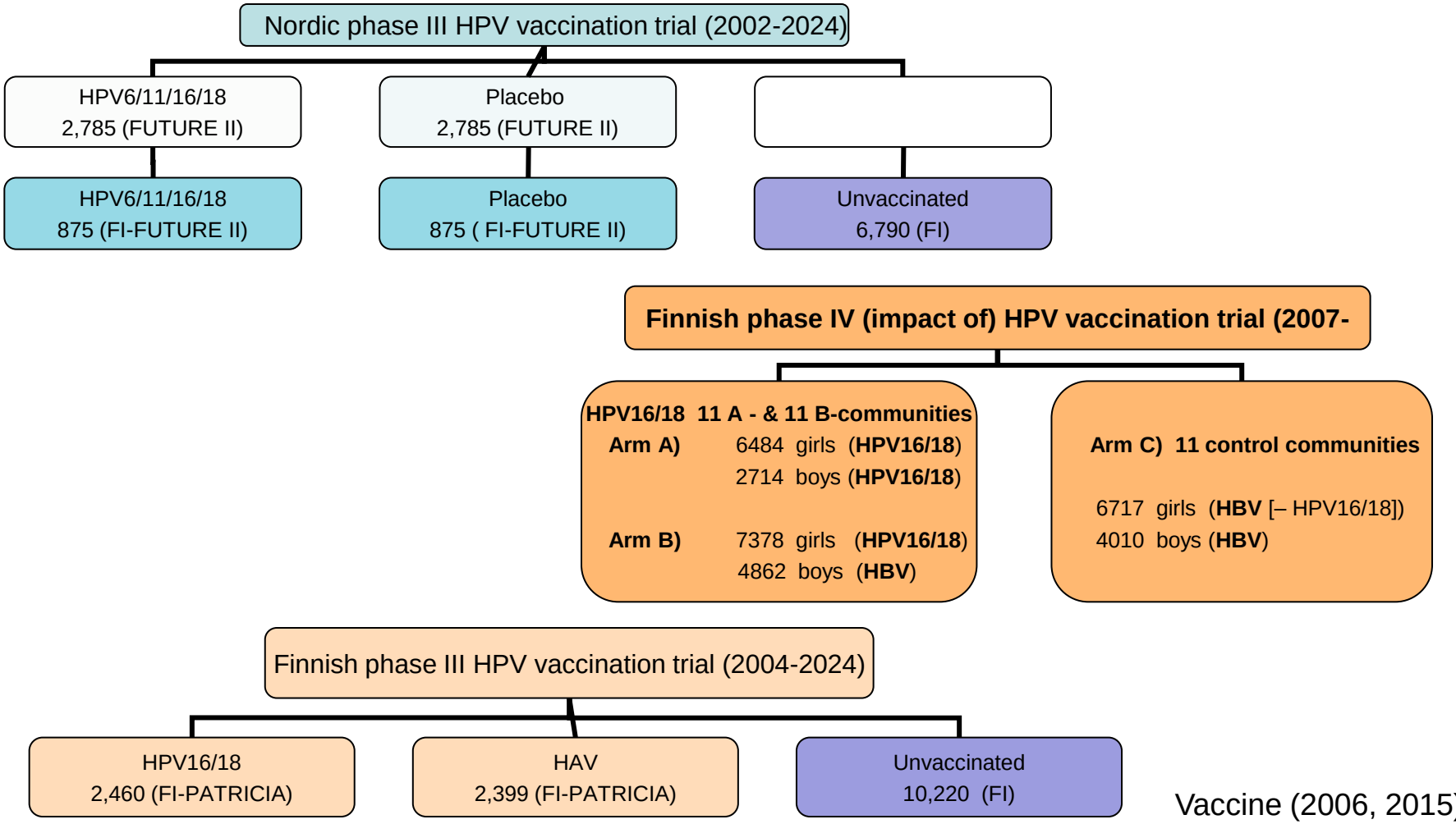
Antwerp 5-6-2025

HPV vaccination policy with superb impact - Evidence from a community-randomized trial

Matti Lehtinen Karolinska Institute&THL

ML has received grants from Merck&Co.Inc. and GSK Biologicals
for his vaccination trials through THL&Tampere University, Finland

Randomized phase III&IV HPV vaccination trials with population-based implementation and follow-up



Vaccine (2006, 2015)

IJC
International Journal of Cancer

(2017)

