



Sexual and reproductive health and rights
today and tomorrow

*ICRH celebrates 20 years of SRHR research,
training and advocacy*

4 & 5 December 2014, Het Pand, Gent (Belgium)

HPV testing in cervical cancer screening Evidence and potential use on self-samples

M Arbyn¹

(1) Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium;

Content

- **Evidence of HPV testing in primary screening**
 - **Summary of systematic reviews**
 - **Which tests are clinically validated?**
 - **How to manage hrHPV+ women?**
- **HPV testing on self-collected samples**
 - **Accuracy to detect cervical precancer**
 - **Attendance among non-responders in regular screening**



ELSEVIER

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Review

Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer

Marc Arbyn^{a,b,*}, Guglielmo Ronco^c, Ahti Anttila^d, Chris J.L.M. Meijer^e, Mario Poljak^f, Gina Ogilvie^g, George Koliopoulos^h, Pontus Nauclerⁱ, Rengaswamy Sankaranarayanan^j, Julian Peto^k

Lancet 2014; 383: 524-32

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

*Guglielmo Ronco, Joakim Dillner, K Miriam Elfström, Sara Tunesi, Peter J F Snijders, Marc Arbyn, Henry Kitchener, Nereo Segnan, Clare Gilham, Paolo Giorgi-Rossi, Johannes Berkhof, Julian Peto, Chris J L M Meijer, and the International HPV screening working group**

INDICATIONS OF HPV TESTING IN EUROPE (EFC-2013)

