



Asturias, 23 October

Role of Pathology in the  
Secondary Prevention of  
Cervical Cancer

# Supplements to the European Guidelines on Prevention of Cervical Cancer

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# New methods for testing

- LBC
- hrHPV testing:
  - Triage ASC-US, LSIL
  - Follow-up after treatment of hgCIN
  - 1ary screening
  - QC of cytology
- Molecular markers
  - HPV genotyping

# Liquid Compared With Conventional Cervical Cytology

*A Systematic Review and Meta-analysis*

*Marc Arbyn, MD, MSc, Christine Bergeron, MD, PhD, Paul Klinkhamer, MD,*

**CONCLUSION:** Liquid-based cervical cytology is neither more sensitive nor more specific for detection of high-grade cervical intraepithelial neoplasia compared with the conventional Pap test.

*(Obstet Gynecol 2008;111:167–77)*

# Comparison of Liquid-Based Cytology With Conventional Cytology for Detection of Cervical Cancer Precursors

A Randomized Controlled Trial

Siebers, Arbyn JAMA 2009, 302:1757-1764

“Conclusion: This study indicates that liquid-based cytology does not perform better than conventional Pap tests in terms of relative sensitivity and PPV for detection of cervical cancer precursors.”

## New trials: Pap vs LBC

- **Strander Eur J Cancer 2007 (Sweden)**
- **Sykes BJOG 2008 (New Zealand)**
- **Siebers, Arbyn JAMA 2009 (Netherlands)**

**Adding newest trials → conclusions  
of meta-analysis unchanged**

# LBC: logistical advantages

- Less unsatisfactory samples
- Microscopic screening is quicker (-1/3)
- Allows ancillary molecular testing: HPV testing
- Usable for biobanking

HPV testing in triage of ASCUS, LSIL

# *Triage with HPV testing from previous meta-analyses / ALTS*

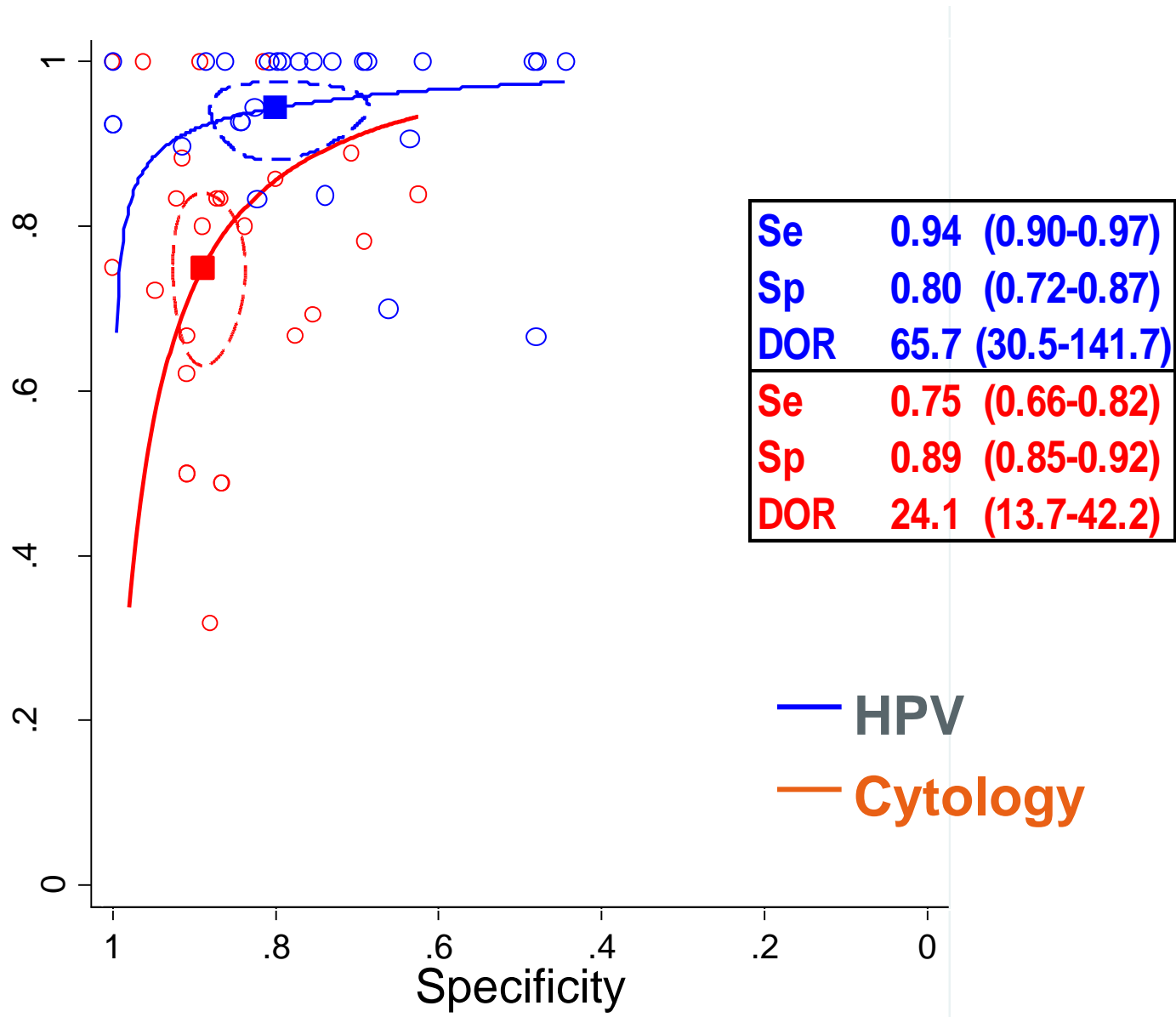
- **Triage of ASCUS:**
  - HC2 more sensitive and similarly specific compared to repeat cytology for detection of underlying CIN2+
- **Triage of LSIL:**
  - LSIL is an expression of HPV infection, and therefore very often HPV positive.
  - Might be useful in triage among older women (>40, >45, >50 years)
  - Research needed to assess triage by biomarkers

