National Cancer Institute

Choice of Outcome for Post-Licensure HPV Vaccine Studies

Symposium on HPV Vaccination: Safety, Sound Efficacy & Public Health Effectiveness

Helsinki, Finland
January 12, 2012

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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Choice of Outcome for Post-Licensure HPV Vaccine Studies:
One Size Does Not Fit All

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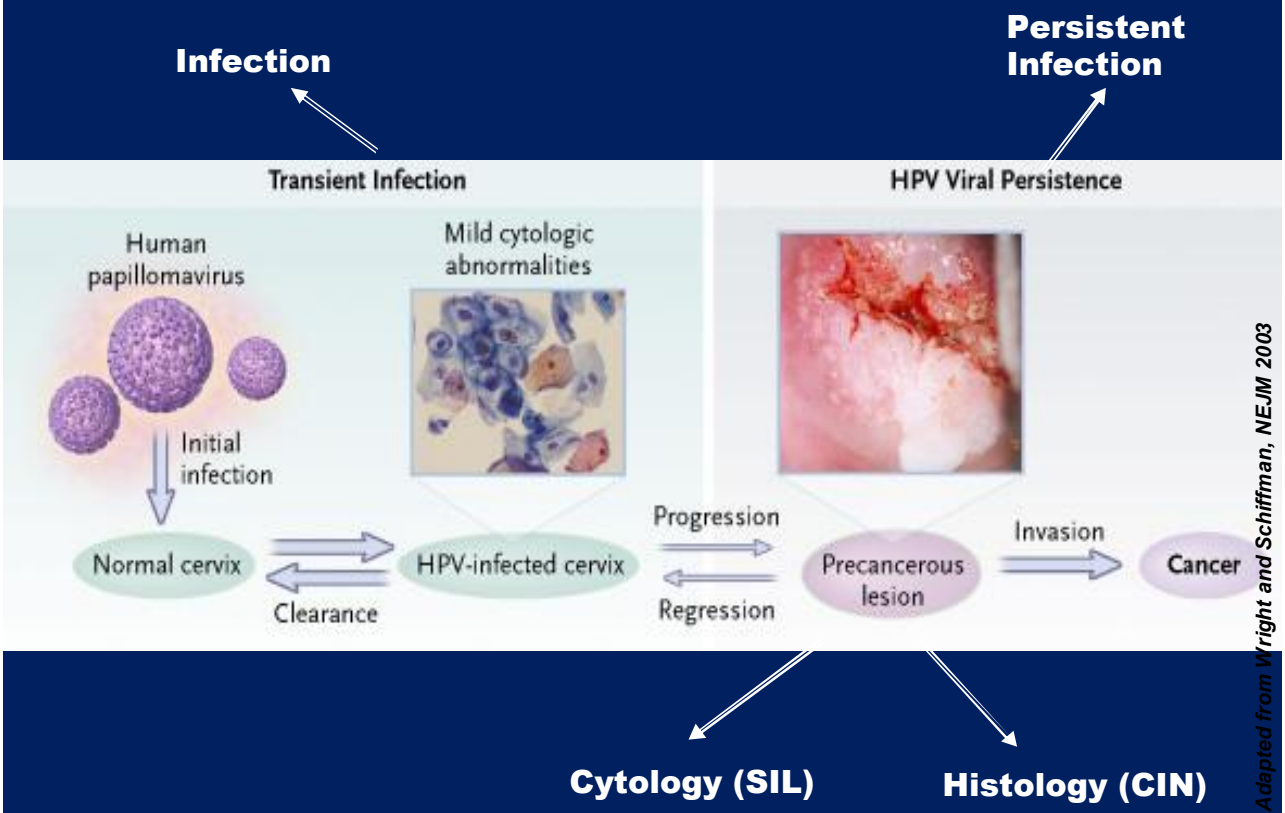
A Wealth of Choices



Adapted from Wright and Schiffman, NEJM 2003

A Bit of History

- In early 2000s, US-FDA convened its advisory committee to review outcomes proposed for pivotal licensure trials
  - Recommendation: Histologic outcomes → CIN2+ (HPV-16/18)

- Rationale
  - Most proximal cancer precursor observable without intervention
  - Clinical (rather than virological/molecular) outcome that would provide evidence required by clinical community
  - Requirement for large studies was not seen as a limitation
    - larger studies important to provide more robust safety data
  - Note: At the time, data demonstrating that persistent HPV-16/18 infection was strongly predictive of CIN2+ was not yet published.