Triage ASC-US

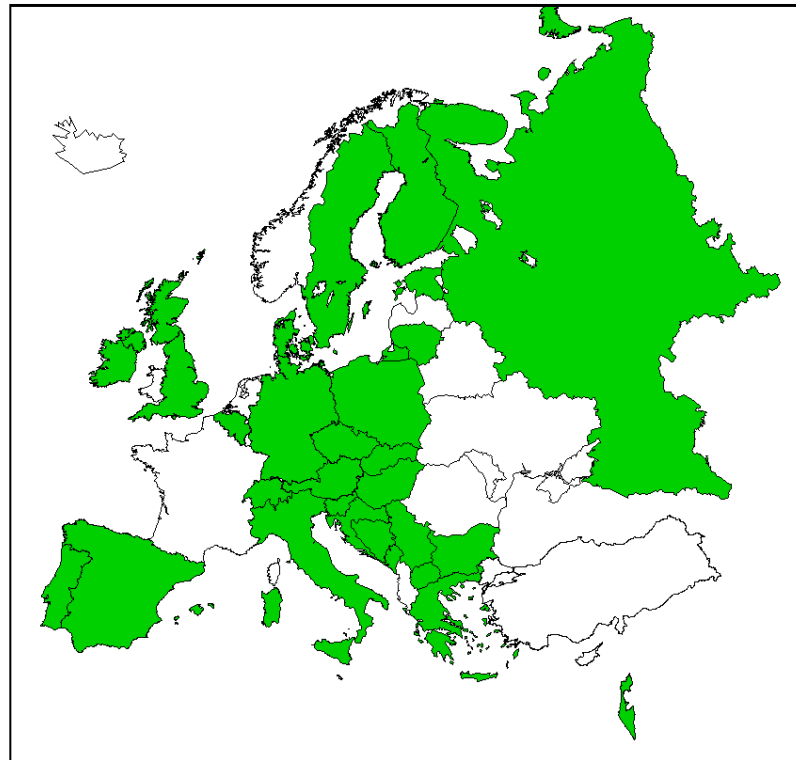


Triage LSIL



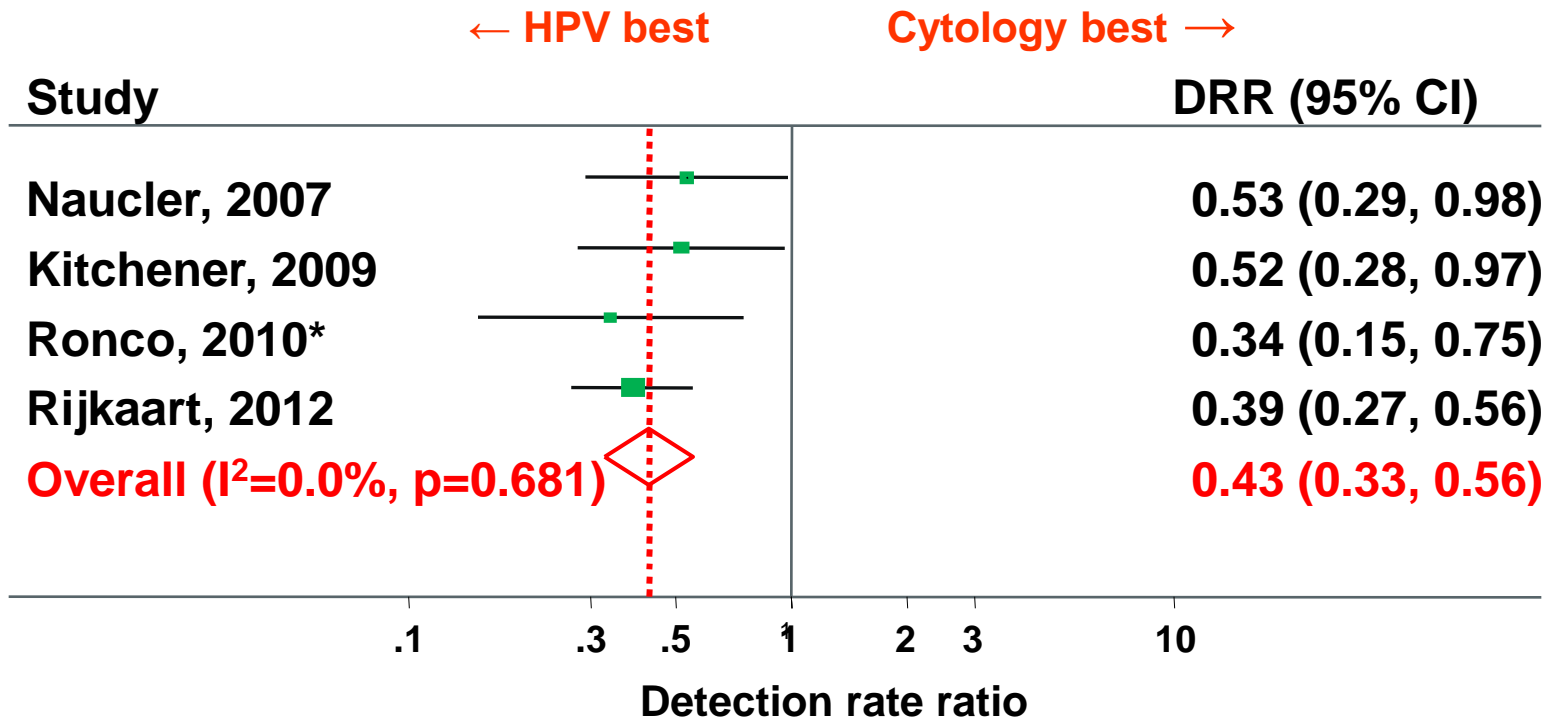
INDICATIONS OF HPV TESTING IN EUROPE (2)