Arbyn et al, JNCI2004a &b, Gynecol Oncol 2005, Vaccine 2006; ALTS group AJOG2003a &b; Solomon Arch Pathol Lab Med 2009



HPV testing in follow-up after  
treatment of cervical precancer

# Prediction of recurrent CIN after T of CIN with HPV or Cytology



# HPV testing after treatment of CIN

- hrHPV DNA testing after treatment predicts residual or recurrent CIN with higher sensitivity than cytology or histology of the section margins
- Specificity of hrHPV DNA does not differ significantly from histology of section margins but is lower than repeat cytology
  - But: cave: heterogeneity of studies, methods, timing of follow-up visits
- Long term follow-up needed, since high sensitivity of HPV testing might be only valid to short term recurrent disease (Stander EJC 2007)

# HPV testing in QA of cervical cytology

## **Triage of women with equivocal or low-grade cervical cytology results: a meta-analysis of the HPV test positivity rate**

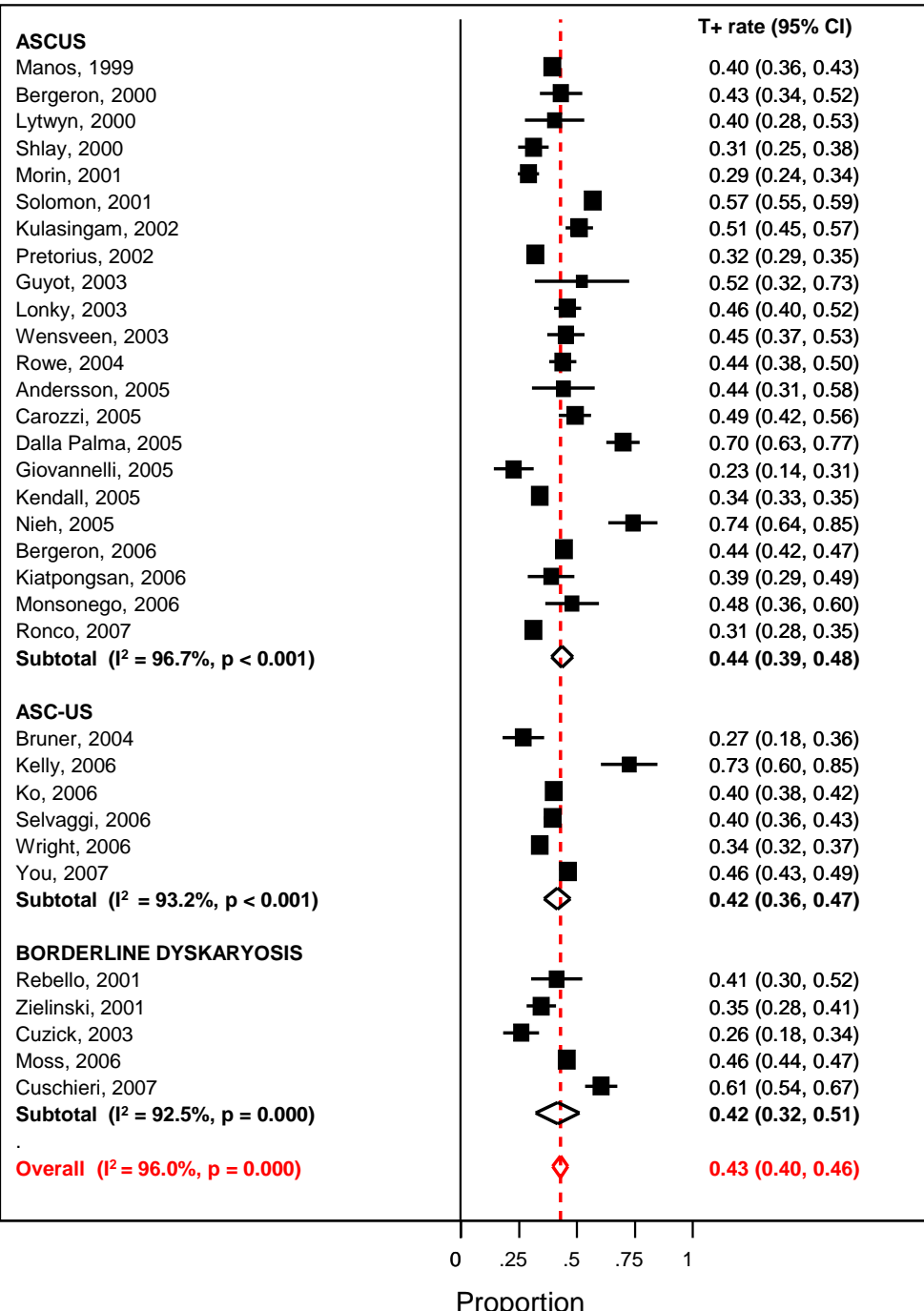
**Marc Arbyn<sup>a, b, c, \*</sup>, Pierre Martin-Hirsch<sup>d</sup>, Frank Buntinx<sup>e</sup>, Marc Van Ranst<sup>f</sup>,  
Evangelos Paraskevaïdis<sup>g</sup>, Joakim Dillner<sup>c, h</sup>**