Vaccination protects against invasive HPV-associated cancers

Tapio Luostarinen [1,2], Dan Apter[3], Joakim Dillner[2], Tiina Eriksson[4], Katja Harjula[4], Kari Natunen[4], Jorma Paavonen[5], Eero Pukkala[1,4] and Matti Lehtinen[2,4]

The NEW ENGLAND JOURNAL of MEDICINE

(2020)

ORIGINAL ARTICLE

HPV Vaccination and the Risk of Invasive Cervical Cancer

Jiayao Lei, Ph.D., Alexander Ploner, Ph.D., K. Miriam Elfström, Ph.D., Jiangrong Wang, Ph.D., Adam Roth, M.D., Ph.D., Fang Fang, M.D., Ph.D., Karin Sundström, M.D., Ph.D., Joakim Dillner, M.D., Ph.D., and Pär Sparén, Ph.D.

Open access Original research

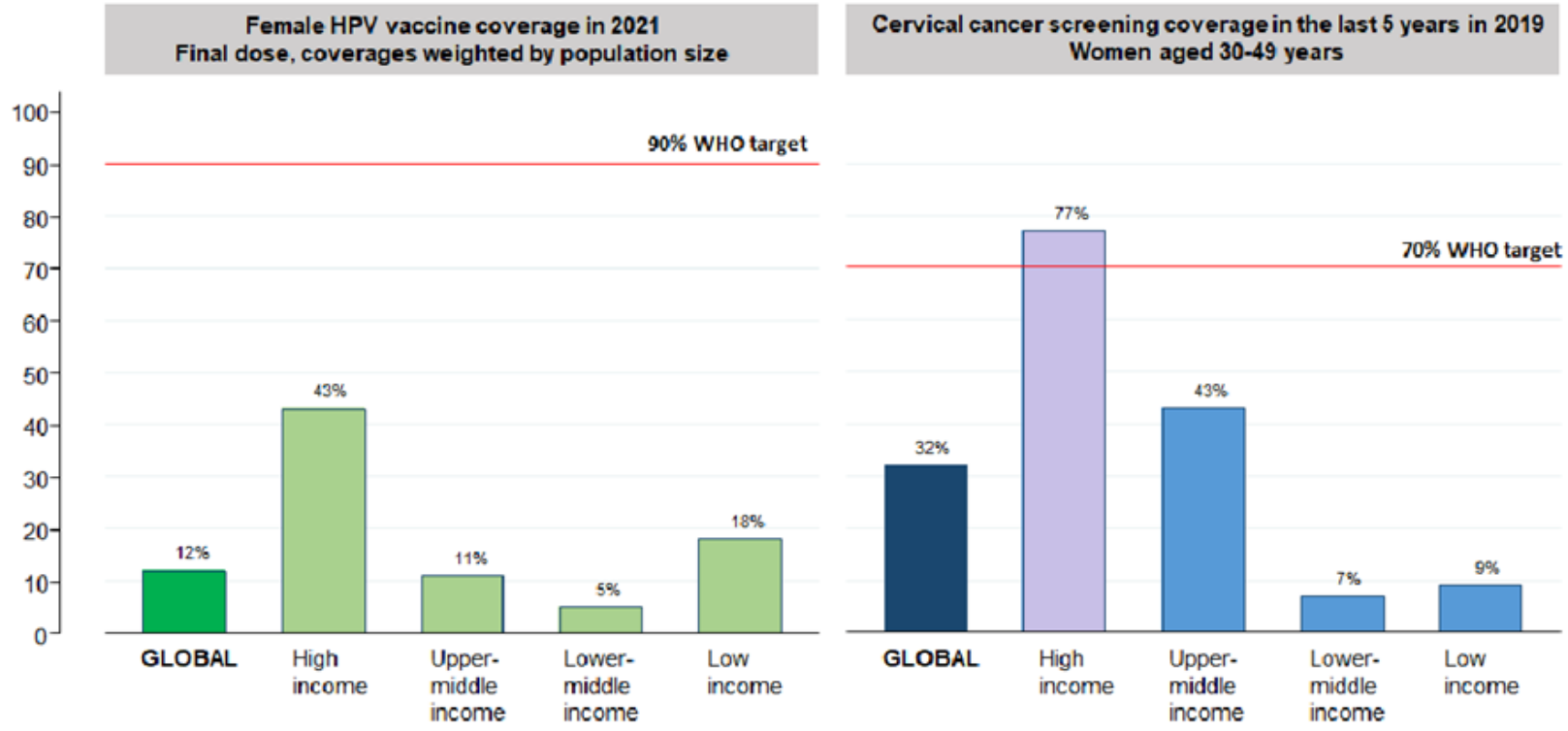
BMJ Open

(2021)

