4th Helsinki Symposium on HPV Vaccination
Universities of Helsinki & Tampere, Finnish Medical Society
Helsinki, 12 January 2012

Cochrane Reviews

1. Cervical Cancer Screening in developing countries
2. Safety, immunogenecity and efficacy of prophylactic HPV vaccines

M. Arbyn

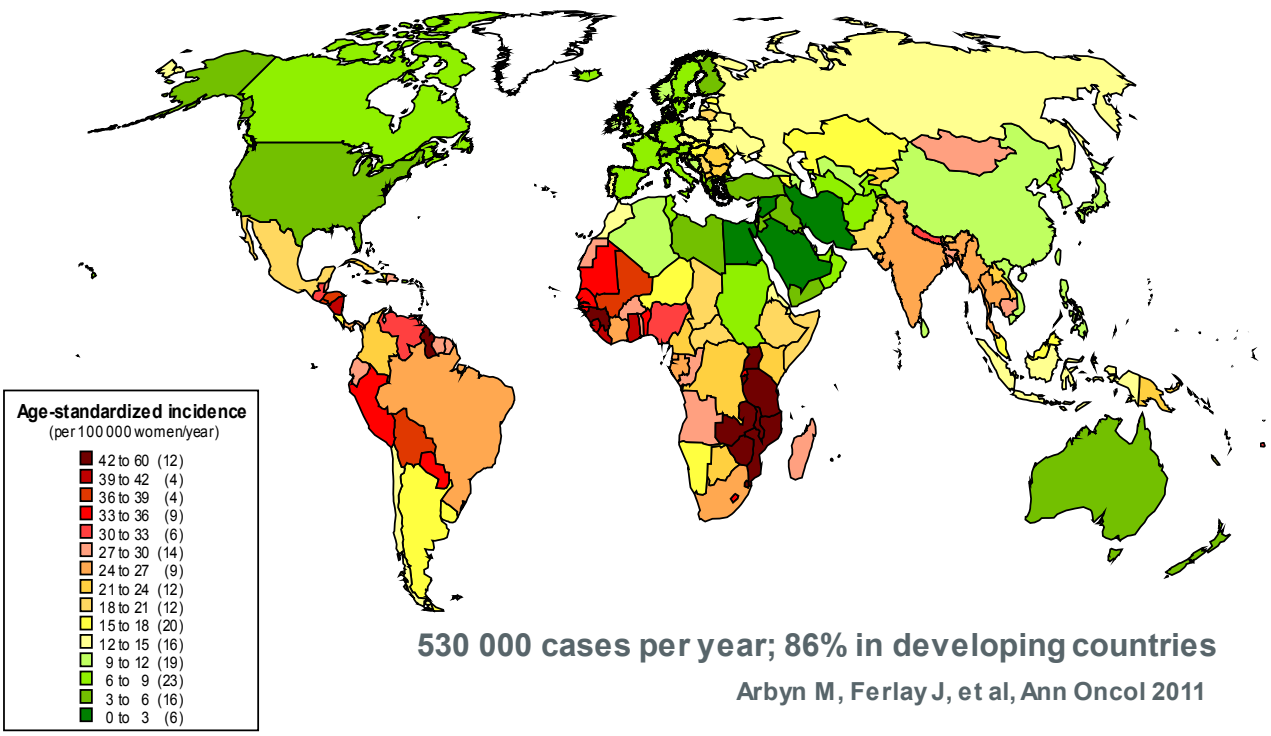
Unit Cancer Epidemiology, IPH, Brussels, Belgium

Rue Juliette Wytsmanstraat 14 | 1050 Brussels | Belgium
T +32 2 642 50 73 | F +32 2 642 54 10 | email: amidu.raifu@iph.fgov.be | http://www.iph.fgov.be

Introduction

- 86% of cervical cancer cases occur in developing countries
- HPV vaccination will not protect infected population. High vaccination coverage not expected in very near future.
- Affordable & accurate screening strategies needed for the next decades
- Contradictory findings regarding accuracy of HPV testing vs visual inspection methods

Incidence of Cervical Cancer
(number of cases/100 000 women-years, 2008)



