassification and may lead to an apparent increase in disease due to "weaker" HPV types (Choi et al, Vaccine 2012).

- **Diagnostic issue.**
  - Boost the development of diagnostic tools aimed at the detection of "weaker" carcinogenic HPV genotypes in in populations vaccinated against HPV16/18 (Valdez et al, IJC 2015).

Conclusions

- **Cross-protection.**
  - Crucial issue to support / discourage the introduction of multivalent vaccines (cost-effectiveness analyses)
  - Crucial issue to project the impact of two-doses vaccination schedule
  - To be evaluated for one-doses vaccination schedules
  - Uncertainties about the duration of protection
- **Type-replacement.**
  - Ecological replacement does not appear to be an issue as it occurs in other IDs (e.g. vaccination *vs. H.influenzae* type b & Streptococcus *Pneumoniae*).
  - Redistribution of the fraction of cervical cancers attributable to HPV type is likely to occur among vaccinated cohorts and screening protocols may need to be adapted accordingly.

Akcnowledgements

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- **Infection section (IARC).**
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Grant sponsors

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HPV Vaccines – Synoptics (backup)

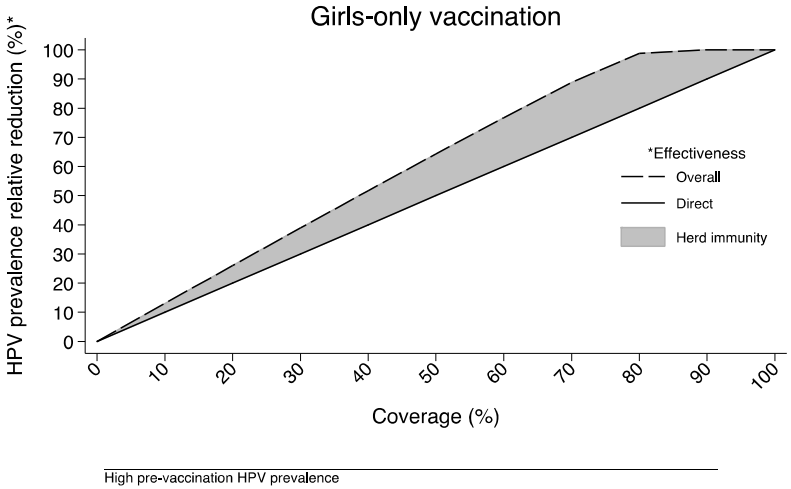
- **Bi-valent** (Cervarix®; GlaxoSmithKline, London, UK)
  - HR-HPV types 16 and 18.
  - PATRICIA trial, final analysis 48 months. 18 644 women, 15–25 years, 14 countries, with ≤6 lifetime sexual partners.
  - Costa-Rica trial, final analysis 48 months. 7 466 women, 18–25 years.

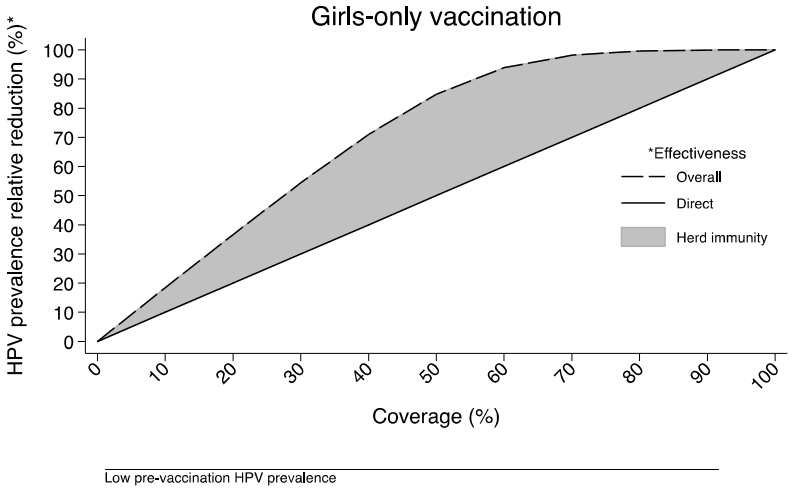
- **Quadri-valent** (Gardasil®; Merck, Whitehouse Station, USA).
  - LR-HPV types 6, 11 and HR-HPV types 16,18.
  - FUTURE I/II, final analysis 42 months. 17 622 women, 16–26 years, 24 countries, with ≤4 lifetime number of sexual partners.

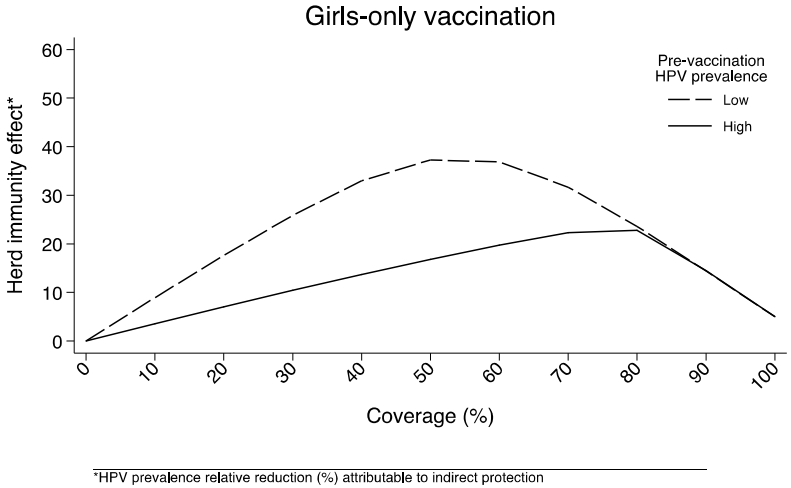
- **Nona-valent** (Gardasil 9 ; Merck, Whitehouse Station, USA).
  - LR-HPV types 6, 11 and HR-HPV types 16,18, *31, 33, 45, 52*, and *58*.
  - 14 215 women, 16–26 years, 4-valent as comparator, analysis 48 months

Lehtinen et al, Lancet Oncol. 2012; Hildesheim et al, Vaccine 2014
Dillner et al, BMJ 2010; Joura et al, NEJM 2015

Herd immunity effect (backup)







- **Major driver.**
  - Background pre-vaccination prevalence
- **Implication.**
  - At population level cross-protection may have different impact in different populations