Safety of HPV Vaccination Compared to Cervical Screening

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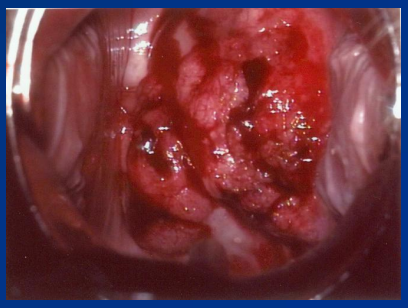
Selected milestones

- Organised cervical screening programs
- HSV2
- Harald zur Hausen et al.
- HPV disease burden
- VLPs
- Phase III HPV vaccination trials
- Phase IV CRT
- Implementation of HPV vaccination

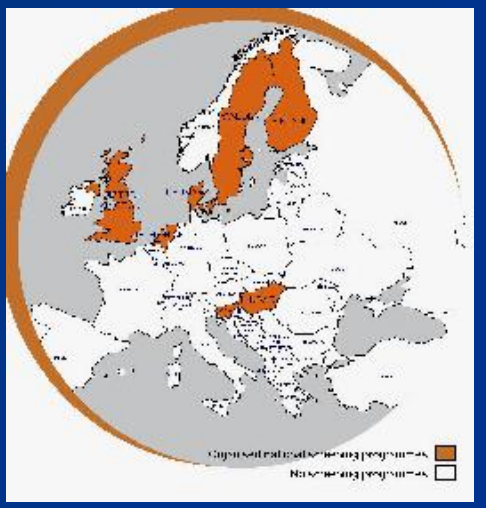


Prevention of cervical neoplasia

- Secondary prevention
  - Early detection by screening
    - Disease burden has shifted to management of CIN
- Primary prevention
  - Vaccination
    - Eradication of disease

Secondary prevention

- Pap test is >70 years old
- Cervical screening programs have reduced cervical cancer rates
- Surprisingly few countries have organised screening programs

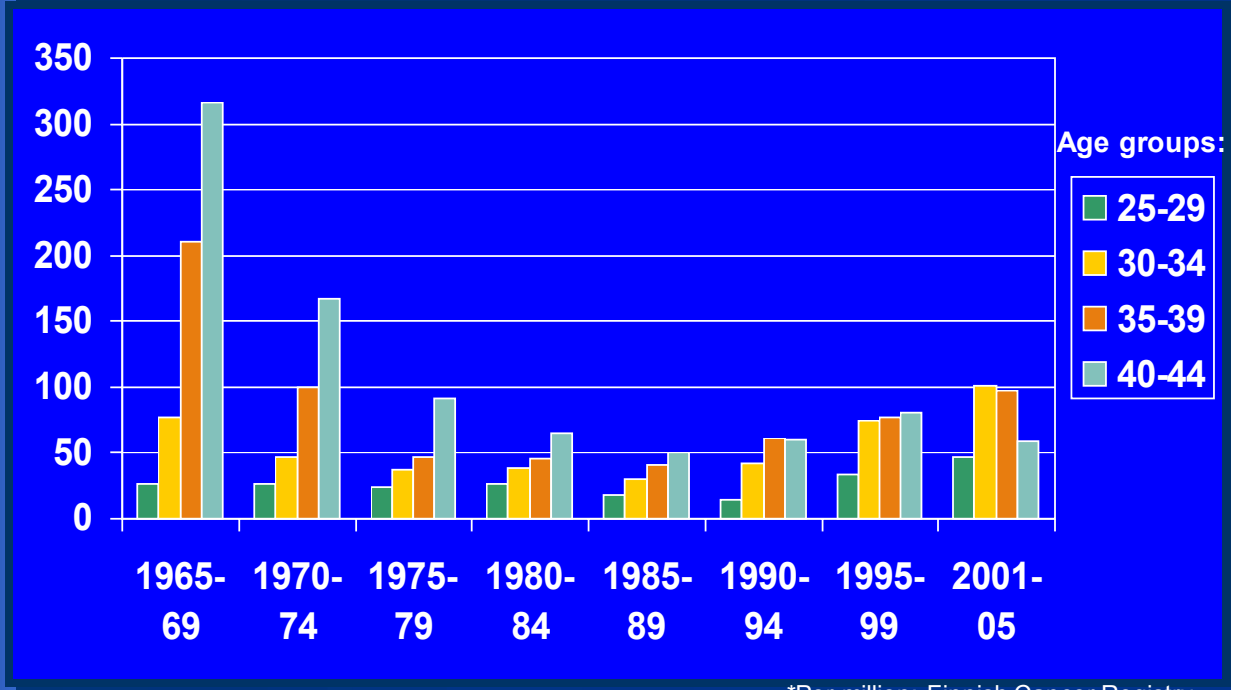


Cervical Cancer Screening Programs in Nordic countries

Finland	Sweden	Norway	Denmark	Iceland
1963*	1964	1995	1962	1964
5**	3	3	3-5	2
30-60***	20-60	25-70	23-75	20-69

*Year started; **Screening interval, yrs; ***Age range screened; from age 25 in Helsinki metropolitan area

Age-specific incidence of cervical cancer in Finland*



*Per million; Finnish Cancer Registry

Attendance to Screening Program: Recent data from Finland

Age group	No. invited (% of population)	% screened of those invited
25	10,470 (33)	54.8
30	22,554 (81)	59.4
35	30,023 (86)	65.2
40	33,363 (88)	71.0
45	32,291 (89)	73.4
50	34,891 (90)	76.8
55	37,761 (88)	77.6

Cancer in Finland, 2008

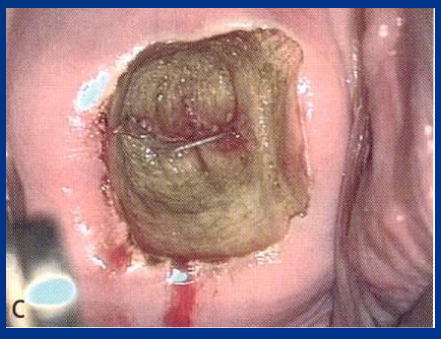
Invasive cervical carcinoma in young women: Data from Helsinki metropolitan area during 2000-2008

	Age group		
	<30	30-40	>40
No. of cases	26	54	94
Time interval (months)*	26mo	25mo	47mo
Smokers (%)	41%	48%	37%
Adeno-carcinoma**	46%	39%	41%