530 000 cases per year; 86% in developing countries

Arbyn M, Ferlay J, et al, Ann Oncol 2011

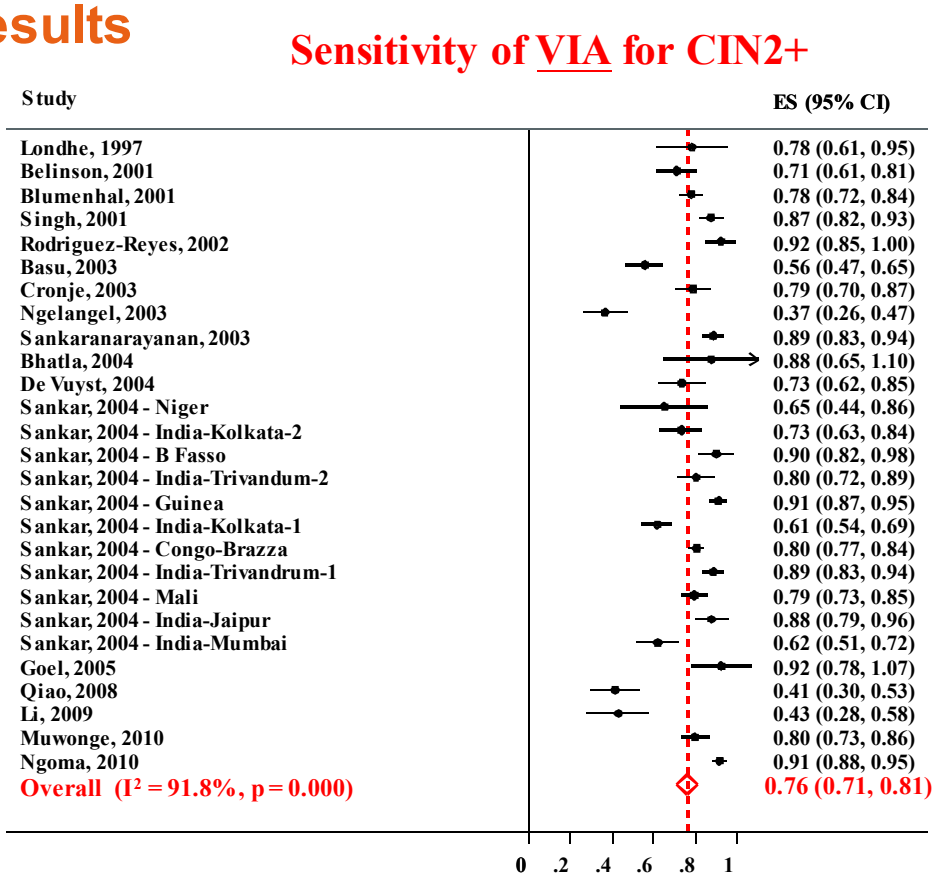
Methods

- **Literature search: 1982-present**
- **Screening tests included: VIA and VILI**
- **Comparator tests: cytology and HPV (HC2)**
- **2 Outcome measures: CIN2+ and CIN3+**
- **27 of studies with complete verification**
- **Several reference standards:**
  - colposcopy targeted biopsies, accepting negative satisfactory colposcopy as ascertainment for no CIN2+, sometimes ECC if unsatisfactory colpo
  - additional random biopsies even if colpo-

