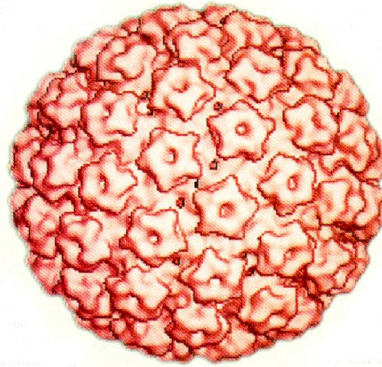


Effectiveness of HPV interventions in Finland

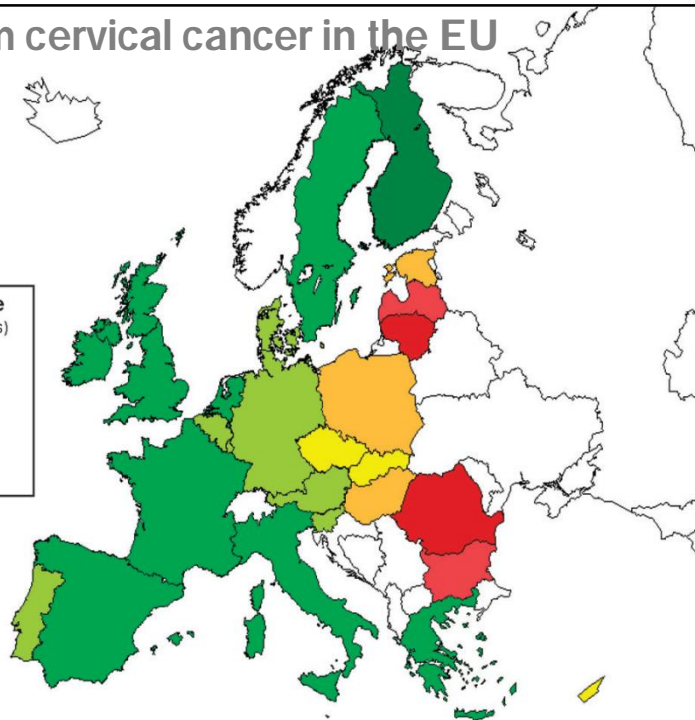
Matti Lehtinen, University of Tampere, Finland



Matti Lehtinen has received grants for his HPV vaccination studies through his employer University of Tampere, Finland from Merck & Co., Inc., and GlaxoSmithKline Biologicals

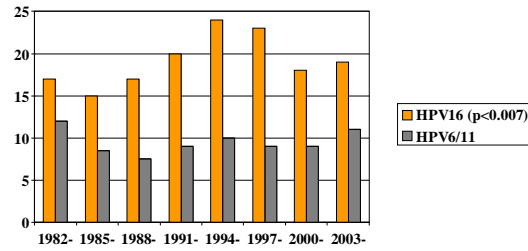
Mortality from cervical cancer in the EU

(Arbyn et al. 2007)

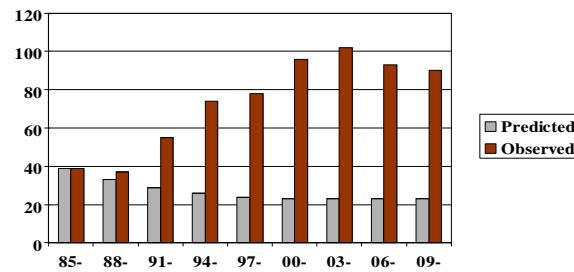


Occurrence of HPV6/11&16 and cervical cancer in Finns at 20-29 & 30-39 yrs of age (JGV 2003, IJC 2011 www.cancer.fi)

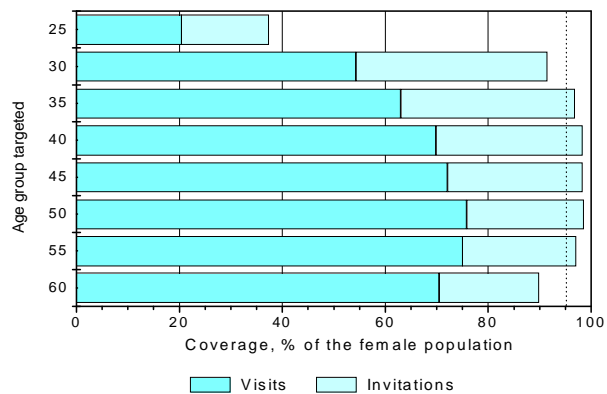
HPV seroprevalence (%)