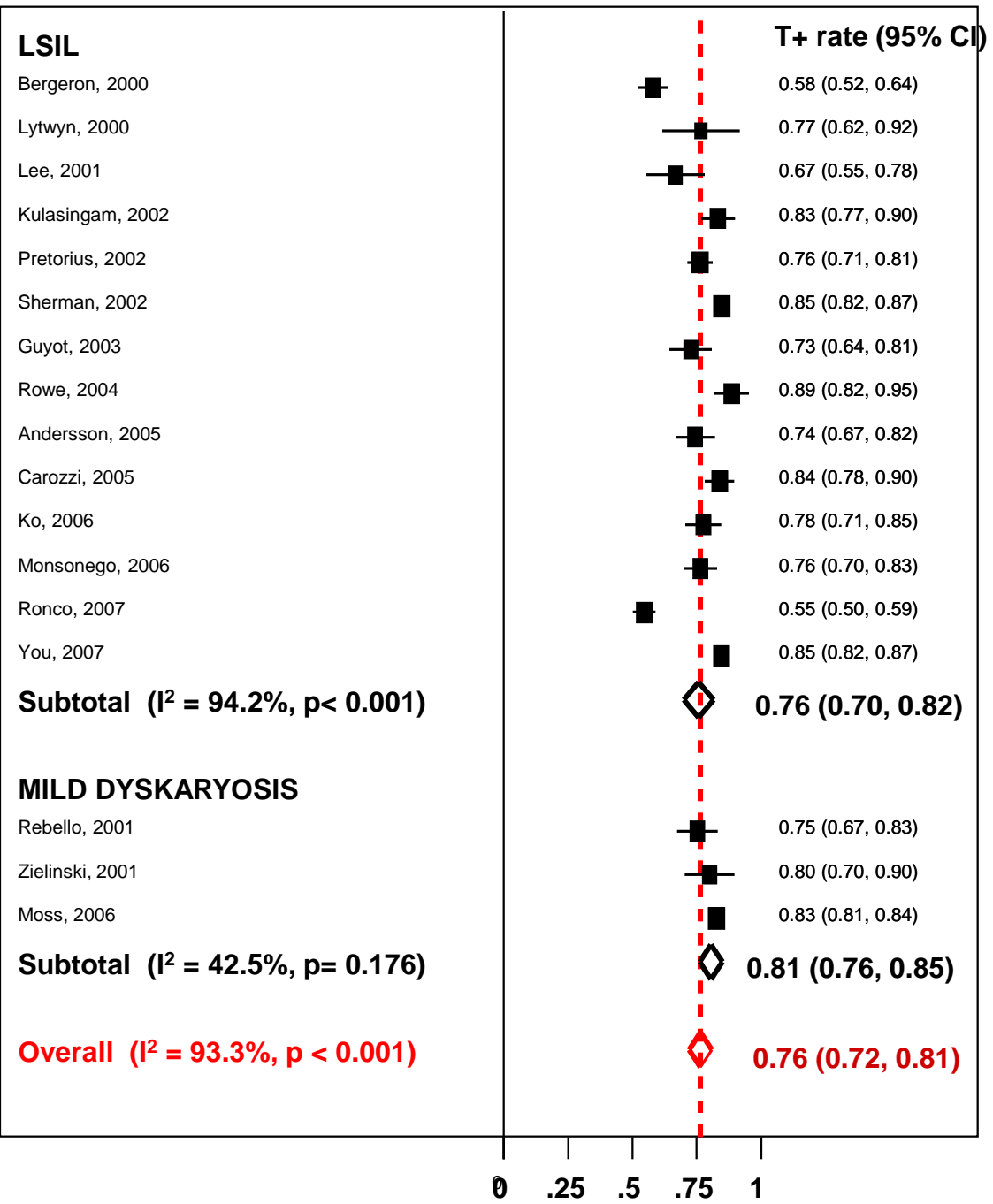
JOURNAL OF **Cellular AND Molecular Medicine**  
A JOURNAL OF TRANSLATIONAL MEDICINE