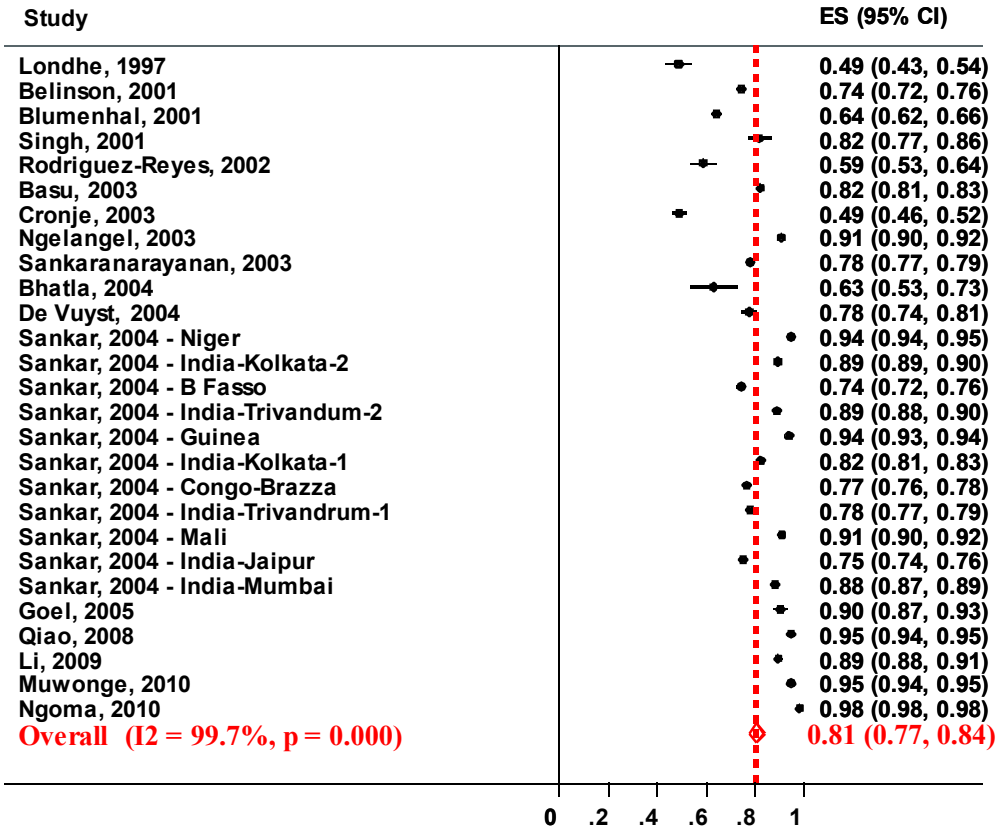
Statistical analysis

- Separate pooling of sensitivity and specificity using random effects model
- Multi-level Hierarchical Summary ROC regression & bivariate normal model for between-study variation of the logarithms of odds of sensitivity and specificity (Chu J Clin Epidemiol 2006; Rutter J Med Stat 2002).
- = new method recommended by Cochrane Collaboration for diagnostic test accuracy assessment