ICC incidence / 1000000



Coverage of the cervical cancer screening programme in Finland (FCR 2005)



BMJ
9 August 2008 | bmj.com

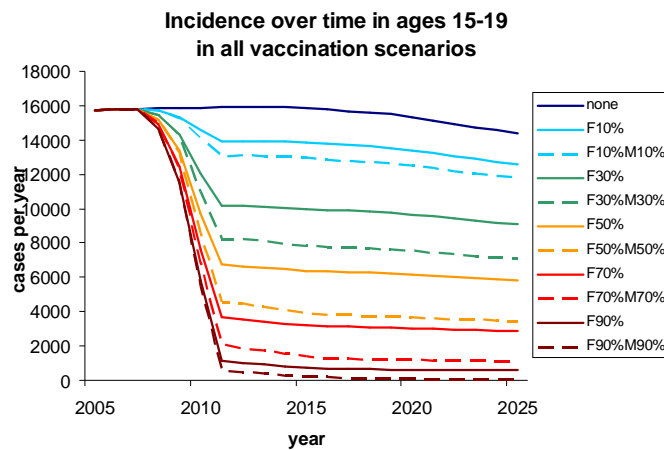
PROTECTING GIRLS AGAINST HPV
WHICH VACCINE?

Coverage/Trial participation	(♀)	Marginalization
UK	84%	destroys (impact of) public health policy
Australia	73%	
Finland	>50%	
N-lands, Germany	40%	
USA	<30%	

WHICH STRATEGY?

Modelled effectiveness of HPV vaccination

(Barnabas et al 2006, French et al. 2007)



International Journal of STD & AIDS 2003; 14: 787-792

REVIEW

Effectiveness of preventive human papillomavirus vaccination

M Lehtinen MD PhD and J Paavonen MD PhD

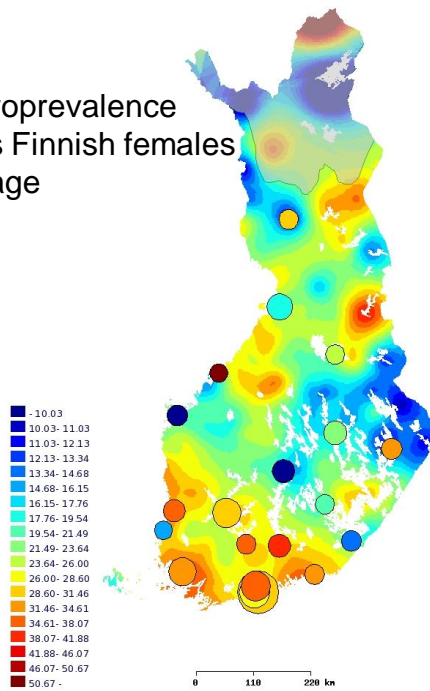
Power of community-randomized trials* to assess significant HPV16/18 prevalence reduction among adolescents in 7 yrs assuming 70% coverage by coefficient of variation (CV) in background prevalence

(Future Medicine 2008)

comparison between arms	power to show reduced HPV prevalence with different coefficients of variation (CV)		
	(CV 0.50)	(CV 0.20)	(CV 0.10)
♀&♂ vs. HBV	73%	100%	100%
♀ vs. HBV	55%	99%	100%
♀&♂ vs. ♀	13%	34%	<u>51%</u>