# Triage of atypical cytology with HC2

## T+ rate

- ASCUS (22 studies)
  - 44% (CI: 39-48%)
- ASC-US (6)
  - 42% (CI: 36-47%)
- Borderline dyskaryosis (5)
  - 42% (CI: 32-51%)
- Overall:
  - 43% (CI: 40-46%)





# Triage of LSIL/mild

## T+ rate of HC2

- LSIL (14 studies)
  - 76% (CI: 70-82%)
- Mild dyskaryosis (3)
  - 81% (CI: 76-85%)

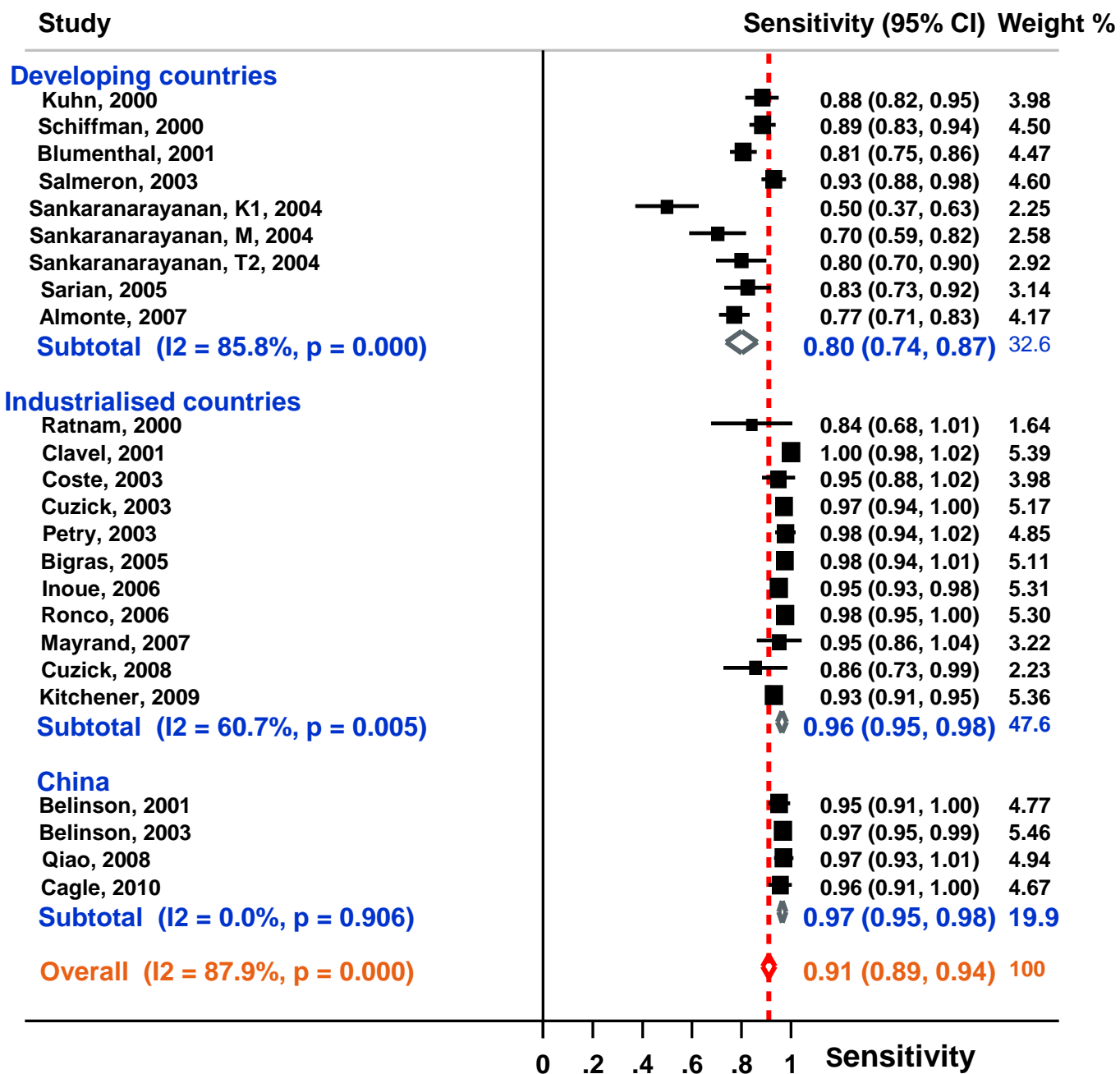
# Conclusion:

**HPV testing could be used in  
quality control of cytology**



**HPV testing in 1ary screening:  
Accuracy to detect hgCIN  
(cross-sectional studies)**

# Sensitivity of HC2 to detect CIN2+ in 1ary screening



# Accuracy of HC2 to detect high-grade CIN

## 1. Absolute sensitivity:

- CIN2+: 91% (95% CI: 88.6-93.6%) [24 studies]
- CIN3+: 98% (95% CI: 96.4-98.9%) [7 studies]

## 2. Specificity:

- CIN2+: 88% (95% CI: 86.7-90.2%) [23 studies]

## 3. Relative sensitivity vs cytology

- 1.23 (1.14-1.33) if ASCUS+; 1.38(1.25-1.52) if LSIL+

## 4. Relative specificity vs cytology

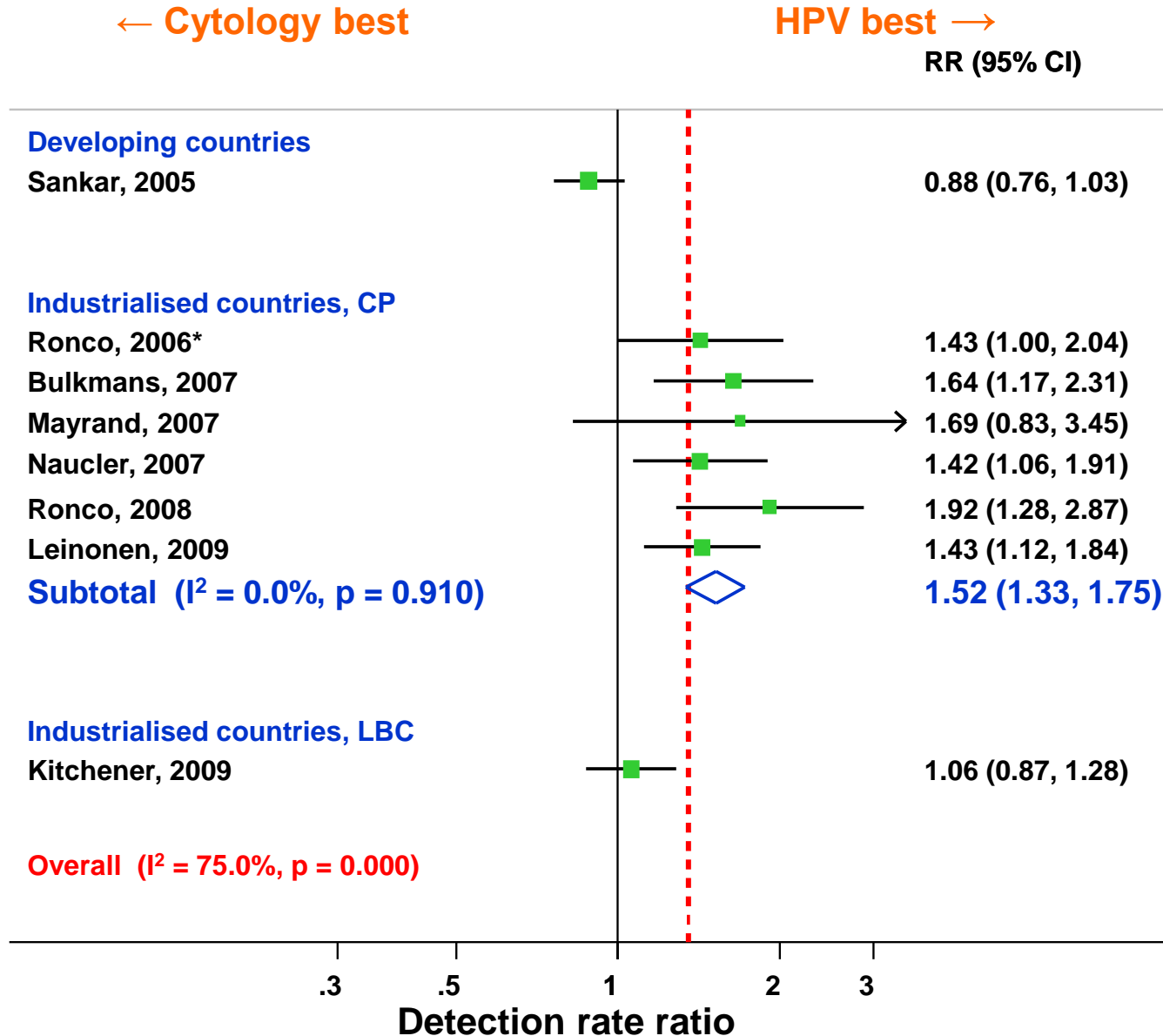
- 0.97(0.96-0.98) if ASCUS+; 0.91(0.90-0.92) if LSIL+