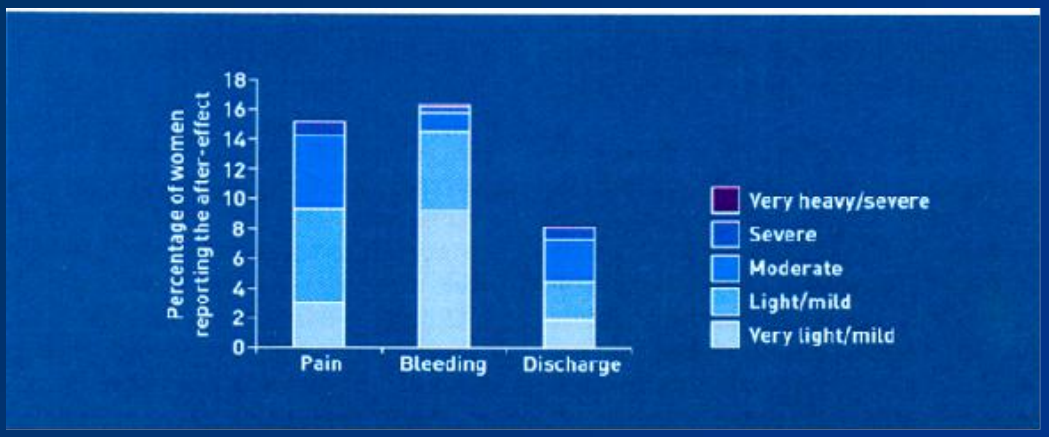
*Time from most recent Pap smear to diagnosis;**Includes adedosquamous carcinomas; N=174; Pakarinen et al. unpublished 2011

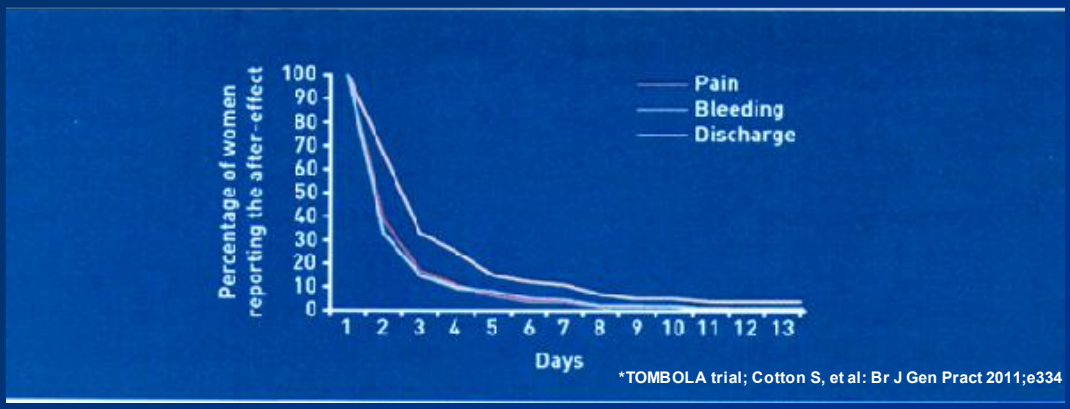
Secondary prevention has multiple steps

- Screening cytology
  - Efficacy depends on repeated screening cycles
- Colposcopy biopsy
- Decision of treatment
- Treatment by surgery
  - Loop conisation
- Post-treatment follow-up
- Return to screening intervals



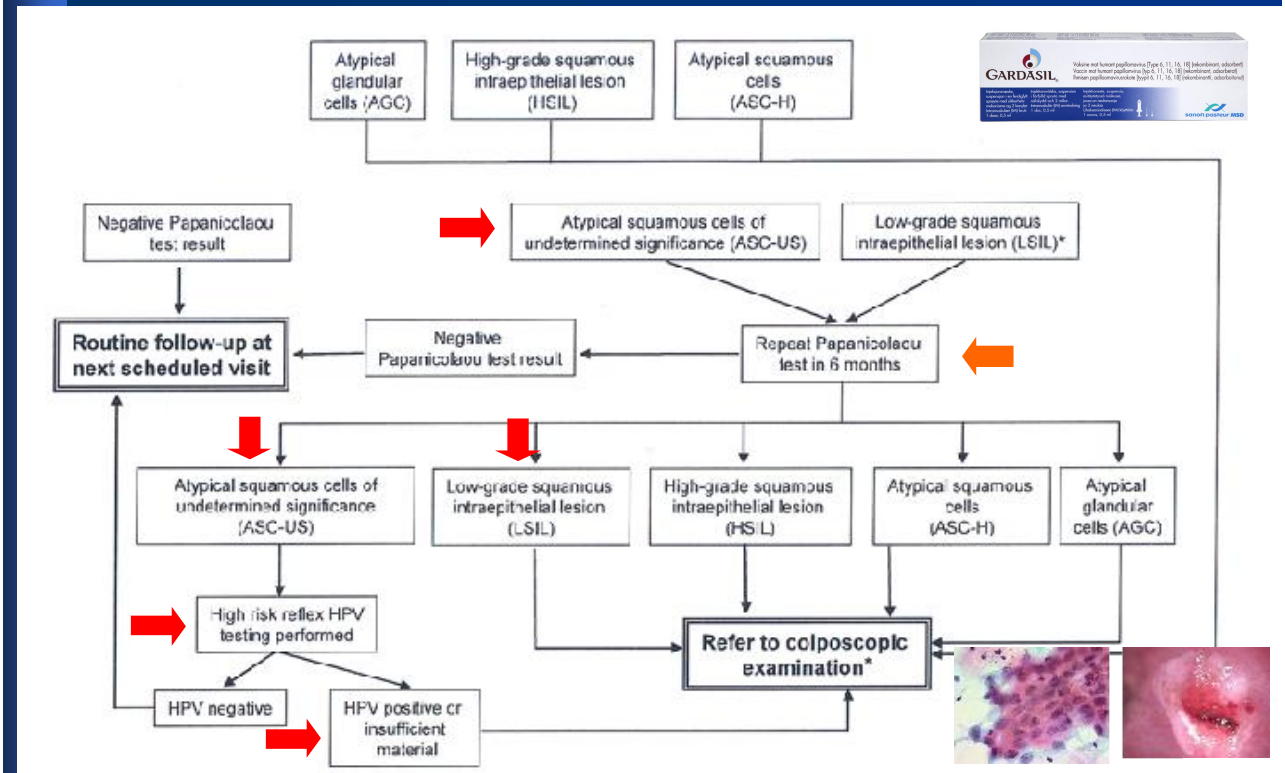
After-effects of having Pap smear*





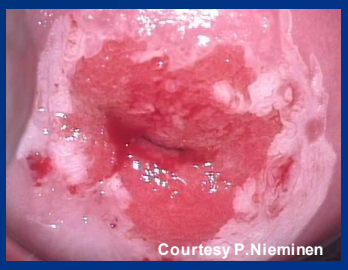
*TOMBOLA trial; Cotton S, et al: Br J Gen Pract 2011;e334