*8 communities/arm, p = 0.05

HPV16/18 seroprevalence
in primiparous Finnish females
<23 years of age

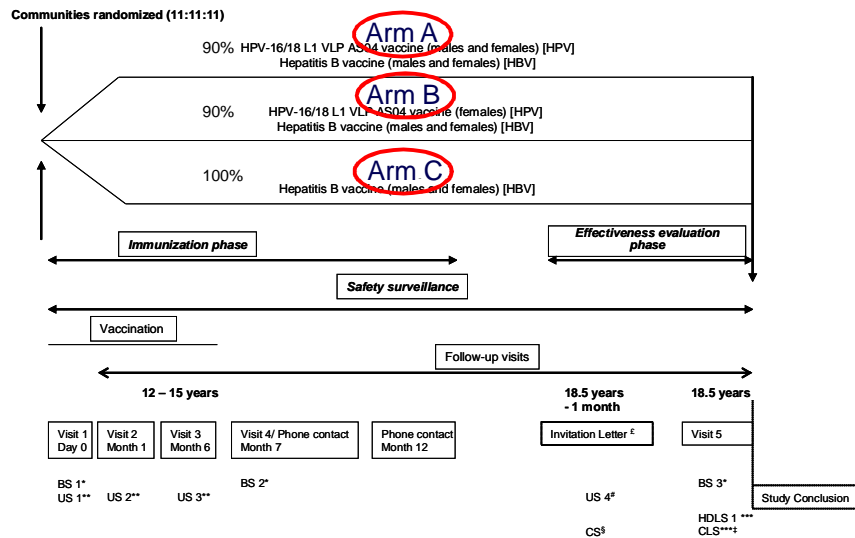


Community-randomized phase IV trial on the
effectiveness of different HPV vaccination strategies



- **33 communities** (11 communities/arm):
 - A-arm:** HPV16/18 vaccinated boys&girls
 - B-arm:** HPV16/18 girls, boys HBV
 - C-arm:** HBV vaccinated boys&girls
- **End-points:** Reduction of HPV prevalence in 18.5-yr old girls (overall effectiveness)
Reduction of HPV prevalence in unvaccinated girls (herd immunity)

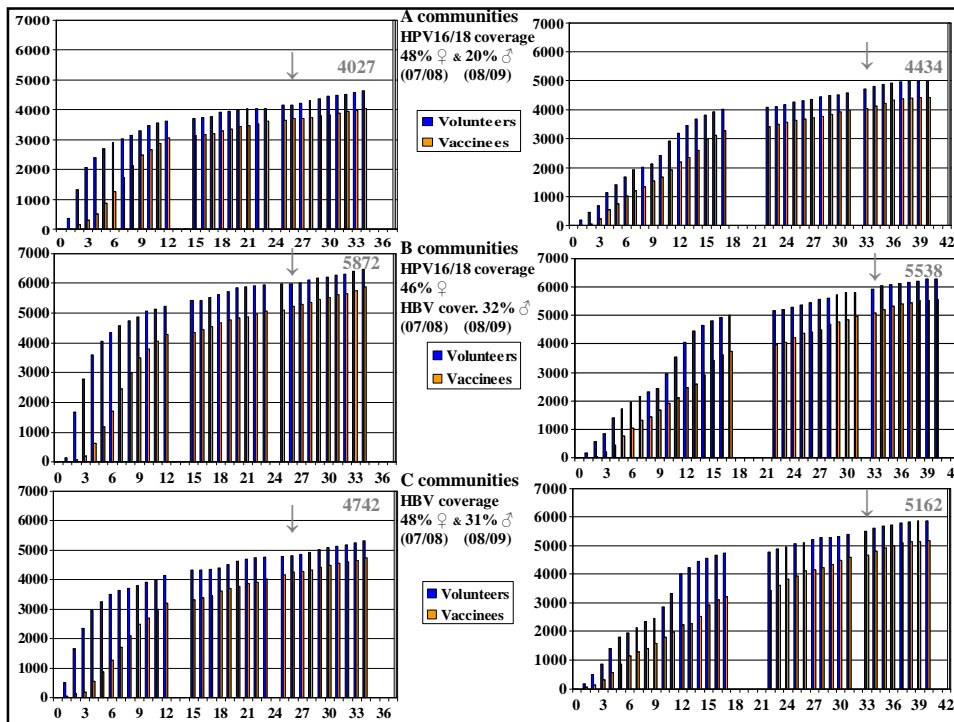
Phase IV (HPV-040 Study) Study design



Community-randomized phase IV trial on the effectiveness of different HPV vaccination strategies



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 - 1992/93 in 2007/08
 - 1994/95 in 2008/09(10)
- total eligible 80 000 early adolescents**



Community-randomized phase IV trial on the effectiveness of different HPV vaccination strategies



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 Reduction of HPV prevalence in unvaccinated girls (herd immunity)
- **Birth-cohorts invited:**
 1992/93 in 2007/08
 1994/95 in 2008/09(10)
total eligible 80 000 early adolescents
- **Enrolled:**

	vaccinated/	volunteers
1992/93 born	16 000	17 000
1994/95 born	16 200	18 000
total	32 200	35 000