Vaccine Efficacy Results Using CIN2+ as Outcome

Per-Protocol Analysis for HPV-16/18

Vaccine	Arm	Women	Events	Rate /100py	Efficacy (95% CI)
Gardasil (FUTURE I/II + HPV-007) [42mo FU]	HPV	7,864	2	0.0	98% (93, 100)
	Control	7,865	110	0.5	
Cervarix (PATRICIA) [44mo FU]	HPV	7,338	5	0.0	95% (88, 98)
	Control	7,305	97	0.4	

Kjaer et al., Can Prev Res 2009;[5]
Lehtinen et al., Lancet Oncol 2011

Problems with CIN2 as an Outcome

- Histological interpretation of CIN2 is highly irreproducible, making it difficult to standardize
- When lesion arises in the context of multiple HPV infections (~30%+), difficult to attribute lesion to a vaccine vs. non-vaccine HPV type
- CIN outcomes not feasible in all circumstances (e.g., evaluation of efficacy in oral region)
- A large proportion of CIN2 lesions regress, so the numbers of CIN2 lesions avoided through vaccination (rate reduction) might not closely reflect reductions for invasive cancer in the future

CIN2 is a Highly Irreproducible Diagnosis

First Reviewer	Second Reviewer			
	<CIN2	CIN2	CIN3	TOTAL
<CIN2	233	7	2	242
CIN2	75	24 (20%)	22	121
CIN3	4	8	57 (83%)	69

Carreon et al., Int J Gyn Pathol 2007

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	Control	7,305	24	0.1	

Kjaer et al., Can Prev Res 2009;[9]
Lehtinen et al., Lancet Oncol 2011

Vaccine Efficacy Results Using CIN3+ as Outcome

Analyses Irrespective of HPV Type
PATRICIA Trial

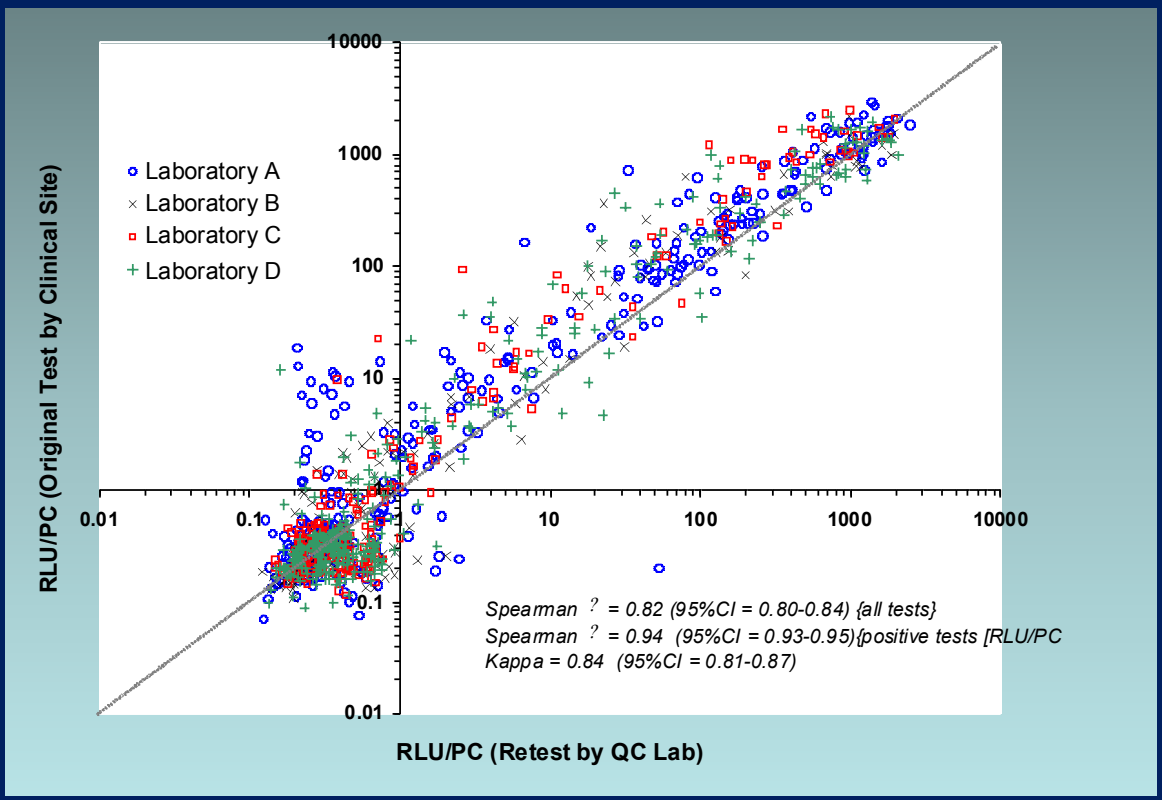
Analytic Cohort	Arm	Women	Events	Rate /100py	Efficacy (95%CI)
Total Vaccinated Cohort – Naïve [44mo FU]	HPV	5,466	3	0.0	93% (79, 99)
	Control	5,452	44	0.2	
Total Vaccinated Cohort [44mo FU]	HPV	8,694	86	0.3	46% (29, 59)
	Control	8,708	158	0.5	