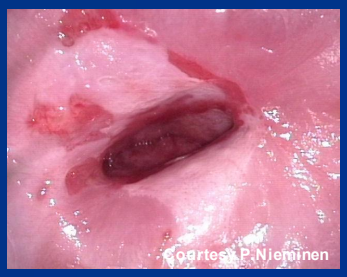
Colposcopy Algorithm used in HPV Vaccination Trials

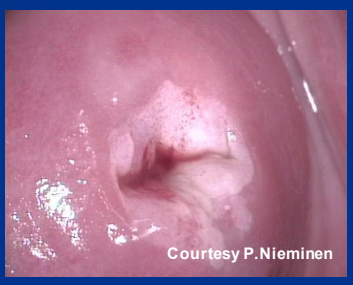


Colposcopy performance

- Severity of referral Pap smear
- Patient age
- Visibility of the squamocolumnar junction
- Lesion size
- Endocervical extension
- Number of biopsies
- Training
- Experience







Colposcopy has problems

- Considerable lack of agreement in reporting colposcopic findings&
- Poor agreement between colposcopic impression and histological diagnosis*
- Colposcopists using the RCI failed to detect CIN2/3**
- Characteristics used to derive colposcopic score are poorly reproducible***
- Colposcopic diagnosis is poorly reproducible and reflects problems in clinical practice#

RCI=Reid Colposcopy Index; &Sellors J, et al: Obstet Gynecol 1990;76:1006; *Wensveen C, et al: EJOG 2007;135:123; **Ferris DG, et al: AJOG 2006;194:704; ***Stewart Massad L, et al: Obstet Gynecol 2008;111:1279; #Jeronimo J, et al: Obstet Gynecol 2007;110:833

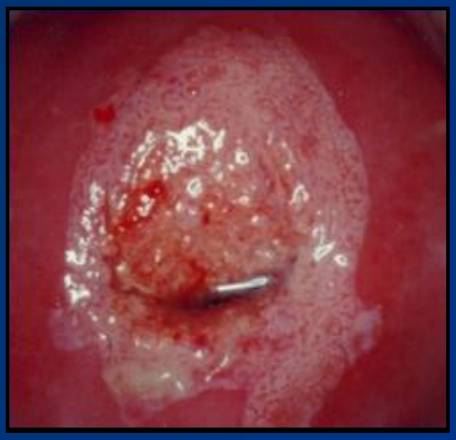
Interobserver agreement by Kappa statistics

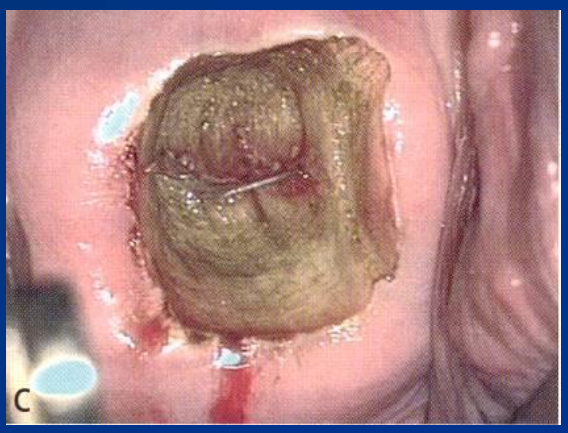
	Observer pair		
Feature	JP/PN	JP/EV	PN/EV
▪ Satisfact exam	0.79	0.45	0.37
▪ Ectopy (%)	0.55	0.34	0.45
▪ ATZ (%)	0.34	0.34	0.36
▪ Borders	0.39	0.41	0.13
▪ Color of AW	0.32	0.47	0.21

Number of paired observations 35-50;
ATZ=Atypical transformation zone; AW=Acetowhiteness
Sellors J, et al: Obstet Gynecol 1990;76:1006

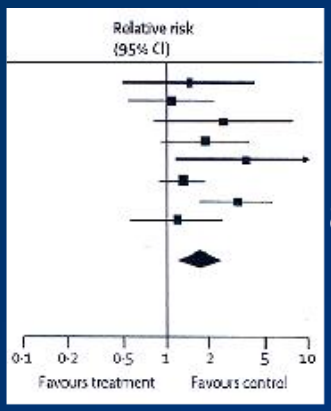
Cervical procedures and adverse pregnancy outcome

- Any treatment for CIN increases the risk of preterm birth
- This should be emphasized when managing young women with CIN

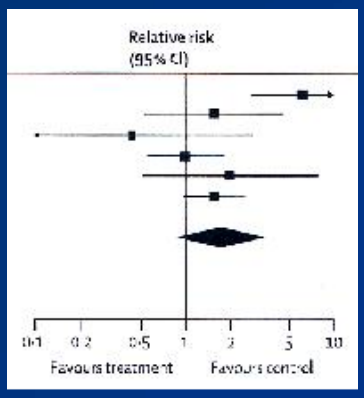




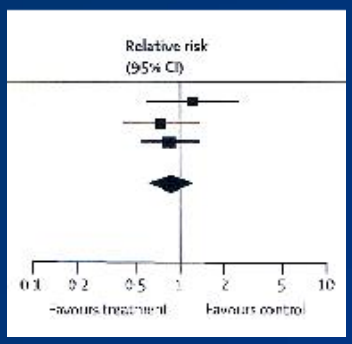
Cervical procedures and preterm delivery: A meta-analysis