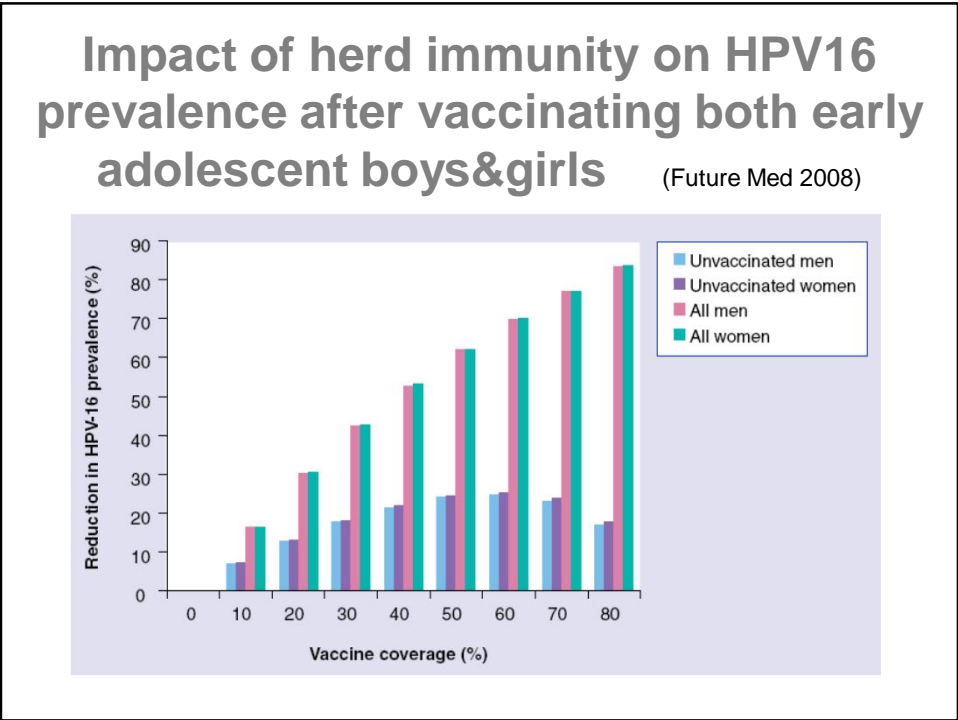
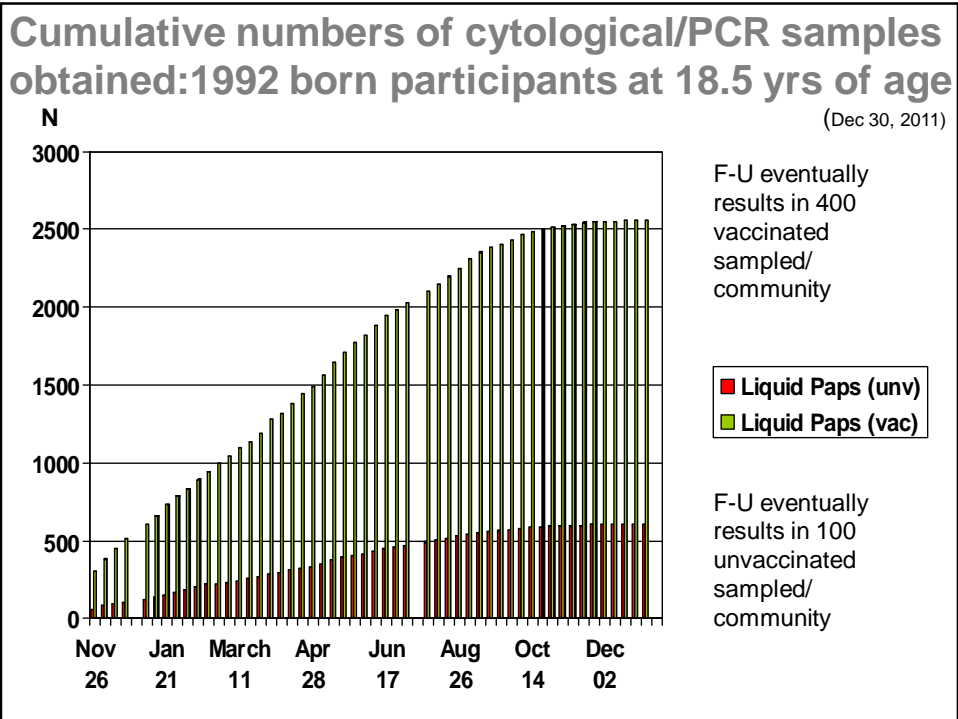
Number of communities/arm required for the demonstration of significant differences in the reduction of hrHPV prevalence by coverage&strategy (with 20% effect variation) assuming VE 70%, and 1000 eligible invitees and 13% co-efficient of variation /community (power 90%, p<0.05)