Follow-up after treatment

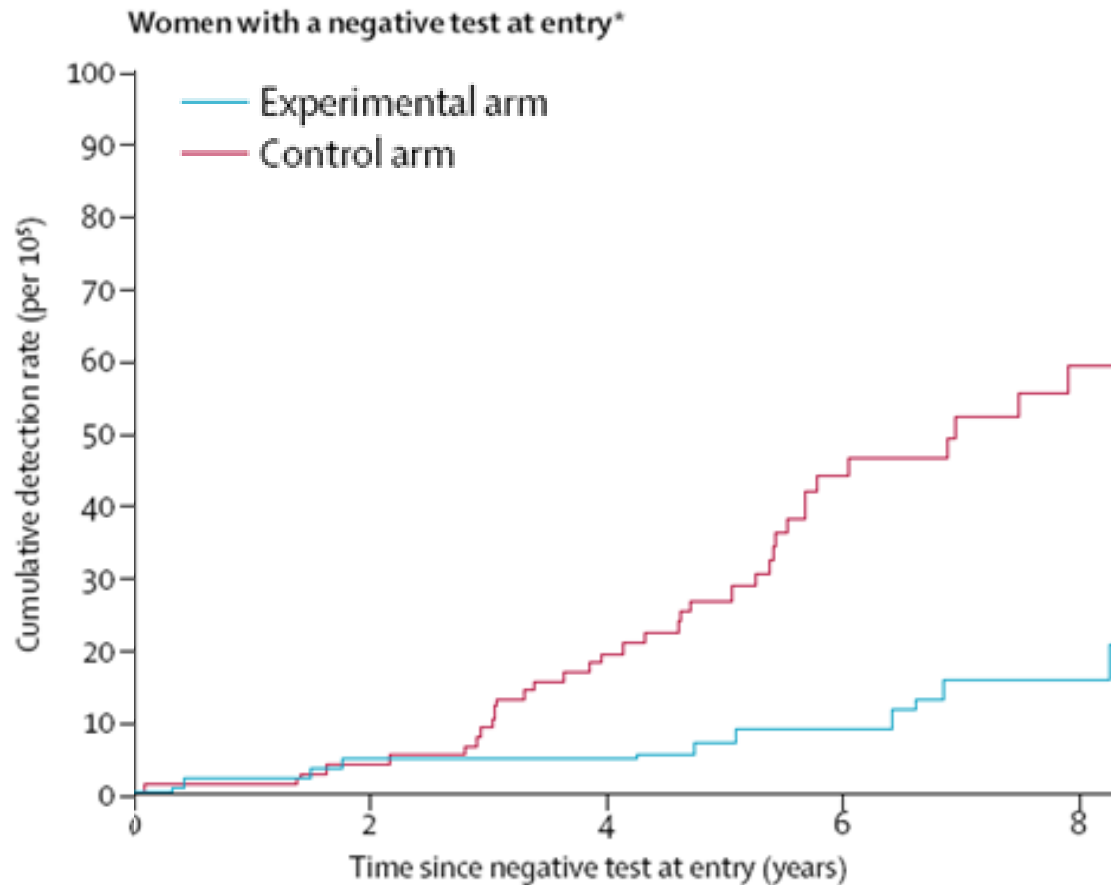


Randomised trials
Primary screening for cervical cancer:
HPV- vs cytology

Reduction in cumulative incidence of CIN3+ in 2nd round if HPV-negative vs cytology-negative women at baseline