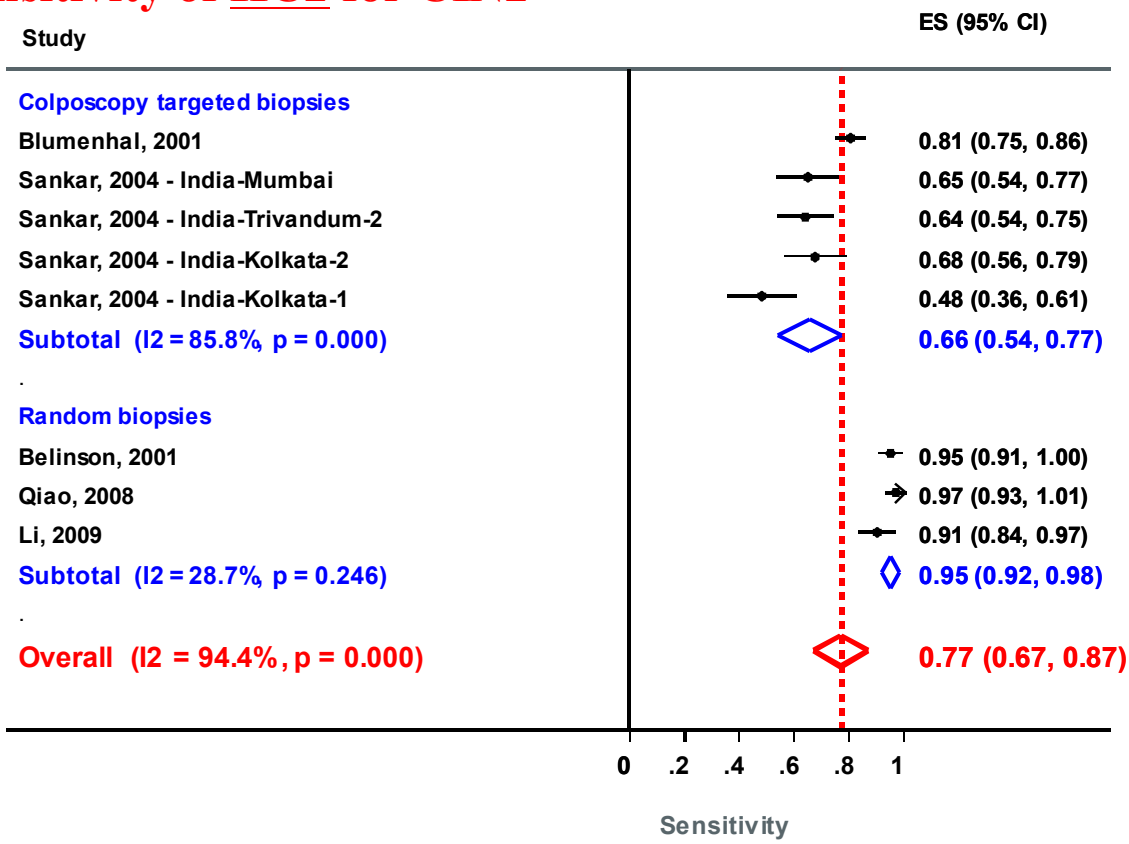
Results



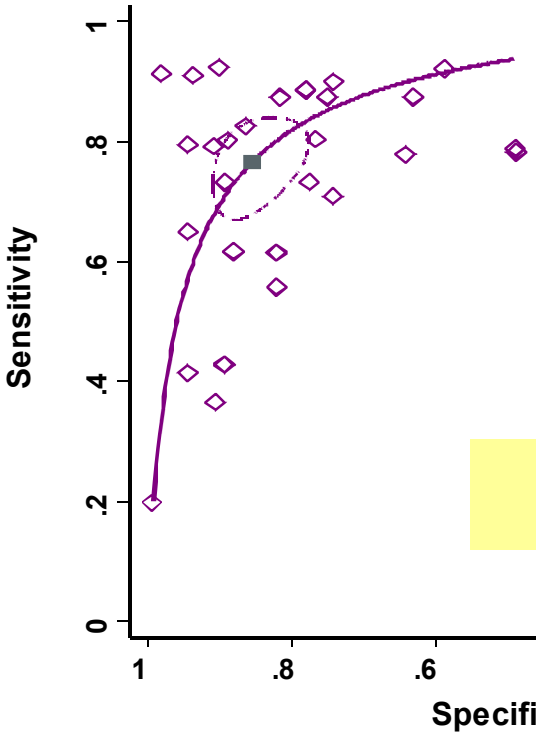
Specificity of VIA for CIN2+



Sensitivity of HC2 for CIN2+



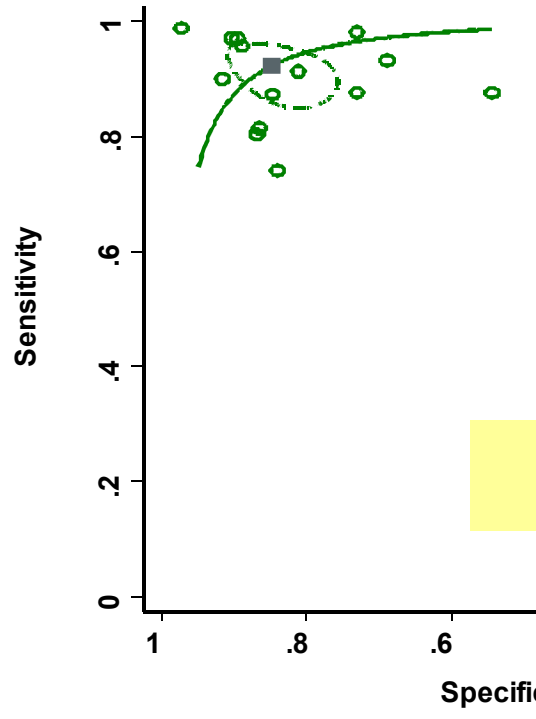
Accuracy of VIA for CIN2+: HSROC/binormal model



Sensitivity: 76.5% (95% CI: 69.5-82.4%)

Specificity: 85.6% (95% CI: 79.7-89.9%)