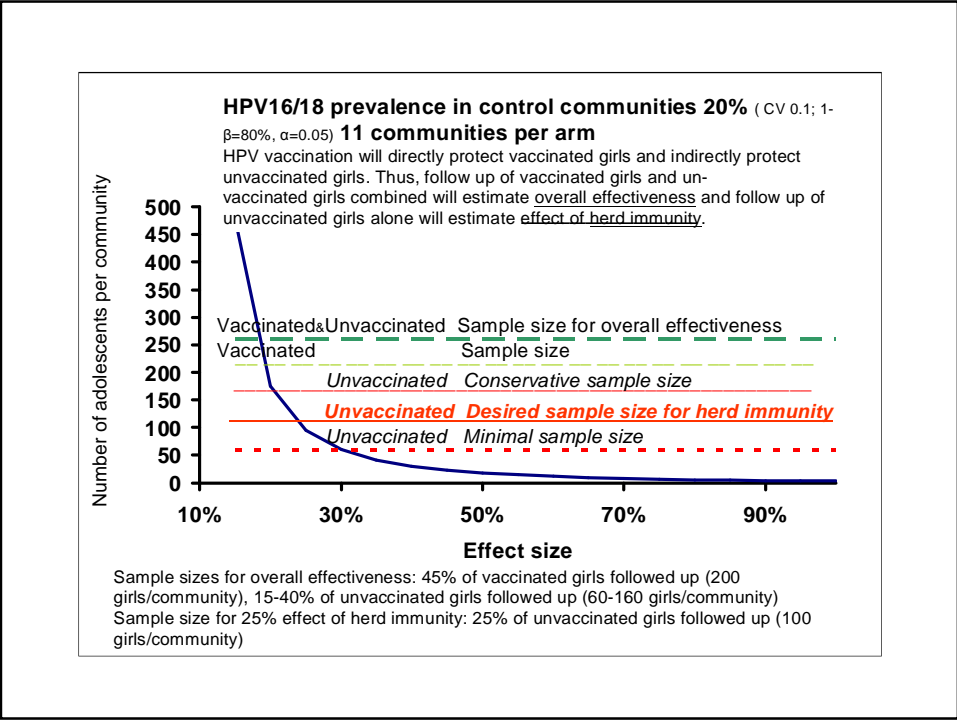
Vaccine coverage	Strategies to be compared	Communities/Arm
50%	Arm A (♀&♂) vs. Arm C (HBV)	4.1 (3.3-6.0)
	Arm B (♀) vs. Arm C (HBV)	6.0 (4.0-13.3)
45%	Arm A (♀&♂) vs. Arm C (HBV)	4.7 (3.5-7.5)
	Arm B (♀) vs. Arm C (HBV)	7.1 (4.2-19.2)
40%	Arm A (♀&♂) vs. Arm C (HBV)	5.3 (3.7-10.0)
	Arm B (♀) vs. Arm C (HBV)	8.4 (4.5-31.0)
35%	Arm A (♀&♂) vs. Arm C (HBV)	6.3 (4.0-14.7)
	Arm B (♀) vs. Arm C (HBV)	10.4 (4.9-60.4)

Participants*/community for assessing overall effectiveness of vaccination by vaccine efficacy (VE) assuming a 13% baseline HPV16/18 prevalence in C communities and 10% co-efficient of variation (power 90%, p=0.05)

VE	Comparison	Effectiveness	Participants*/Community
90 %	A vs. C	53.6 %	44
	B vs. C	44.1 %	79
80 %	A vs. C	49.4 %	55
	B vs. C	40.3 %	106
70 %	A vs. C	44.9 %	<u>74</u>
	B vs. C	36.3 %	<u>158</u>