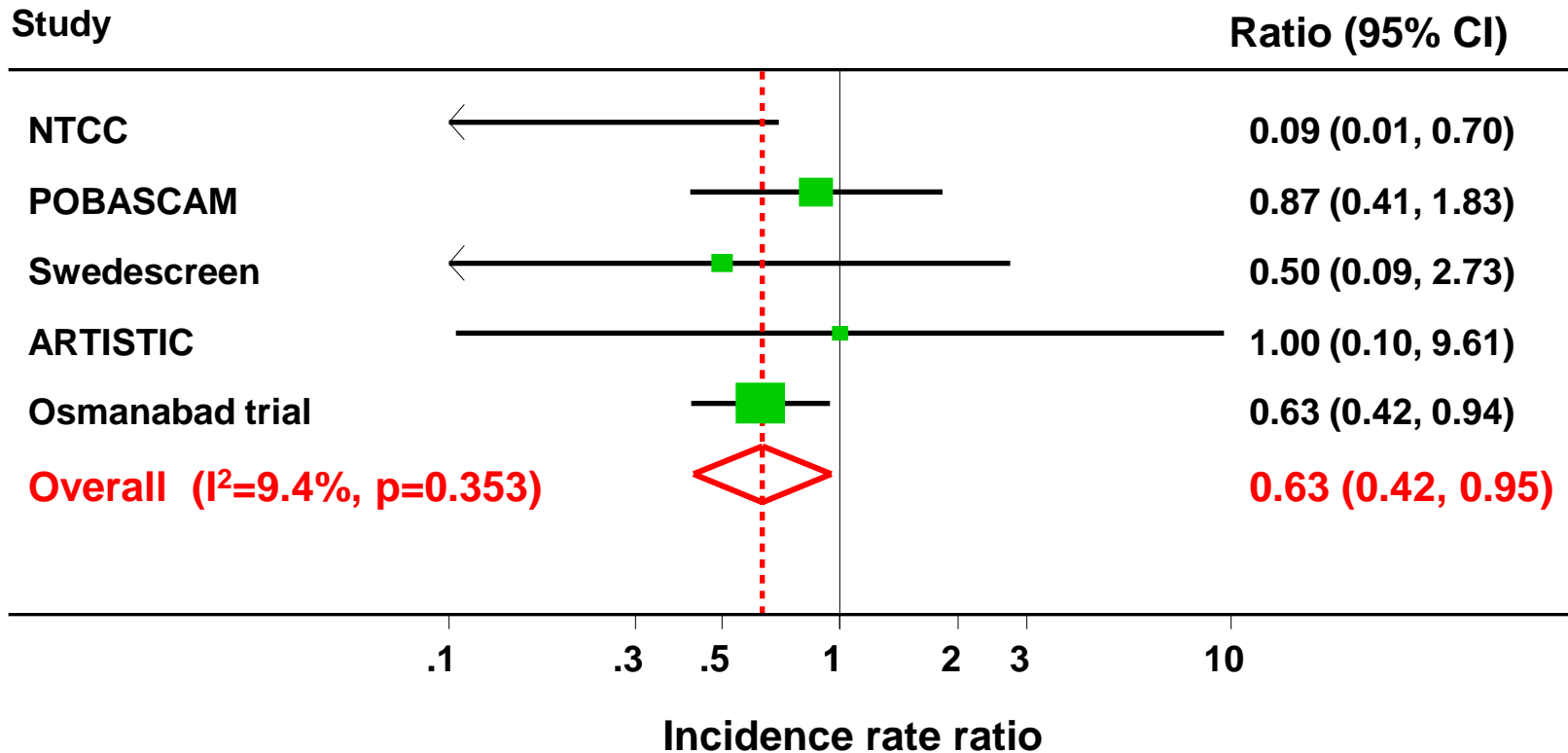


Cumulative detection of invasive cancer after a negative screen test (4 European RCTs)



RCT HPV- versus cytology-based screening: Incidence rate ratio of advanced cervical cancer

All women randomised



Which tests clinically validated for primary screening?

- **See special issue of Vaccine 2012**
- **See presentation of VALGENT studies**

Triage of HPV+ women

Need for triage of HPV+ women

- **Evidence: HPV testing more effective than cytology screening but identifies more women as being test positive.**
- **By increasing screening interval & effective triage => longitudinal specificity of HPV testing can become better than with frequent cytology**
- **Systematic review of 25 triage scenarios**

Conclusions: triage of HPV+ women

- **Twice cytology is good compromise assuring acceptable safety & reasonable referral rate**