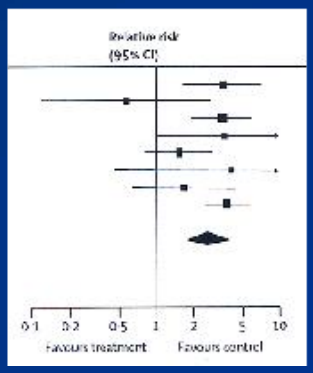
Loop;
8 studies



Laser cone;
6 studies



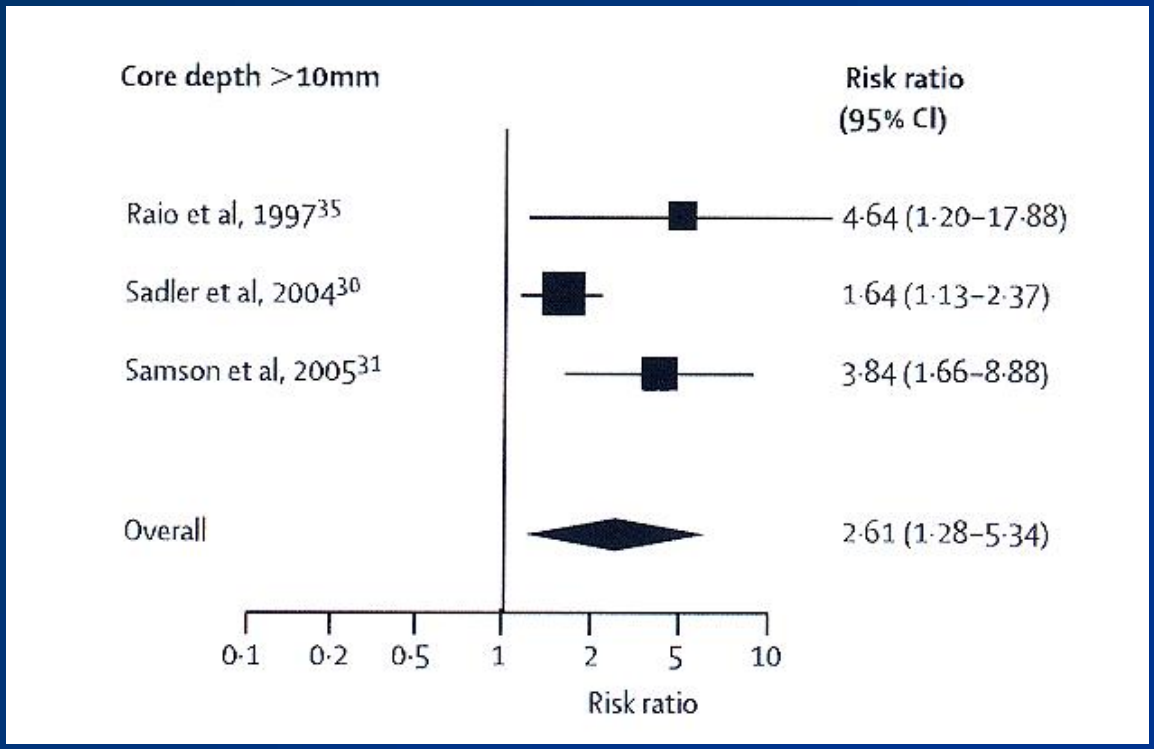
Laser ablation;
3 studies



Cold knife cone;
8 studies

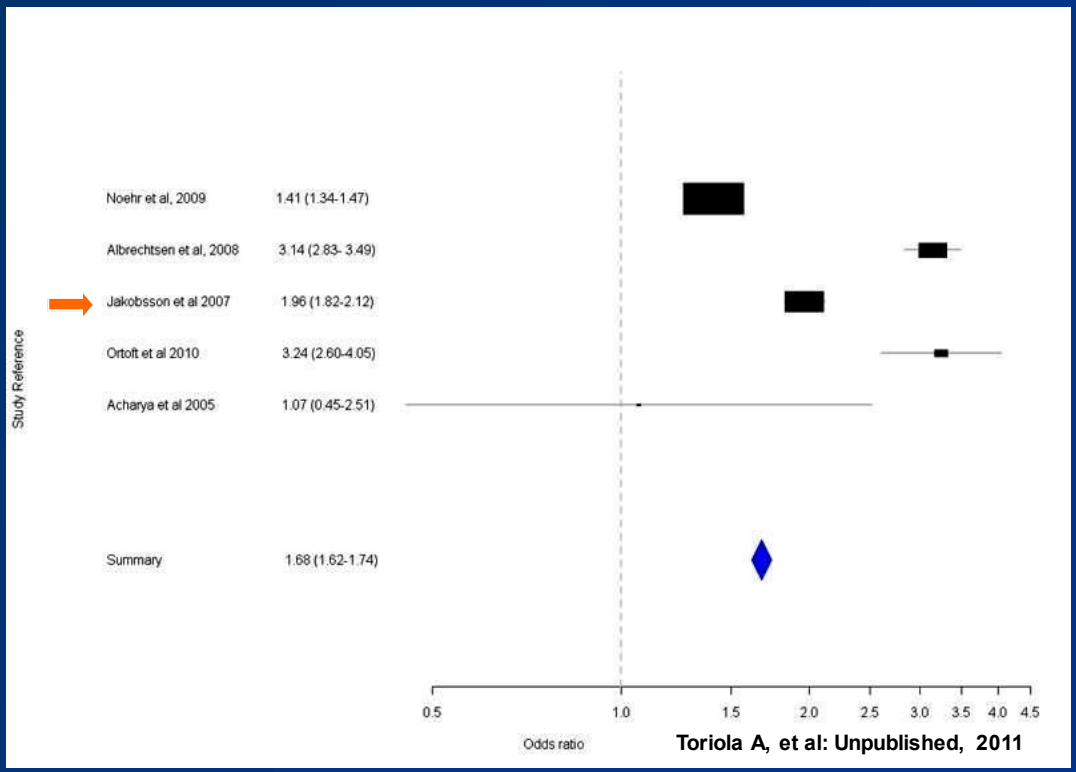
Kyrgiou M, et al: Lancet 2006;367:489

Cone size



Kyrgiou M, et al: Lancet 2006;367:489

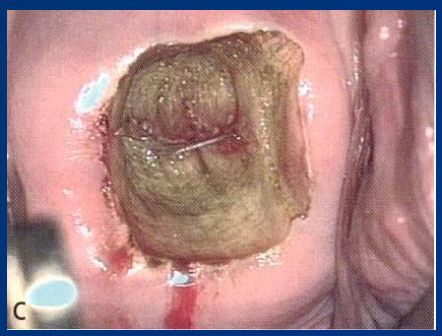
Cervical procedures and preterm delivery: A meta-analysis of Scandinavian studies