# Randomised trials

## Study characteristics (2)

- **Various follow-up protocols for screen+**
- **Sometimes varying by age**
- **Different levels of blinding of gold standard verification**
- **For all trials: PPV, DR of CIN2, CIN3/AIS+**
- **4 trials: CIN3+ at 2<sup>nd</sup> screening round**
- **1 trial: I & M from cervical cancer**

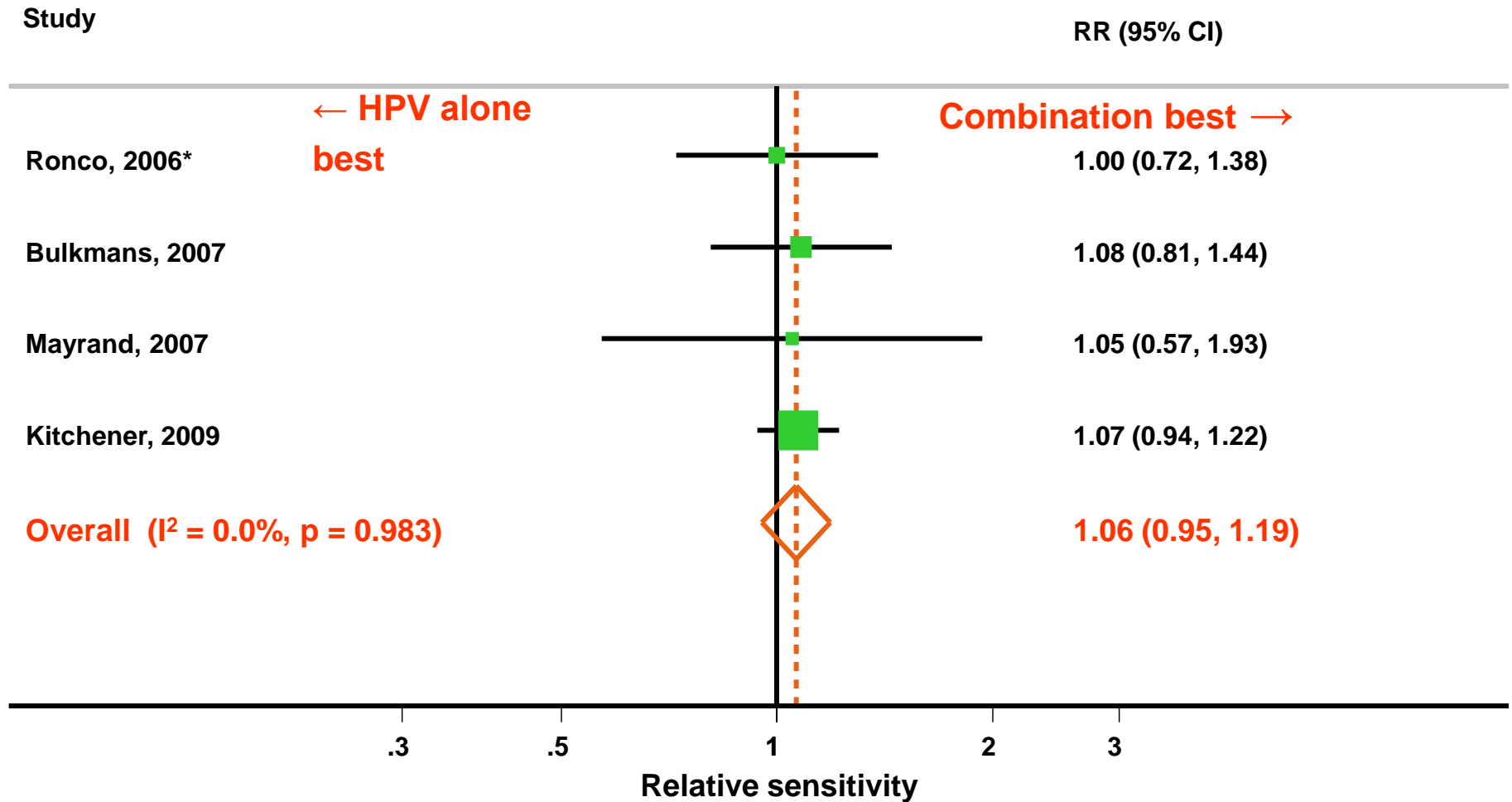
# Baseline results: relative sensitivity for CIN2+