- **HPV16 &18 added to cytology at baseline is preferred if compliance with next triage visit is poor**
- **No triage method is absolutely safe at long term**
- **Screening interval for triage negative women not longer than 5 years**
- **Promising: p16, double staining, methylation markers**
- **! Cytology triage ~ quality of local cytology**
- **! Preferences ~ resources & (cumulative) background risk**

hrHPV testing on self-collected samples

Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis

M Arbyn, F Verdoodt, PJF Snijders, V Verhoef, E Suonio, L Dillner, S Minozzi, C Bellisario, R Banzi, FH Zhao, P Hillemanns, A Anttila

SYSTEMATIC REVIEW

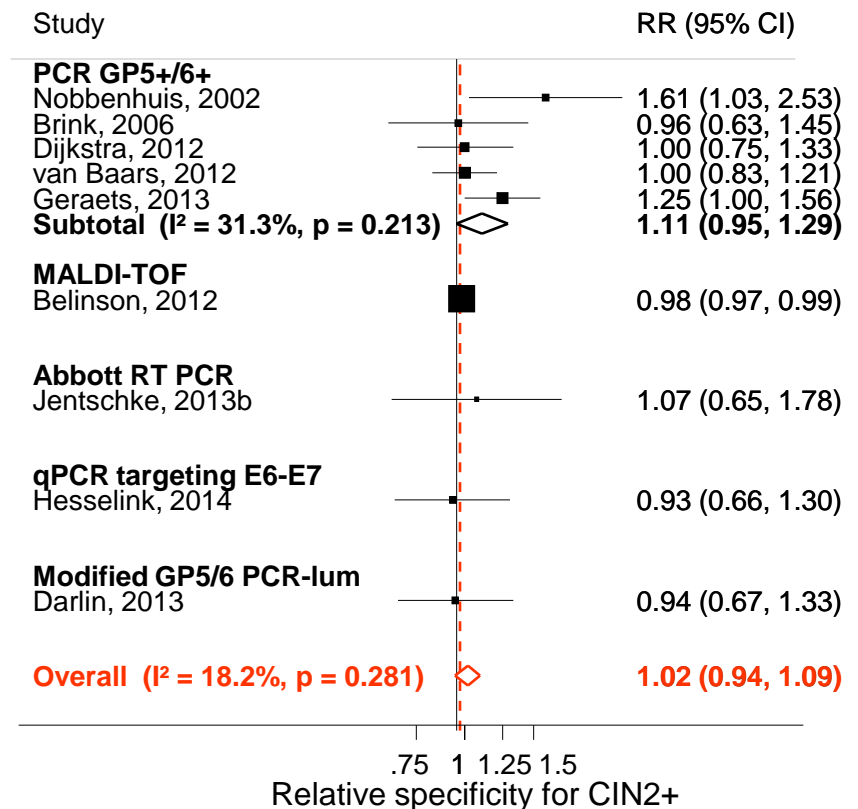
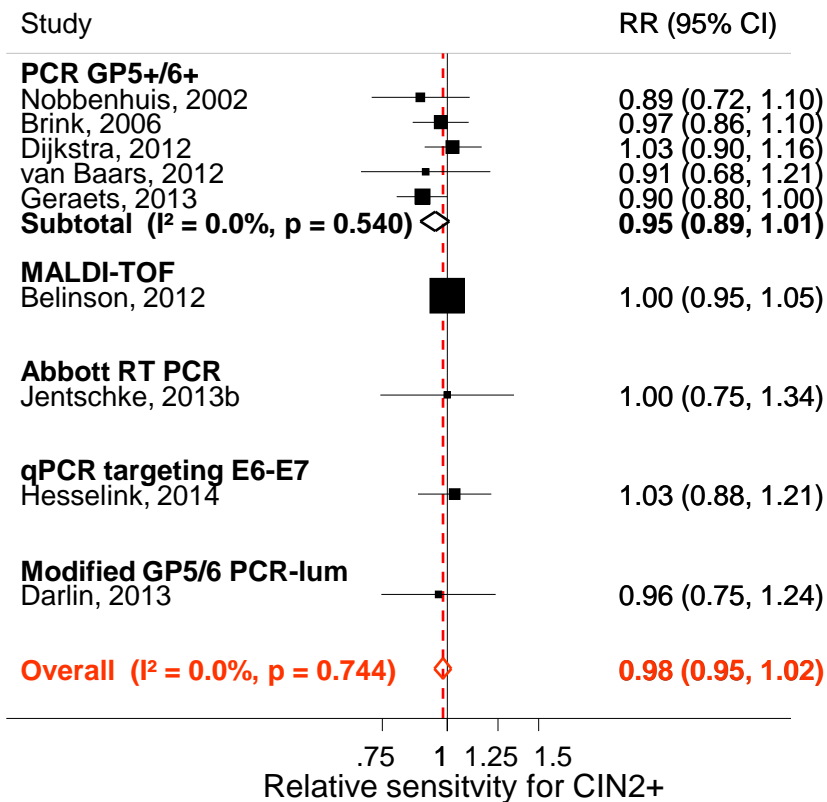
Self-collected HPV Testing Improves Participation in Cervical Cancer Screening: A Systematic Review and Meta-analysis