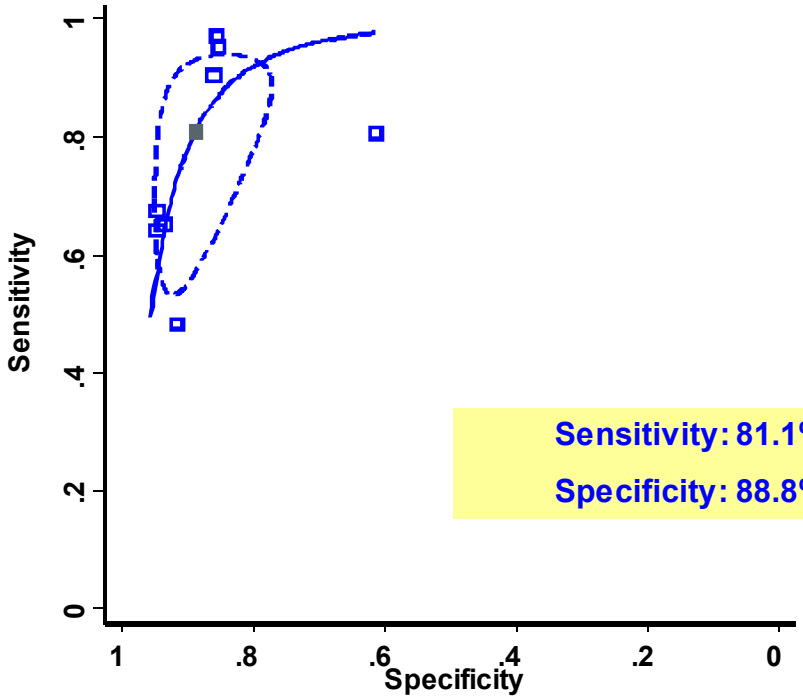
Accuracy of VILI for CIN2+: HSROC/binormal model



Sensitivity: 92.2% (95% CI: 87.5-95.3%)

Specificity: 84.8% (95% CI: 78.7-89.4%)

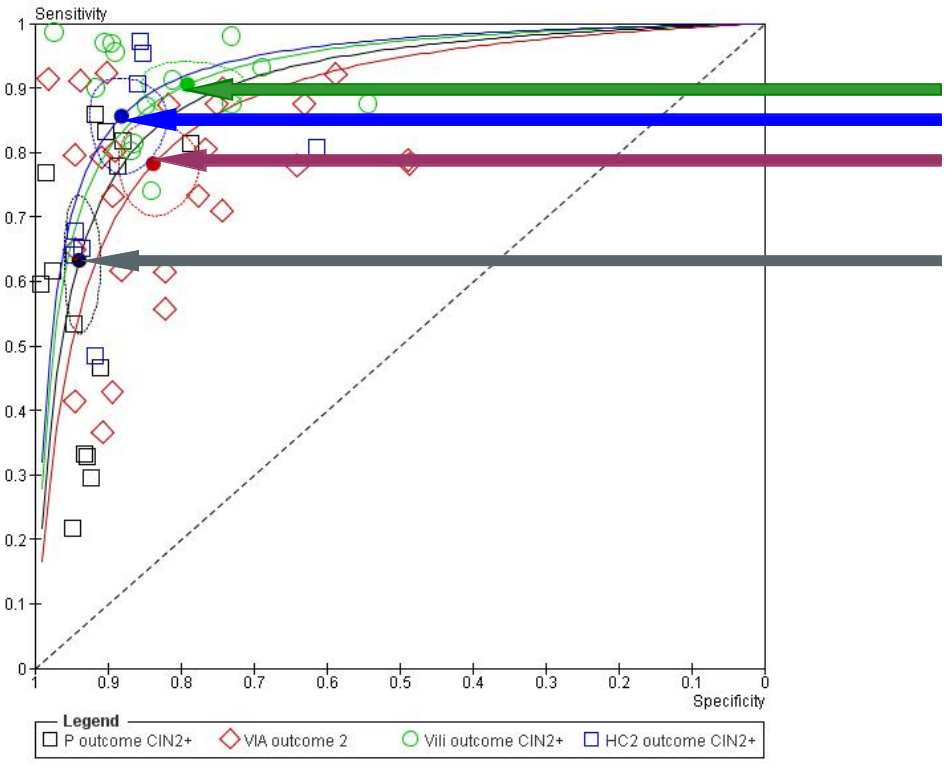
Accuracy of HC2 for CIN2+: HSROC/binormal model



Sensitivity: 81.1% (95% CI: 65.6-90.6%)

Specificity: 88.8% (95% CI: 82.5-90.1%)