\*Age  $\geq 35$  years

# (HPV & cyto) vs HPV alone

Detection of CIN2+, 1st screening round

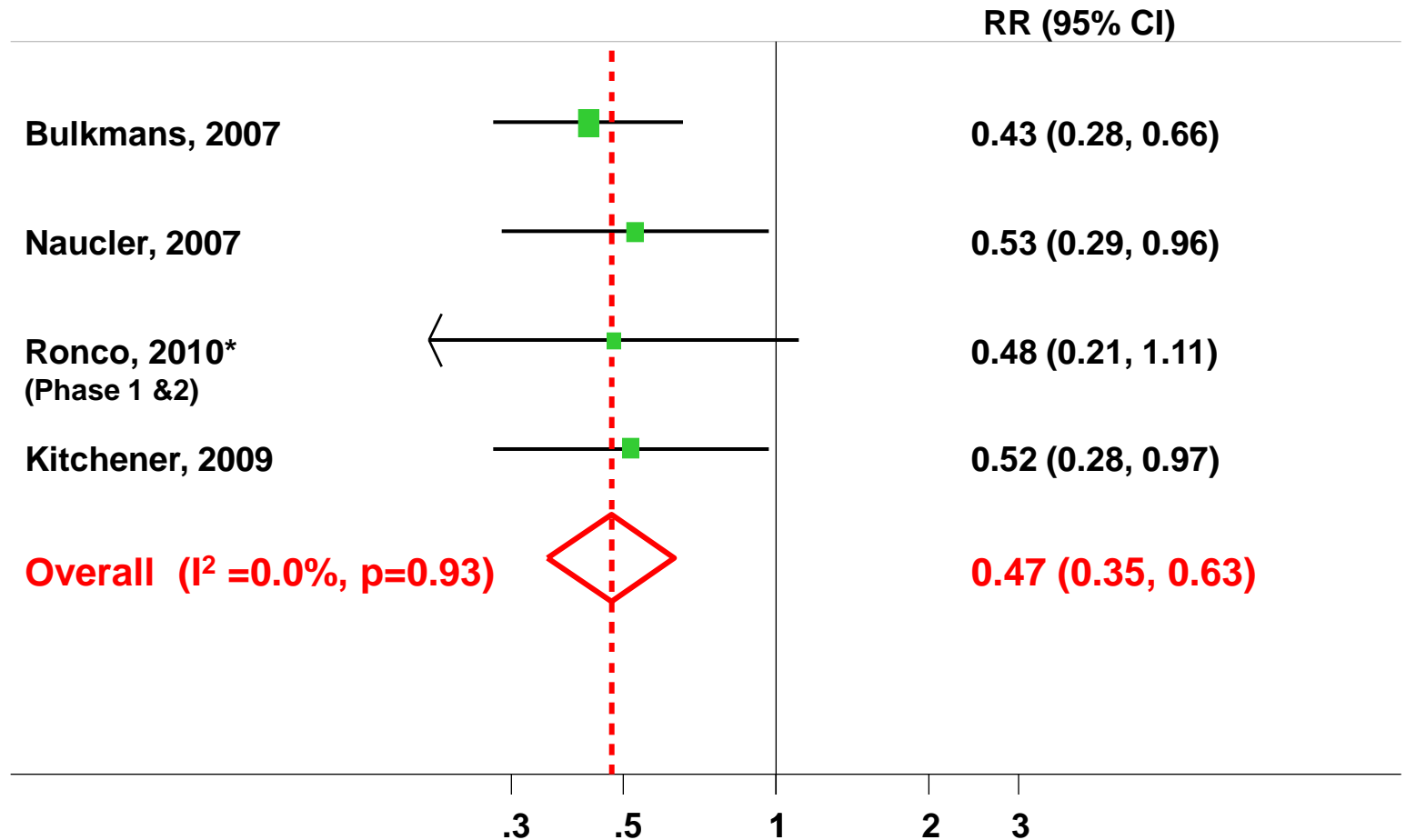


Arbyn, Lancet Oncol 2009

\*Age  $\geq 35$  years

# HPV- vs cytology based screening

## CIN3+ in 2<sup>nd</sup> round among in women with negative screen test at baseline



Arbyn, Lancet Oncol 2009

Ronco, Lancet Oncol 2010

Detection rate ratio

\*Age  $\geq 35$  years



# Longitudinal results RCTs: HPV vs cyto screening

## Incidence of cervical cancer

- **Italian trial: HPV vs. Cyto group: 0 vs 9 cases**
- **Swedish RCT: 1 vs 5 cases**
- **Dutch trial: sign reduction in HPV arm**
- **Indian trial: -53% incidence (II+), -47% mortality**

## Conclusion: hrHPV DNA testing

- **More sensitive but less specific than cyto to detect CIN2+ & CIN3+**
- **Accuracy estimates less variable than cytology**
- **Combined screening (cyto + HPV) does not increase sensitivity but decreases specificity and generates costs & adverse effects**