Toriola A, et al: Unpublished, 2011

Cervical procedures for treatment of CIN increase the risk for preterm delivery

- N=25,827 women, of whom 5,835 had subsequent singleton deliveries
- **Risk for preterm delivery (<h.37)**
  - **Excisional Rx OR 1.99 (95%CI 1.8-2.2)***
  - **Ablative Rx OR 1.60 (95%CI 1.4-1.8)***



*Adjusted for maternal age, parity, and smoking; Jakobsson M, et al, Obstet Gynecol 2007;109:309

Kalliala I, Nieminen P: Duodecim 2006;122:2401

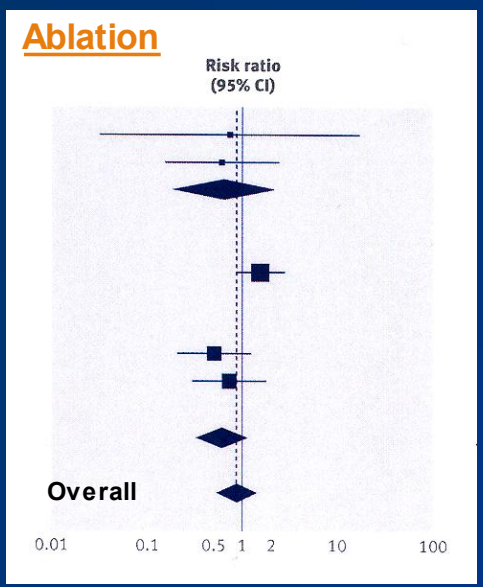
Risk for preterm birth in women with a delivery before and after LEEP

	N=258	RR (95%CI)	SIR (95%CI)**
Before	17 (6.5%)	1.00	1.34 (0.75-2.11)
After	31 (12.0%)	1.94 (1.1-3.4)*	2.61 (1.69-3.52)#

*NNH=18; **SIR=Standardised incidence ratio, compared with MBR population of 25,780 women with singleton PTB rate of 4.6%;#NNH 14; Adjusted for age and parity
Jakobsson M, et al: Obstet Gynecol 2009;114:504

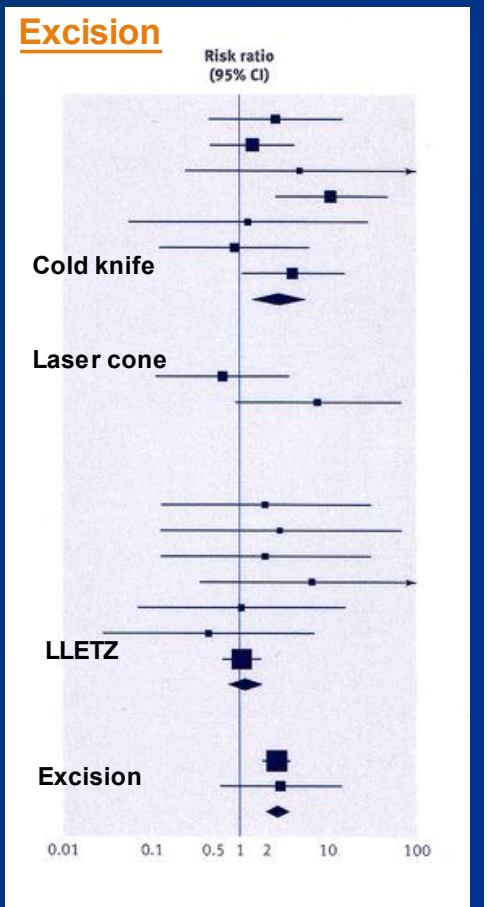
Meta-analysis of perinatal mortality associated with cervical procedures