Lehtinen et al., Lancet Oncol 2011[10]

CIN3 as an Outcome in Future Studies

- More reproducible than CIN2
- Less likely to regress than CIN2
  - Therefore more closely reflects expected impact on cancer rates
- Of note: In some instances CIN3 is reportable to cancer registries, allowing for efficient passive follow-up of vaccinated cohorts

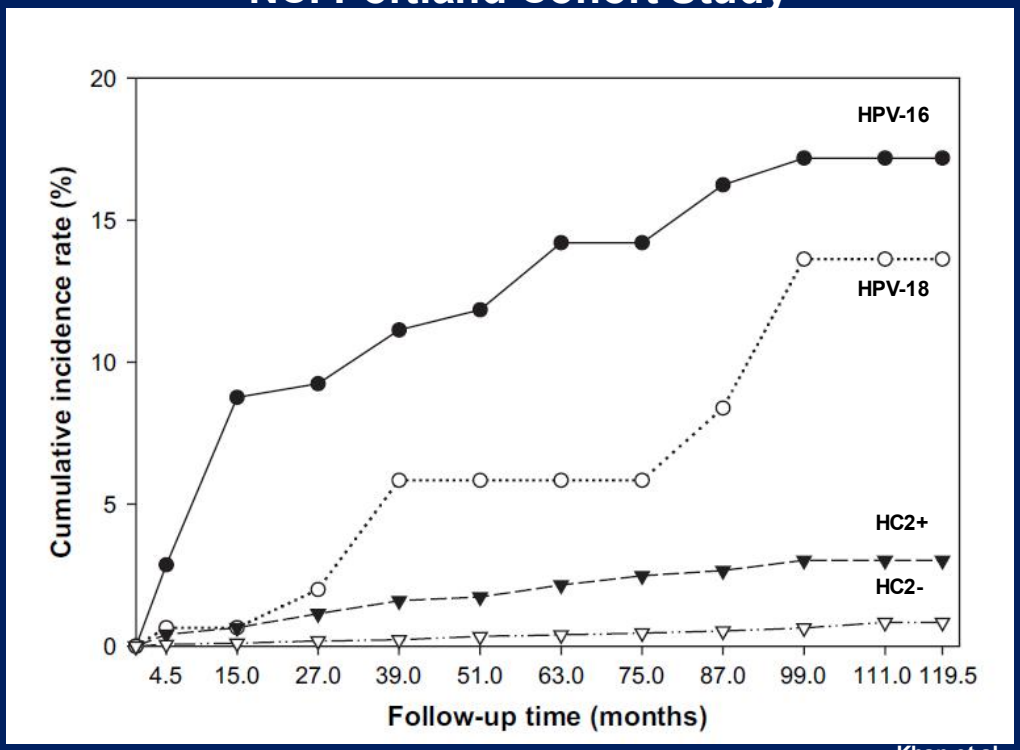
HPV Testing is Highly Reproducible



Castle, AJCP 2004

HPV-16/18 Positivity is Associated with High Absolute Risk of Progression to CIN3+