Can J Public Health 2013;104(2):e159-e166

CS Racey et al

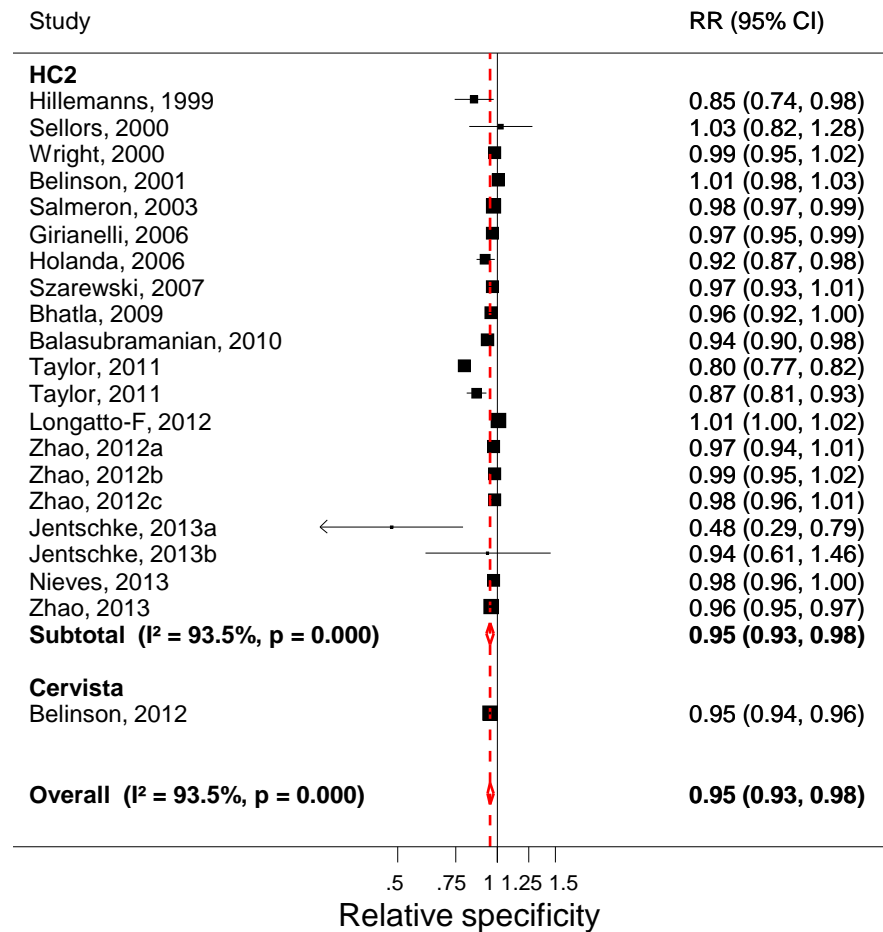
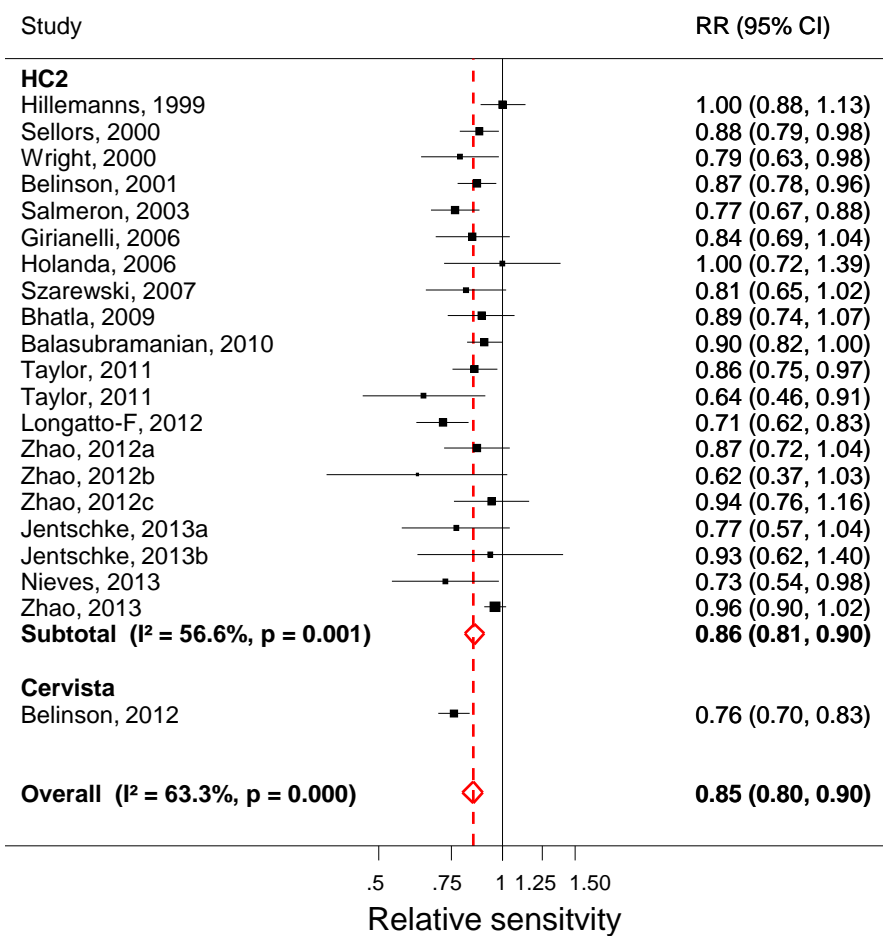
Relative sensitivity and specificity for CIN2+ hrHPV DNA testing of self- vs clinician-collected

Validated PCRs + MALDI-TOF



Relative sensitivity and specificity for CIN2+ hrHPV DNA testing of self- vs clinician-collected

Signal amplification



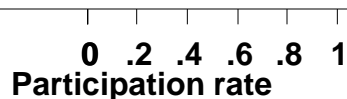
hrHPV testing on self-samples

- **Signal amplification tests less sensitive and specific on self- compared to clinician samples**
- **Validated PCR assays: similar sensitivity and specificity on self- as on clinician samples**
- **Guidelines NL:**
 - **Most cost-effective & user friendly test which fulfils Meijer criteria & which has similar accuracy on self- vs clinician samples**

RCT: participation if self-kit offered vs conventional reminder (per protocol)

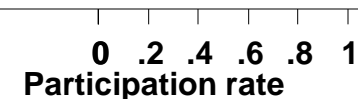
Self-sampling arm

Study	Proportion (95% CI)
Mail to all	
Bais, 2007	0.31 (0.29, 0.33)
Gok, 2010	0.28 (0.27, 0.28)
Giorgi-Rossi, 2011	0.17 (0.14, 0.20)
Piana, 2011	0.26 (0.25, 0.28)
Szarewski, 2011	0.06 (0.05, 0.08)
Virtanen, 2011	0.28 (0.26, 0.29)
Wikström, 2011	0.34 (0.32, 0.36)
Gok, 2012	0.31 (0.30, 0.31)
Darlin, 2013	0.15 (0.13, 0.17)
Sancho-Garnier, 2013	0.18 (0.17, 0.19)
Haguenoer, 2014	0.16 (0.14, 0.18)
Total (I²=99.3%,p=0.000)	0.22 (0.18, 0.26)
Mail if request	
Giorgi-Rossi, 2011	0.06 (0.04, 0.08)
Broberg, 2014	0.12 (0.10, 0.14)
Total (I²=94.1%,p=0.000)	0.09 (0.04, 0.16)