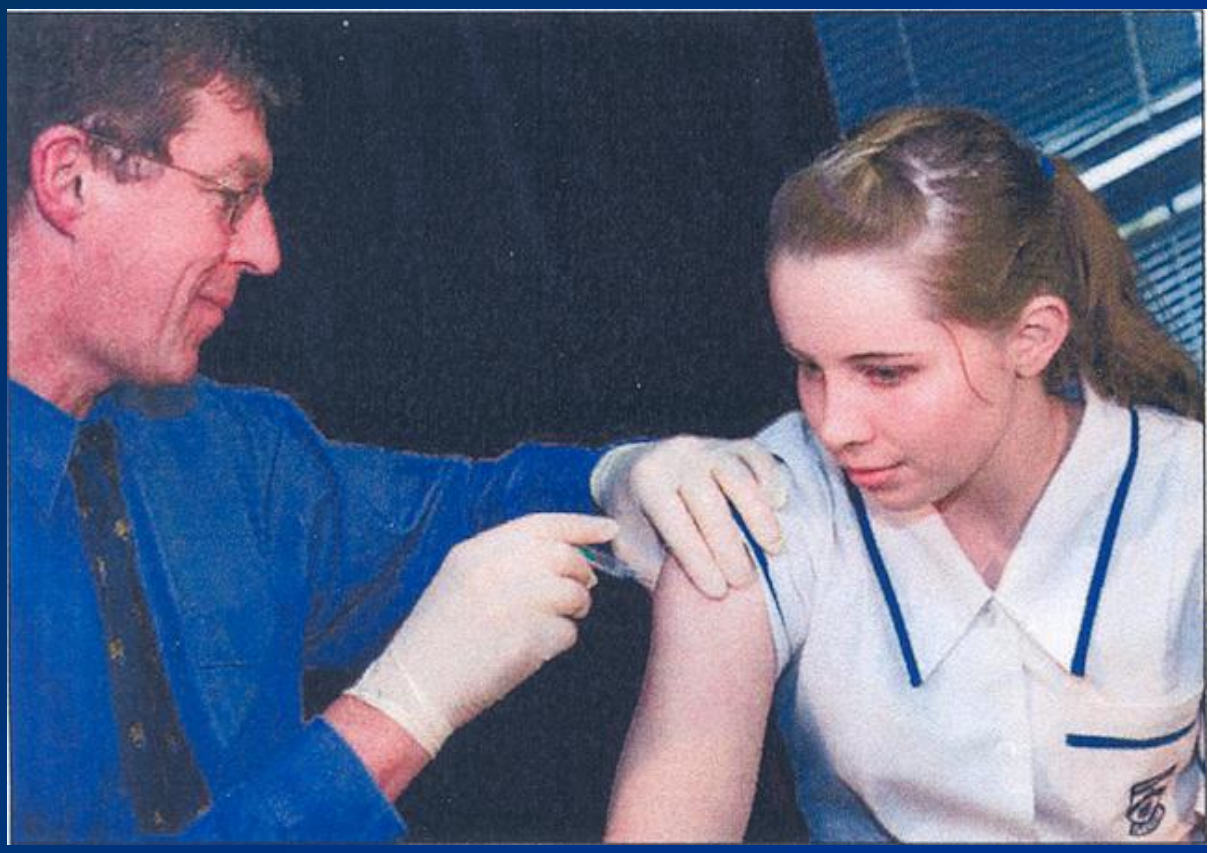
Ablation



Arbyn M, et al: BMJ 2008;337:a1284

Excision





Global phase III efficacy trials with disease endpoints

Quadrivalent vaccine (Gardasil™, Merck Co.)

- **FUTURE** I/II (Protocols 013, 015)
- HPV 6/11/16/18 vaccine vs. placebo (0, 2, 6 mo)
- Alum adjuvant (AAHS)
- Age range 16-26
- N=17,622
- Study start: 2002
- 4-year follow-up (mean 3.6yrs)
- Europe, Asia-Pacific, Latin America, North America

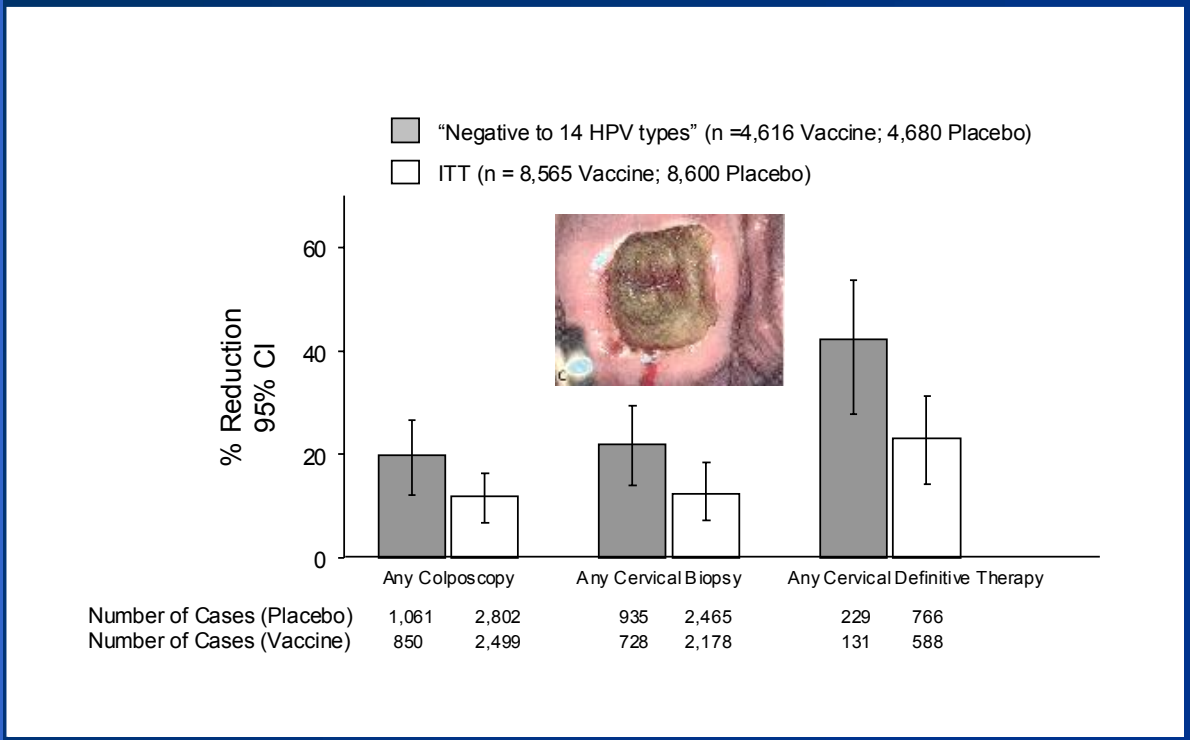
Bivalent vaccine (Cervarix™, GlaxoSmithKline)

- **PATRICIA** (HPV-008)
- HPV 16/18 vaccine vs. Havrix (0, 1, 6 mo)
- Alum+MPL adjuvant (ASO4)
- Age range 15-25
- N= 18,644
- Study start: 2004
- 4-year follow-up (EOS)
- Europe, Asia-Pacific, Latin America, North America