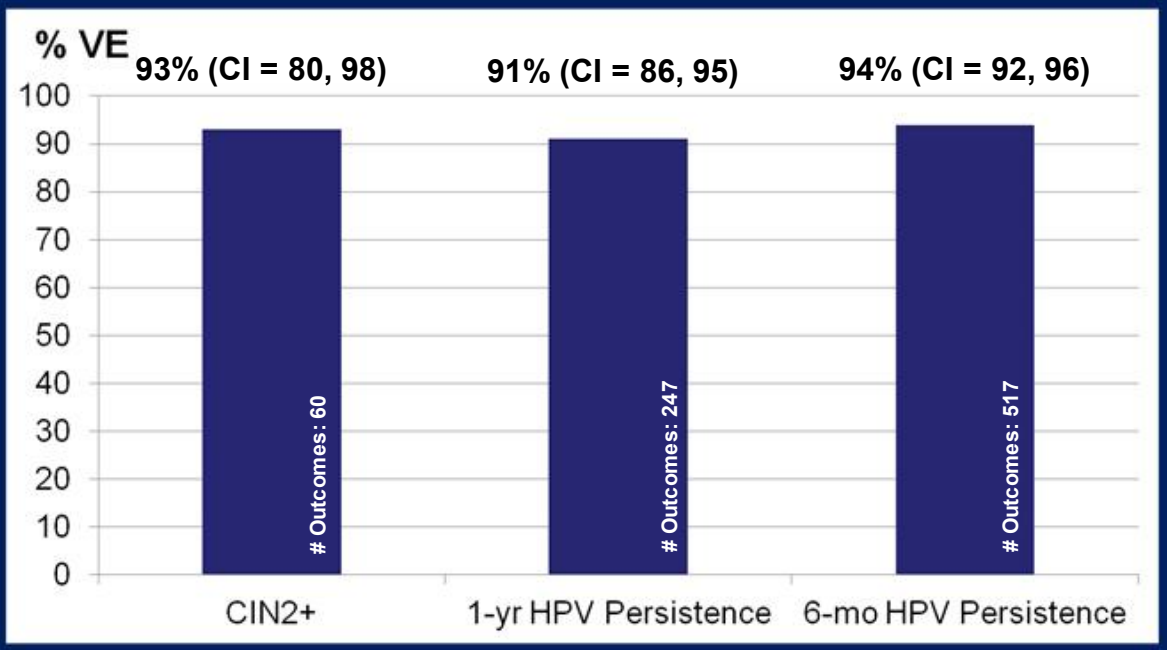
NCI Portland Cohort Study



Khan et al., JNCI 2005

Vaccine Efficacy Results Using Alternative Outcomes

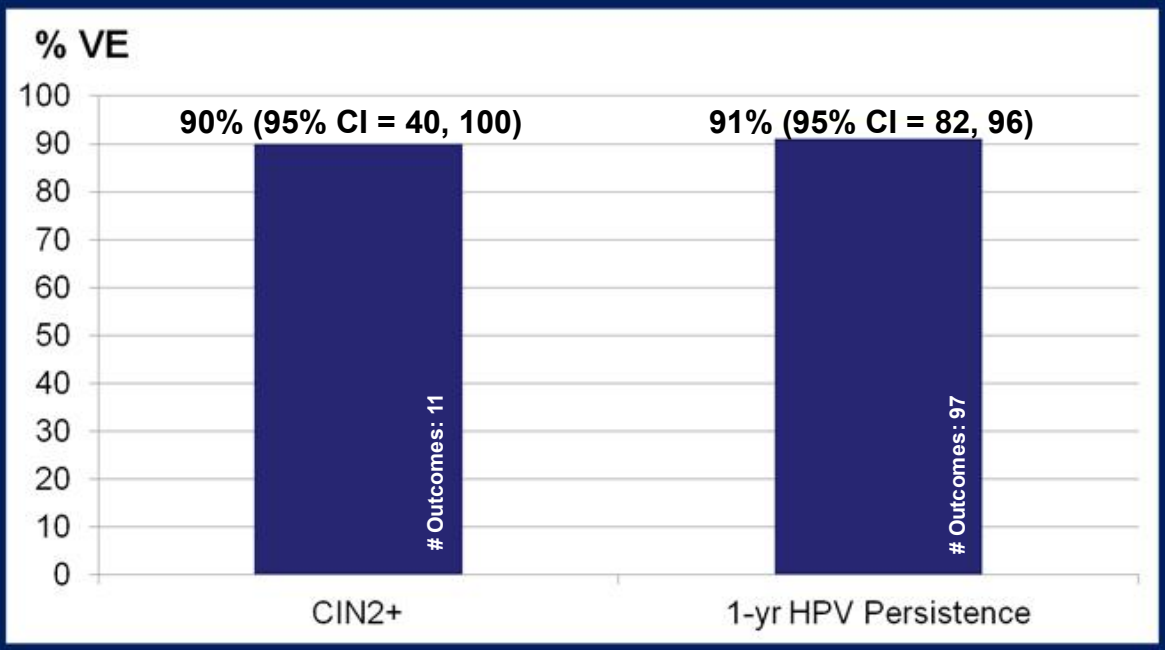
Per-Protocol Analysis for HPV-16/18 Outcomes
PATRICIA Trial



Paavonen et al., Lancet 2009

Vaccine Efficacy Results Using Alternative Outcomes

Per-Protocol Analysis for HPV-16/18 Outcomes
Costa Rica HPV Vaccine Trial (CVT)



Herrero R et al Cancer Discovery 2011;
Hildesheim et al (www.clinicaltrials.gov)

HPV (Persistent) Infection as an Outcome in Future Studies

- Highly reproducible measure
- Predictive of risk of progression to precancer
- Can be measured in context of multiple infections without concern for incorrect attribution
- More common than clinical outcomes
  - Reduced study size requirements
- First evidence of vaccine failure

One Size Does Not Fit All

Optimal Outcome Depends on Question Being Asked

Examples

Question to be Evaluated	Preferred Outcome
What is the duration of protection @ cervix?	HPV
Should I vaccinate individuals to protect them against oral-pharynx cancer?	HPV
To what extent will HPV vaccination reduce rates of referral to colposcopy?	SIL/HPV
What will be the impact of vaccination on cancer burden among vaccinated cohorts?	CIN3+

Thank you