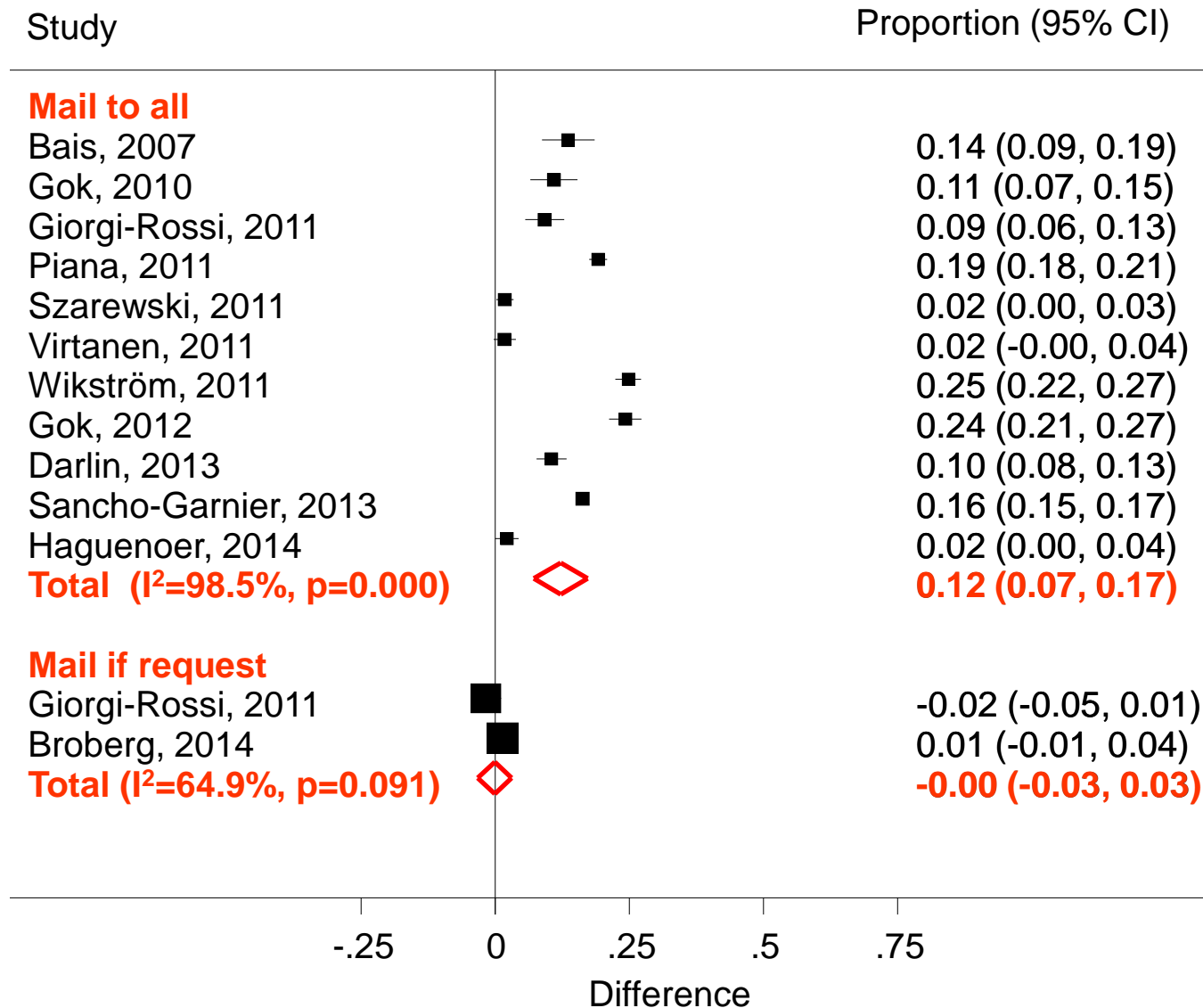
Control arm

Study	Proportion (95% CI)
Mail to all	
Bais, 2007	0.18 (0.14, 0.23)
Gok, 2010	0.17 (0.13, 0.21)
Giorgi-Rossi, 2011	0.14 (0.10, 0.18)
Piana, 2011	0.07 (0.06, 0.08)
Szarewski, 2011	0.05 (0.04, 0.06)
Virtanen, 2011	0.26 (0.25, 0.27)
Wikström, 2011	0.09 (0.08, 0.10)
Gok, 2012	0.07 (0.04, 0.10)
Darlin, 2013	0.04 (0.03, 0.06)
Sancho-Garnier, 2013	0.02 (0.02, 0.02)
Haguenoer, 2014	0.14 (0.12, 0.15)
Total (I²=99.6%,p=0.000)	0.10 (0.05, 0.17)
Mail if request	
Giorgi-Rossi, 2011	0.14 (0.10, 0.18)
Broberg, 2014	0.11 (0.10, 0.12)
Total (I²=68.7%,p=0.074)	0.12 (0.09, 0.15)