Efficacy of HPV vaccines

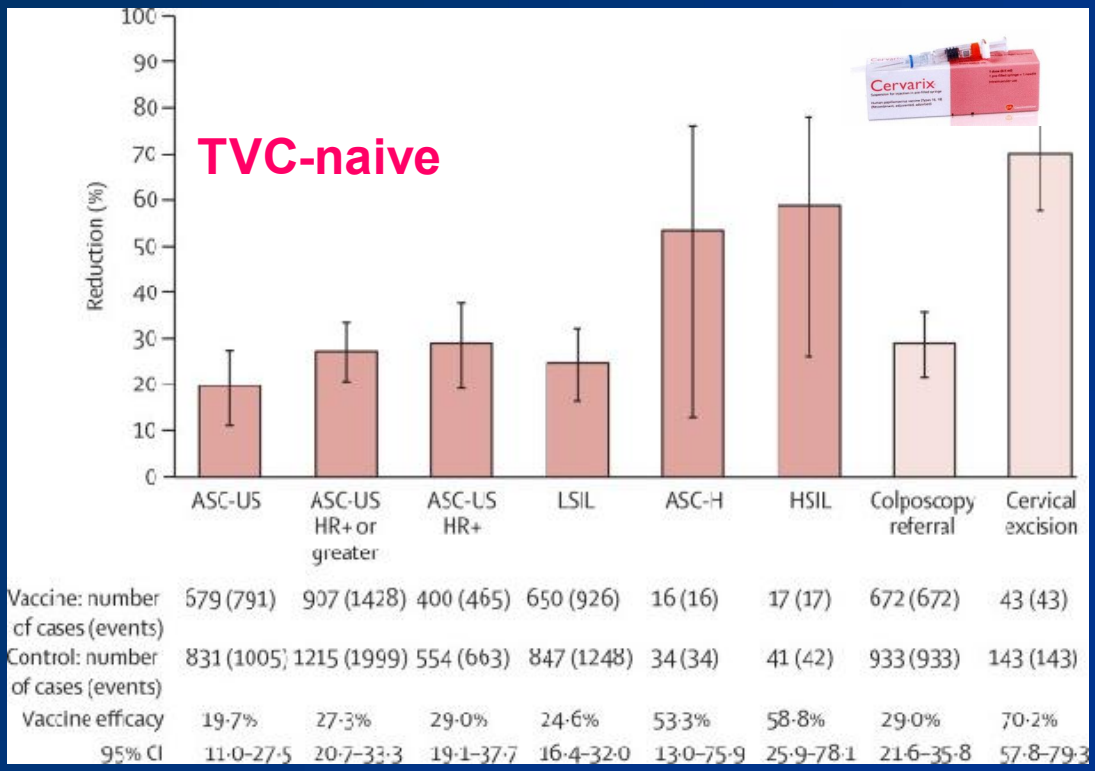
Overall vaccine efficacy = **Efficacy against HPV 16/18** + **Efficacy against non-vaccine oncogenic types**

Reduction in cervical procedures irrespective of causal HPV type



ITT=Intention-to-treat; Munoz N, et al: JNCI 2010;102:325

Reduction in cytological atypias, colposcopy referrals and cervical excision procedures



	ASC-US	ASC-US HR+ or greater	ASC-US HR+	LSIL	ASC-H	HSIL	Colposcopy referral	Cervical excision
Vaccine: number of cases (events)	579 (791)	907 (1428)	400 (465)	650 (926)	16 (16)	17 (17)	672 (672)	43 (43)
Control: number of cases (events)	831 (1005)	1215 (1999)	554 (663)	847 (1248)	34 (34)	41 (42)	933 (933)	143 (143)
Vaccine efficacy	19·7%	27·3%	29·0%	24·6%	53·3%	58·8%	29·0%	70·2%
95% CI	11·0–27·5	20·7–33·3	19·1–37·7	16·4–32·0	13·0–75·9	25·9–78·1	21·6–35·8	57·8–79·3

TVC=Total vaccinated cohort; Lehtinen M, et al: Lancet Oncology 2011;Nov 9

Clinical trial and post-licensure safety profile of qHPV vaccine

- Clinical trial data-median F/U time 3.6 year
  - 5 trials with 21,480 girls/women and boys aged 9-26
- Up to 3 years of post-licensure surveillance
  - US Vaccine Adverse Event Reporting System database; 14,072 reports June 2006-June 2009
- HPV-vaccine caused more injection-site pain than placebo
- Similar incidences of systemic and serious AEs or non-serious AEs
- Similar incidences of new medical conditions c/w autoimmune phenomena

Block SL, et al: Pediatr Infect Dis J 2010;29 (2) (Feb 2010)

Pregnancy outcomes in clinical trials of the qHPV vaccine

Fetal loss	Vaccine N=10,126	Placebo N=10,425
No./Total	559/2,008	602/2,029
Spont ab	366 (65.5%)	395 (65.6%)
Late fetal death	17 (3%)	15 (2.5%)
Elect abortion	175 (31.3%)	191 (31.7%)
Ectopic	2 (0.1%)	3 (0.15%)

5 phase III trials among women aged 15-45 resulting in 4,037 pregnancies with known outcomes; Garland S, et al: O&G 2009;114:1179

Bivalent vaccine trial safety outcomes: Adverse events

	Vaccine N=9319	Control N=9325
Serious	9.0%	8.9%
Vaccine-related	0.1%	0.1%
Medically significant	35.4%	36.2%
New onset CD*	3.1%	3.3%
New onset AID*	1.1%	1.0%
Deaths**	0.1%	0.1%

*CD=Chrpnic disease; AID=Autoimmune disease; **10 deaths in the vaccine arm, 13 deaths in the control arm
Lehtinen et al: Lancet Oncol 2011: Nov 7

Bivalent vaccine trial: Pregnancy and pregnancy outcomes

	Vaccine	Control
No. of pregnancies	2257	2257
Ongoing pregnancies	0.5%	0.5%
Normal infant	72.8%	74.0%
Congenital anomaly	0.8%	0.6%
Med sign cond	0.4%	0.4%
Spontaneous abortion	9.1%	8.6%
Elective termination	9.4%	10.1%

Lehtinen et al: Lancet Oncology 2011; Nov 7

Pregnancy outcomes in pooled data from 26,130 women in two bivalent vaccine trials*

Outcome	Vaccine	
	HPV16/18	HAV
Miscarriages	197 (11.0)	176 (9.7)
0-6 wks	43	38
7-12 wks	108	107
13-20 wks	44	30
Ind abortions	127 (7.1)	128 (7.1)
Stillbirths	15 (0.8)	13 (0.7)
Live births	1401	1449
Total pregn	1786	1813

*PATRICIA (HPV008); CVT=Costa Rica Vaccine Trial; 26,130 women randomized to HPV vaccine (Cervarix) or Hepatitis A Vaccine (HAV); Wachholder et al: BMJ 2010;340:c712

Pregnancy outcomes in pooled data from 26,130 women in bivalent vaccine trials*

	Miscarriage rate	
Study	HPV (%)	HAV (%)
PATRICIA*	10.6	9.0
CVT*	12.8	11.8
Interval**		
<90 days	13.7	9.2***
>90 days	10.7	10.5

*HPV008; CVT=Costa Rica Vaccine Trial; 26,130 women randomized to HPV vaccine (Cervirix) or Hepatitis A Vaccine; **Interval between estimated date of conception and nearest vaccination; ***p<.031; Wachholder et al: BMJ 2010;340:c712