- **Less CIN3+, less invasive cancer among women with negative HPV test at base line**

## **Conclusion: hrHPV DNA testing**

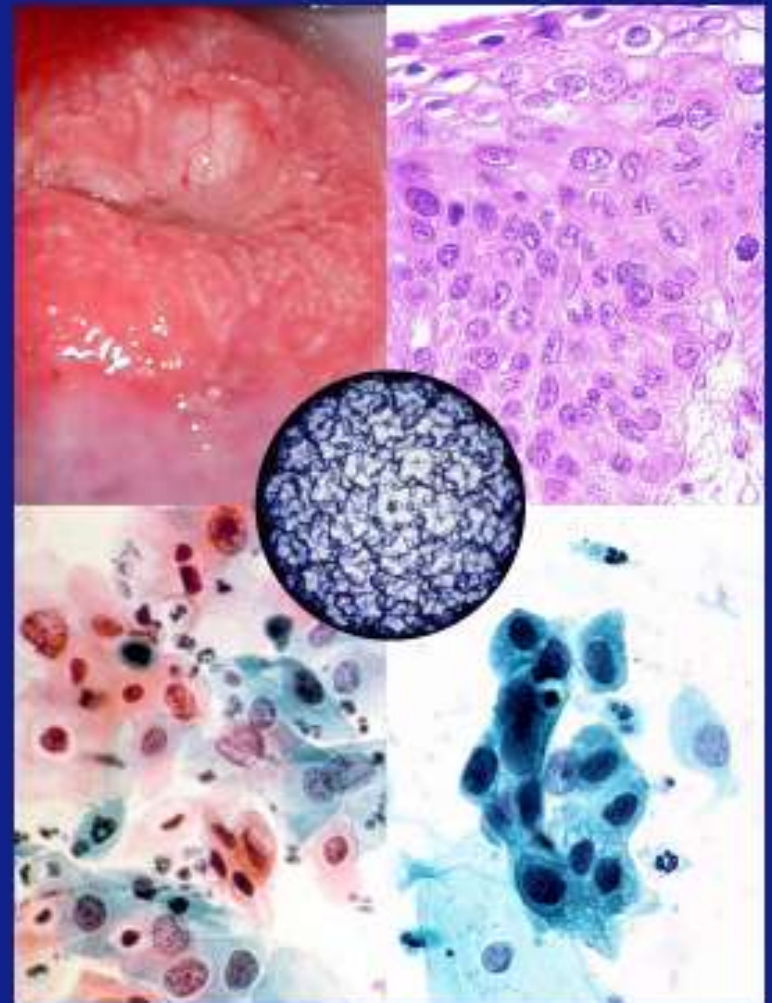
- **HPV screening with validated tests: good reproducibility, less ~ skilled human resources**
- **HPV screening will allow extending intervals, but this will require a high level of organisation otherwise explosion of follow-up examinations**
- **Reduced specificity requires appropriate triage (cytology, typing 16/18, p16, RNA-5 types, persistent (type-specific) infection**

## Conclusion: hrHPV DNA testing

- **Whatever the choice of future 1ary screening : the main factor of success will be the availability of a good organised and monitored system**

# Supplements to EU guidelines on HPV screening and vaccination

- Ready by end 2011...



**European guidelines for quality assurance  
in cervical cancer screening** *Second Edition*



European Commission

# Acknowledgements

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