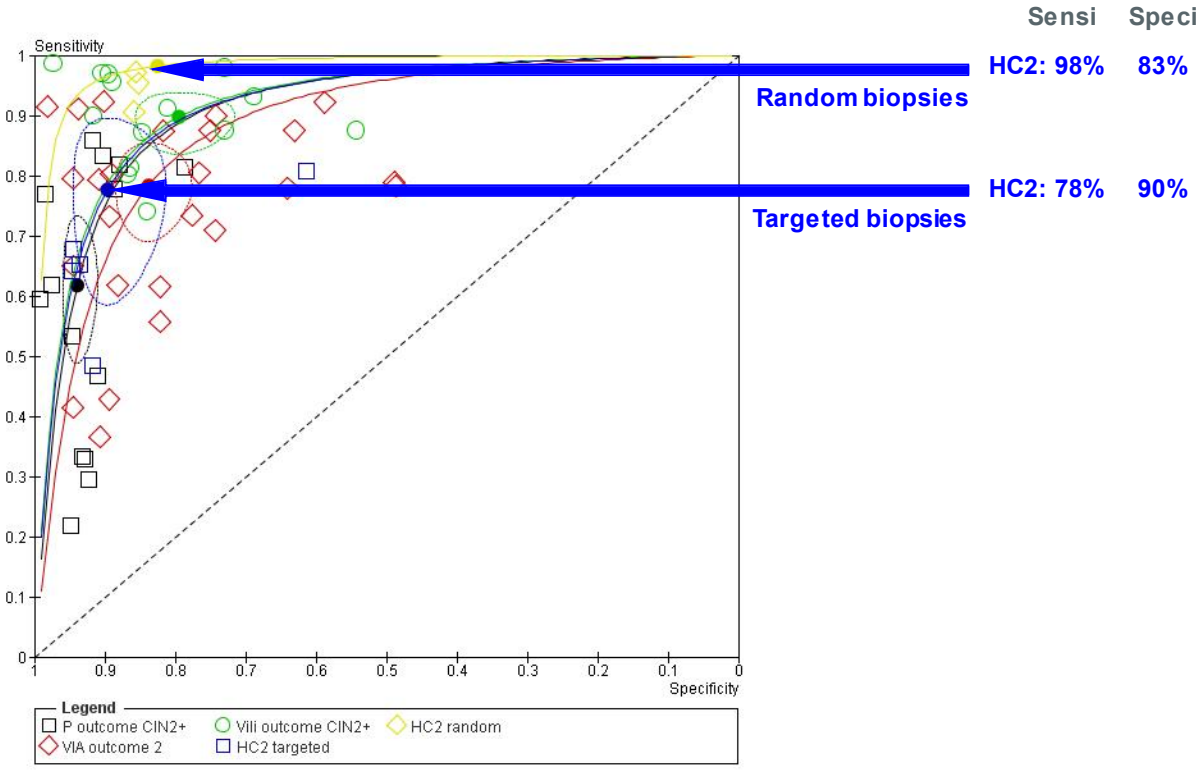
Accuracy of all tests for CIN2+: HSROC/binormal model



	Sensi	Speci
VILI:	90%	79%
HC2:	86%	88%
VIA:	78%	84%
Cyto:	60%	94%

Accuracy of all tests for CIN2+: HSROC/binormal model

Type of reference standard as covariate



Relative accuracy compared to VIA for CIN2+: HSROC/binormal model

Comparison	Relative sensitivity		Relative specificity	
VILI vs VIA	1.15	(1.10-1.21)	0.95	(0.93-0.96)
Pap smear vs VIA	0.77	(0.71-0.84)	1.12	(1.09-1.16)
HC2 random vs VIA	1.26	(1.17-1.35)	0.99	(0.97-1.00)
HC2 targeted vs VIA	1.00	(0.94-1.05)	1.07	(1.05-1.09)

Conclusion + sectional studies

- **Full verification allows assessment of absolute accuracy without verification bias**
- **Full verification of ten thousands of women unfeasible and implies high risk of gold standard misclassification**
- **Colposcopy-based confirmation inflates accuracy of visual screening tests**
- **Verification of screen test+ women only and assessment of relative accuracy more adequate design (Arbyn IJC 2009; Arbyn Lancet Oncol 2010)**

Conclusion + sectional studies (2)

- **Assessment of completely new screen method requires longitudinal randomised design**
- **Outcome: ↓ incidence of invasive cancer, ↓ mortality from cancer**
- **↓ CIN3+: ~acceptable as surrogate marker**