*vaccinated and unvaccinated





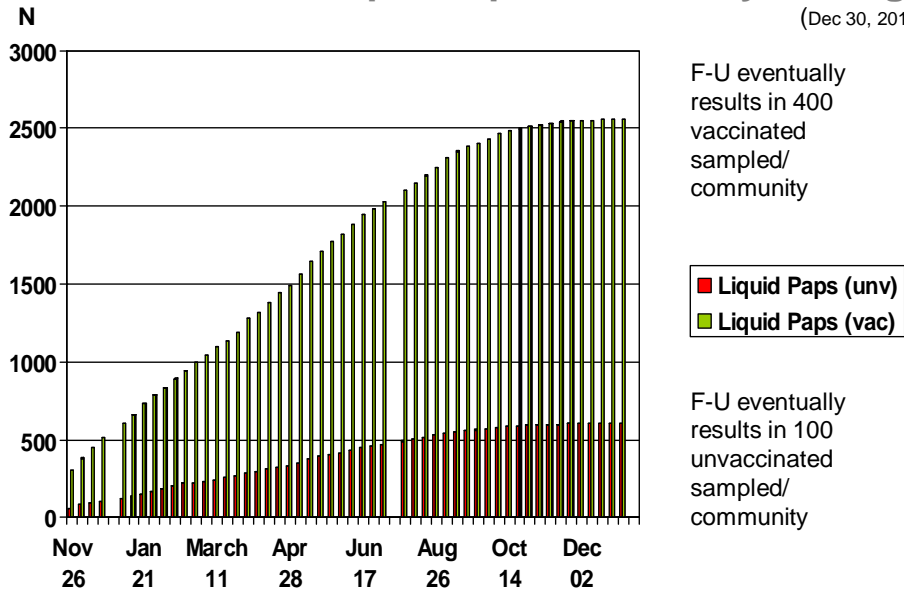
Participants*/community for assessing indirect effectiveness of vaccination (herd immunity) by assuming a 13% baseline HPV16/18 prevalence in C communities and 10% co-efficient of variation (power 80%, p=0.05)

Comparison	Effectiveness	Participants*/Community
A vs. C	30 %	86
	25 %	<u>136</u>
	20 %	246
B vs. C	30 %	113
	25 %	<u>181</u>
	20 %	344

*non HPV-16/18 vaccinated

Cumulative numbers of cytological/PCR samples obtained: 1992 born participants at 18.5 yrs of age

(Dec 30, 2011)



Main data sources for pharmacovigilance with SIRs

Whole population

Population sample

Statistics Finland

- * Longitudinal Census files 1950 –1970 –1975 –1980 –1985 –1990 –1995...: occupation, education, SES, place of residence
- * **causes of death 1971+**

Hospital laboratories

- * **diagnostic biopsies**

Natl Agency of Medicines

- * **prescribed drugs&vaccines**

Finnish Cancer Registry

- * **cancer incidence 1953+**
- * **cancer screening 1963+**

Phase III/IV HPV Vaccine Trials

- * register of **24 000 HPV vaccin/ unvaccinated young women** (phase III 2003/5)
- * register of **35 000 HPV / HBV vaccinated adolescents** (phase IV 2007/9)

Population Register Center (VRK) 1967+

- * **complete ID**
- * **place of birth**
- * **residential history**
- * **living coordinates**
- * **living conditions**
- * **parent-child links**
- * **PIDs of children**
- * **immigration/emigration**
- * **date of death**

National Research and Development Centre for Welfare & Health, THL

- **in-&outpatient ICD dg:s 1995+**
- **pregnancy&birth data 1987+**
- **malformations 1987+**

Natl Inst for Health & Welfare (THL)

- * survey data (Mini Finland 1967, FinRisk 1972+, Adult Population Health Survey 1978+): life habits (smoking, alcohol, diet, BMI, physical exercise etc)
- **Biobank, Finnish Maternity Cohort 1983+**