RCT: Difference in participation rate (PP)

$(P_{\text{self}} - P_{\text{control}})$



HPV on self-samples: conclusion

- HPV testing on self-samples as accurate as on clinical samples if validated PCR assays are used
- No evidence for a self-sample device effect
- Sending self-sampling kits is more effective than conventional reminders to reach non-attenders
- Increase in coverage varies widely among studies
- Compliance of screen-positive women tends to be lower in self-sampling arm (data not shown)
- Cytology triage of self-sample HPV+ women requires a visit, methylation markers are promising for triage on the self-sample
- Detection rate of CIN2+ higher in self-sampling arm (data not shown)
- Success of self-sampling requires careful planning and pilot testing in local settings before national roll-out

Discussion & Conclusions: HPV-based screening

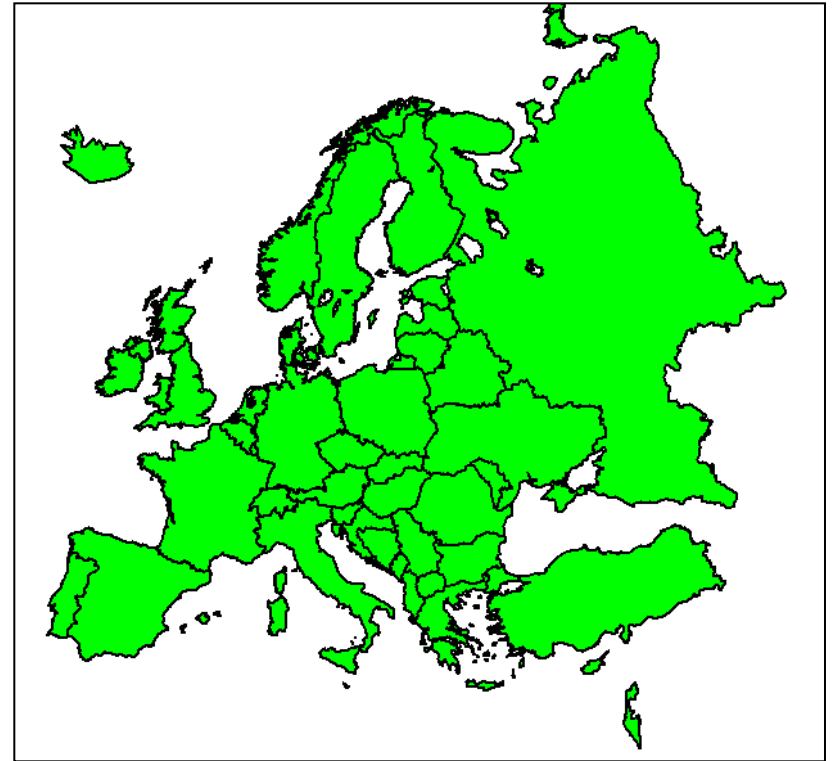
- **Strong evidence that HPV-based screening is more effective than cytology-based screening among women age 30 year or older**
- **Interval can be extended safely to 5 years or more**
- **For women <30 years: cytology-based (EU, USA guidelines).**
- **? HPV-screening among women <30 years using more specific marker ?? Not needed if good vaccination coverage**
- **Only validated hrHPV tests**
- **HPV-screening more cost-effective (increased efficacy, increased interval, lower cost prices of HPV assays)**
- **Appropriate triage needed: reflex & 1-year repeat test, other markers**
- **Implementation will require a well-organised and monitored system**
- **HPV testing can be done on self-samples**

Where is 1ary HPV screening applied

Today



Next 3 decades?



Acknowledgements

- **Freija Verdoodt: Unit Cancer Epidemiology (WIV)**
- **European Commission: ECCG, COHEARH (FP7)**
- **International Agency for Research in Cancer**
- **Belgian Foundation Against Cancer**
- **European Federation of Colposcopy**
- **Gynaecological Cancer Cochrane Review Collaboration (Bath, UK)**
- **National Institute of Public Health (NL)**
- **German guidelines Programme**