RCT in India: 1x/life time screening

hrHPV DNA-based:

- ↓ **Incidence of advanced CC (IIb+) (-53%)**
- ↓ **Mortality from CC cancer (-48%)**

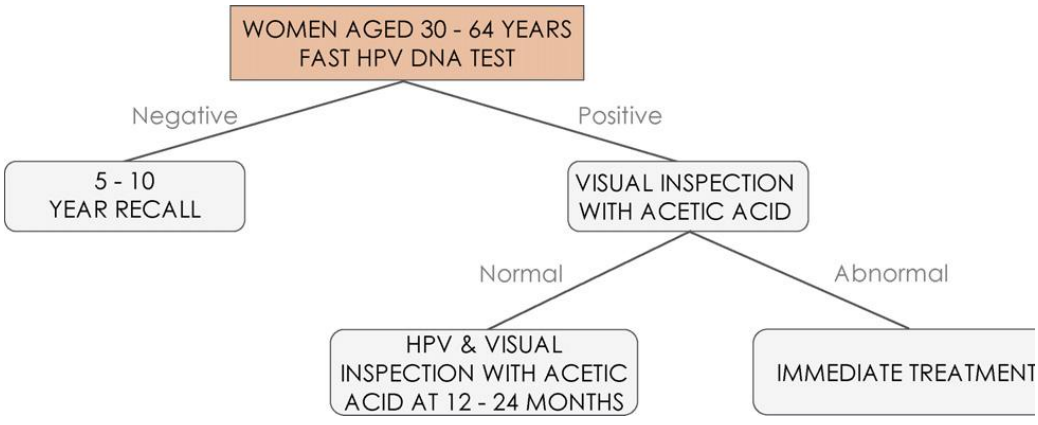
VIA and cytology screening:

- **no significant effect**

Sankar, NEJM 2007

Possible algorithm for developing countries

- **HPV screening with validated tests: good reproducibility, less ~ skilled human resources**



Cuzick, Arbyn, Vaccine, 2008

HPV testing of self-collected samples vs cytology

(RCT, Mexico, N=~20,000 women 25-65 Y, Lazcano-Ponce, Lancet 2011)

	HPV self (HC2, RLU>1)	cytology (LSIL+)	ratio
test+ rate	9.8%	0.4%	25.8
detection rate CIN2+	1.17%	0.34%	3.4
detection rate CIN3+	0.52%	0.16%	3.3
PPV CIN2+	12.20%	90.50%	0.13

Self-sampling is feasible and accepted

Sensitivity of self-HPV >> local cytology

Need for a specific HPV test (RLU>5, more specific assay, less cross-reactivity)

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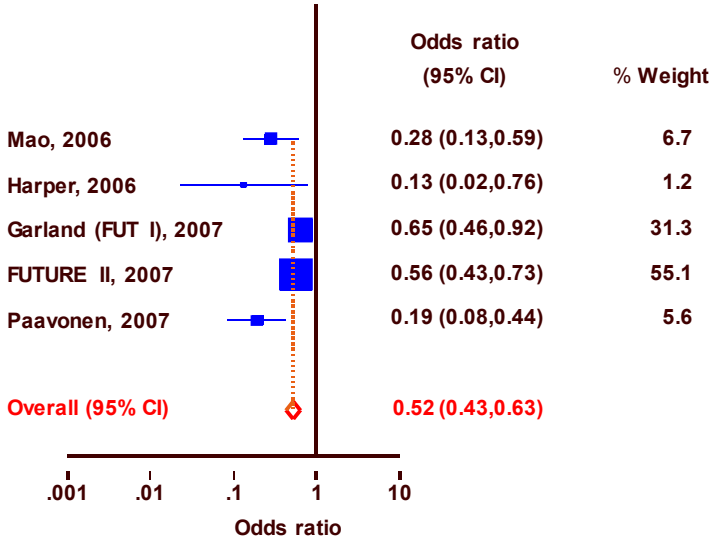
2. Cochrane review: prophylactic vaccination against HPV

New methods for testing

- Registered protocol
- Why a Cochrane review?
- Objectives
- Selection of reports
- Methods
- Previous reviews

Published Cochrane protocol: PG19

Rambout, Can Med Assoc J 2008
Protection against CIN2+ associated with HPV16/18
(Modified ITT analysis)