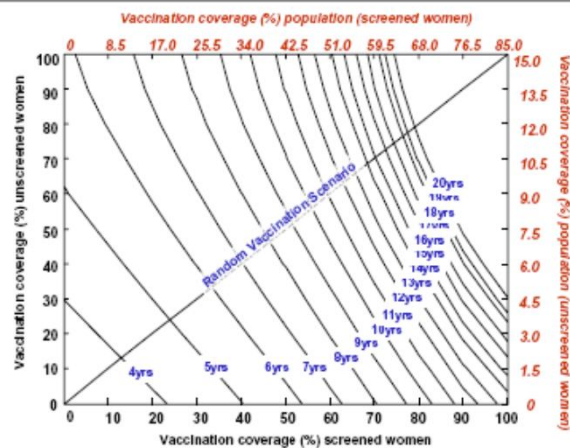
Table Incidence (/10⁵ person years) of common, new onset autoimmune diseases in baseline 12-15 year old HPV16/18 or HBV vaccinated Finnish adolescents during 22 000 and 29 000 years of registry-based follow-up in 2008-2010

Category	HPV16/18 or HBV vaccinated Number	Incidence (95%CI)	Standardized incidence rate ratio (SIR, 95% CI)
Arthritis	35	68.6 (45.9-91.4)/100 000	not available
Coeliac disease (CD)	20	39.2 (22.0-56.4)/100 000	1.2 (0.7-1.8)
Inflammatory Bowel Diseases (IBD)	43	84.3 (59.1-110)/100 000	1.2 (0.9-1.6)
Juvenile diabetes (IDDM)	25	49.0 (29.8-62.4)/100 000	1.0 (0.7-1.4)

SIR = standardized incidence rate ratio, CD incidence 34/100 000, IBD incidence 73/100 000, IDDM incidence 50/100 000 (Virta L, et al. 2011, Lehtinen P, et al. 2010, Harjutsalo V, et al. 2008)

Integration of HPV vaccination and screening is being modelled (Baussano 2011)

Figure 3. Potential consequences of increasing the intervals between screening rounds, allowing for different vaccination coverage levels for women who will be, and will not be screened. See text below for details.



Evaluating integration of HPV vaccination & screening programmes in two subsequent randomized trials

Interventions:

- Arm 1: HPV screening of 7000 HPV vaccinated women* with 4-yr interval** at the ages of 18/22/26/30 yrs (*18 years of age)
- Arm 2: HPV screening of 7000 vaccinated adolescents* with 4-yr interval** at the ages of 18/22/26/30 yrs (*12-15 years of age)
- Arm 3: Once in a life-time HPV screening of 7000 vaccinated adolescents*** at the age of 30 yrs (*12-15 years of age)

Study objectives:

1. To show that CIN3+ incidence in Arm 3 equals that of Arm 2
2. To show that CIN3+ incidences in Arms 3 is lower than in Arm 1
3. To verify absence of type-replacement between 18 to 22 years of age
4. To show that HPV disease burden is lowest in Arm 3
5. To show that quality of life is the highest in Arm 3

End-points:

1. & 2. CIN3+ incidence rate ratios by arms
3. hrHPV incidence rate ratios by arms
4. Cost-effectiveness comparisons between the different arms
5. Standardized incidence ratios of health registered adverse effects

Most cost-effective integrated vac&screen strategy to be identified while implemented

Deliverables

- In **2014 effectiveness data on different vaccination strategies** from a community-randomized phase IV study
- **Population-based, quantitative pharmacovigilance** (standardized incidence rate ratio) **data** for sizeable cohorts of vaccinated/ un-vaccinated individuals (altogether 60 000) **from 2012 onwards**
- A population-based, **randomized study on the impact of different combinations of HPV vaccination & screening on HPV disease burden** launched in 2014

Acknowledgements

- Dan Apter (FFF)
- Tiina Eriksson, Kari Natunen (UTa)
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- Gary Dubin, David Jenkins, Markku Pulkkinen, Maaria Soila (GSK)

Sample sizes for a community-randomized trial on the effectiveness of HPV vaccination (USA 2003)

Table 3. Sample sizes for assessment of eventual reduction of human papillomavirus (HPV) prevalence in a community randomized trial in naive adolescents during eight years (Refs 30, 36). See footnote for assumptions/example

Expected HPV prevalence without vaccination	Number of communities in one study arm/actuarial reduction of HPV prevalence		
	65%	75%	85%
15%	44	37	27
20%	27	21	16
25%	18	14	12
30%	14	11	9
35%	10	8	7