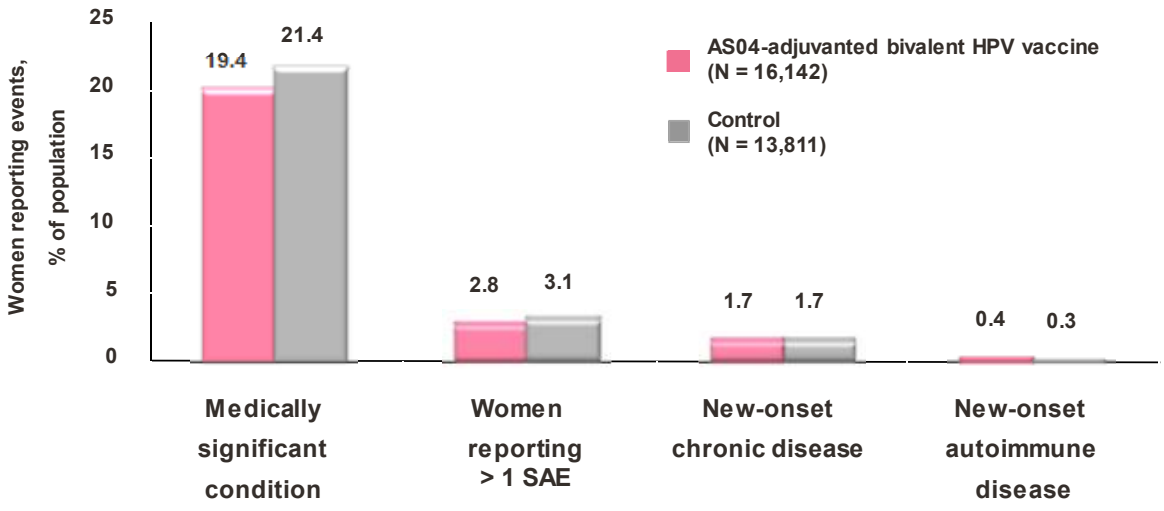
Risk of miscarriage with the bivalent vaccine: Passive registry based 4-year follow-up in Finland

Cohort	Total	Miscarriages	IR
	No.	No.	(95% CI)
HPV*	2,409	22	219 (137-331)
HAV*	2,399	20	200 (122-308)
Unvacc**	15,744	162	246 (210-288)

Women aged 17-18 at baseline; Passive follow-up started 6 months from the last vaccination; Registry of vaccinated and unvaccinated individuals linked with Hospital Discharge Registry; *HPV=Received HPV 16/18 vaccine; HAV=Received hepatitis A vaccine; **Unvacc=Women adjusted by age and duration of the follow-up; IR=Incidence ratio; IR=Incidence ratio per 100,000; Lehtinen M, et al: Unpublished results

Pooled safety data from bivalent vaccine trials

Eleven studies with the same vaccination schedule and similar methodology of safety assessment



SAE = severe adverse event.

Descamps D, et al. Hum Vaccin 2009; **5**:1–9

Phase IV HPV16/18 community randomised vaccination trial

- 33 communities (11 communities per arm):
  - A: HPV16/18 to boys and girls
  - B: HPV16/18 to girls, HBV to boys
  - C: HBV to boys and girls
- Birth cohorts enrolled (from Oct 2007):
  - 1992/1993 in 2007-2008
  - 1994/1995 in 2008-2009
- Total enrolled:
  - 32,200 vaccinated*
  - 35,000 volunteers not vaccinated**
- End-point:
  - Rate of hrHPV by birth-cohort by 2010-2014 (A vs. C; B vs. C; A vs. B)

*1992/1993 N=16,000; 1994/1995 N=16,200; **1992/1993 N=17,000; 1994/1995 N=18,000
Lehtinen M, et al: Unpublished

Incidence of new onset autoimmune diseases among Phase IV community randomised trial participants in Finland

	Vaccine recipients**		SIR (95% CI)
	No.	Incidence (95% CI)	
Arthritis	35	68.6 (45.9-91.4)	NA
Coeliac dx	20	39.2 (22.0-56.4)	1.2 (0.7-1.8)
IBD	43	84.3 (59.1-110)	1.2 (0.9-1.6)
Juvenile DM	25	49.0 (29.8-62.4)	1.0 (0.7-1.4)

SIR=Standardised incidence ratio; Coeliac Dx=Coeliac disease; IBD=Inflammatory bowel disease; DM=Diabetes mellitus;
Incidence of coeliac disease=34; Incidence of IBD=73; Incidence of juvenile diabetes mellitus=50;
Virta L, et al: Scand J Gastroenter 2009;44:933; Lehtinen P, et al: Inflamm Bowel Dis 2011;17:1778;
Harjutsalo V, et al: Lancet 2008;371:1777
*Baseline 12-15 year old Cervarix or HBV vaccinated adolescents during 22 000 and 29 000 years of health registry-based follow-up 2008-2010; **HPV16/18 vaccine (Cervarix) or Hepatitis B Vaccine);
Lehtinen et al: Unpublished

Incidence rate ratios of new onset autoimmune diseases among Phase IV community randomised trial participants in Finland

	IRR (95% CI)
Arthritis	1.57 (0.80-3.04)
Coeliac disease	1.32 (0.55-3.17)
IBD	1.15 (0.64-2.07)
Juvenile DM	0.25 (0.08-0.63)

IBD=Inflammatory bowel disease; DM=Diabetes mellitus; IIR=Incidence rate ratio=
Incidence rate among HPV16/18 recipients divided by incidence rate
among Hepatitis B Vaccine recipients

Conclusions

- Secondary prevention has no major safety problems, but is associated with performance problems
- Secondary prevention by organised mass screening has decreased cervical cancer rates
  - Disease burden has shifted to cervical precancer
- Cervical procedures increase the risk for adverse pregnancy outcome
- Primary prevention target is eradication of disease
  - Safety data based on reported adverse effects during clinical trials or postmarketing surveillance are reassuring but weak and not definitive
  - Health registry-based surveillance provides best quality population level safety data
  - No signals of safety problems have been discovered
  - Health registry based quantitative pharmacovigilance is an important adjunct to clinical trial safety data

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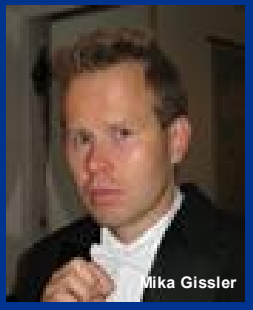
Mika Gissler