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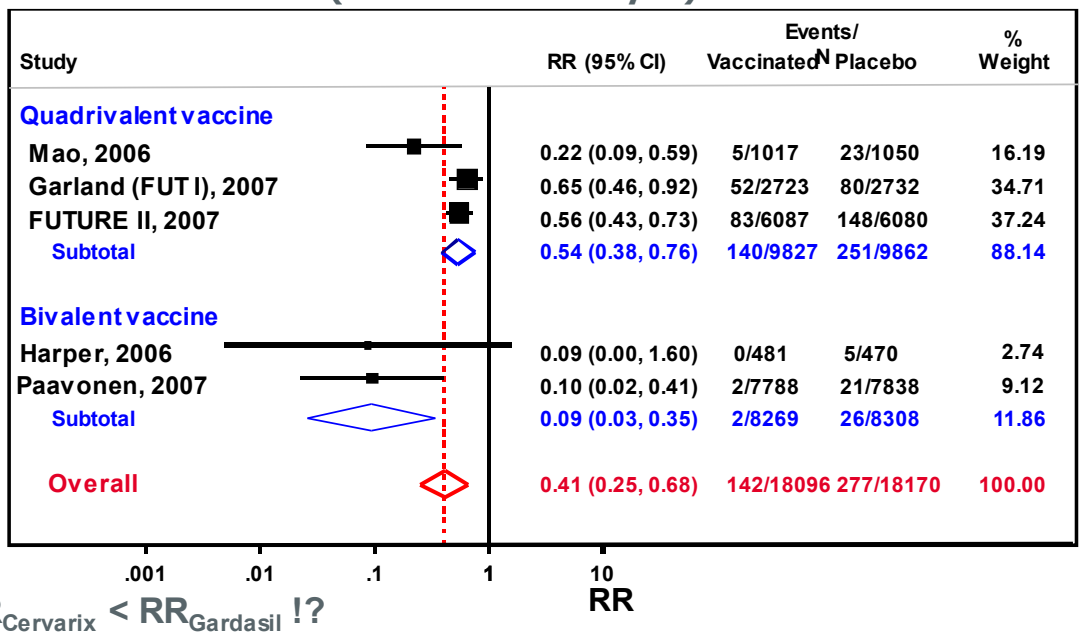

$RR_{Cervarix} < RR_{Gardasil}$!?

prevalent HPV16/18+ cases included in 4-valent >< 2-valent excluded

Unacceptable to pool in the same meta-analysis

Systematic reviews of RCTs?

- Need for uniformily defined outcomes
- Current reports cannot be pooled
- Health authorities should claim such reports
- Without uniform definitions, difficult to compare outcomes of trials and surveillance studies
- Standardisation in definitions, methods & designs required to answer pending key questions :
  - Duration of protection
  - Cross-protection
  - Type replacement

Why Cochrane Review

No reviews that present all available endpoints separated by initial HPV status (DNA, serology).

No previous reports by fine categories of age and time since sexual debut.

No reports on protection against re-infection

Objectives

•To evaluate the immunogenicity, clinical efficacy, and safety of prophylactic HPV vaccines in females.

•Protection against:

- •HPV infection for vaccine types and heterologous HPV types (incident and persistent) and reinfection
- •Cervical cancer and its precursors (CIN2+/AIS) ~ HPV status at enrollment.
- •Evaluation by fine age group and time since sexual debut categories is also planned.

Outcomes

- **Histologically confirmed high-grade cervical intraepithelial neoplasia (CIN2, CIN3, AIS), invasive cervical cancer**
  - **~ vaccine types, non vaccine types, unrelated to HPV**
- **Type-specific incident & persistent HPV infections (>=1 years)**
- **Immunogenicity**
  - **% women vaccinated that seroconverted after 3th dose**
  - **mean antibody level in IU**
- **Safety**

Time line

- **2011: publication of protocol**
- **Early 2012: development of grid with uniformly defined variables**
- **2012:**
  - **Interim report of published data**
  - **data request**
  - **statistical analyses**
- **2013: final report**

Acknowledgements

- Amy Walker, Cindy Simoens & Jolien Roelens
- European Commission:
  - PREHDICT
  - ECCG
- Belgian Foundation Against Cancer
- Gynaecological Cancer Cochrane Review Collaboration (Bath, UK)