Human papillomavirus vaccine efficacy against invasive, HPV-positive cancers: population-based follow-up of a cluster-randomised trial

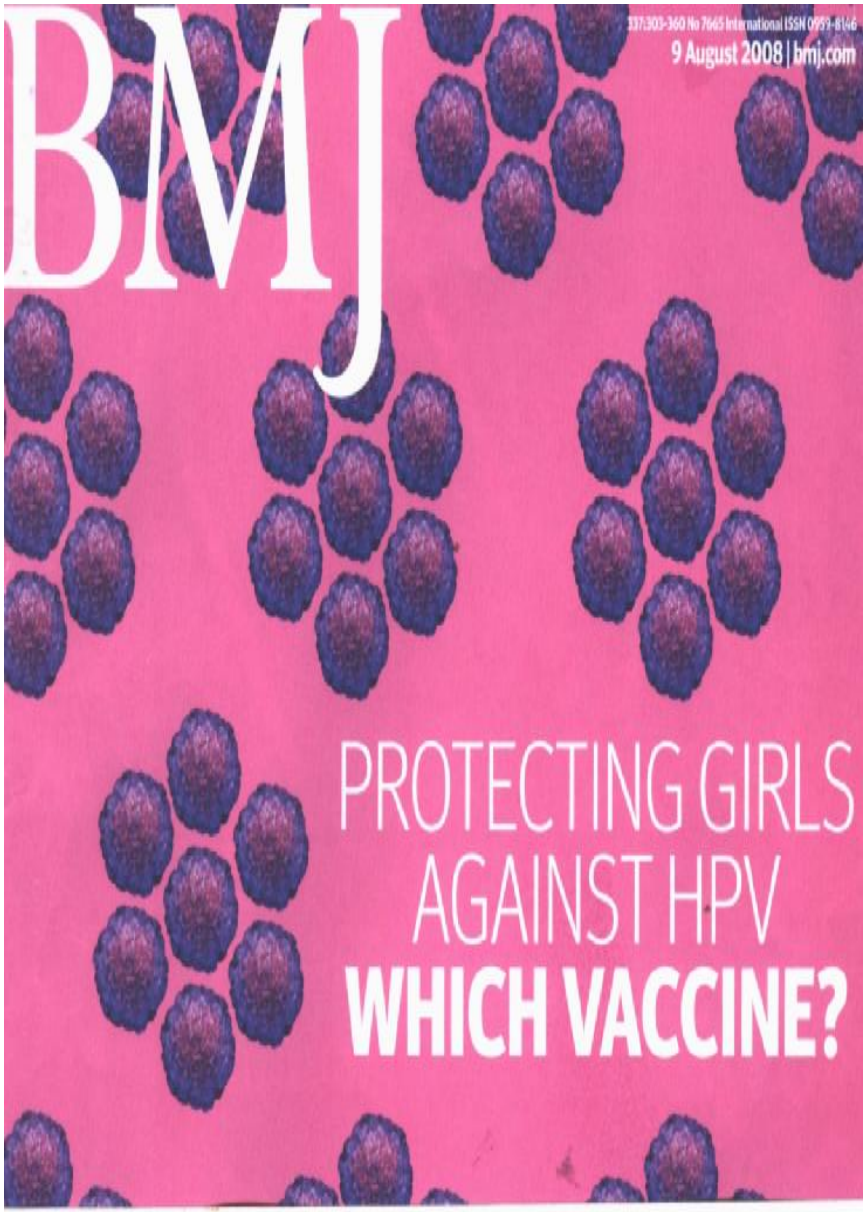
Matti Lehtinen [1,2] Camilla Lagheden,[1] Tapio Luostarinen [3] Tiina Eriksson,[4] Dan Apter,[5] Anne Bly,[2] Penelope Gray,[1] Katja Harjula,[2] Kaisa Heikkilä,[2] Mari Hokkanen,[2] Heidi Karttunen,[2] Marjo Kuortti,[6] Pekka Nieminen,[7] Mervi Nummela,[2] J Paavonen,[8] Johanna Palmroth,[9] Tiina Petäjä,[10] Eero Pukkala,[11] Anna Soderlund-Strand,[12] Ulla Veivo,[2] Joakim Dillner [13]

Figure 1. Global estimates of HPV vaccine coverage and cervical cancer screening by income



Data Sources: Bruni 2022 Lancet Global Health, Bruni et al 2021 Prev Med, WHO Immunization Data portal: https://immunizationdata.who.int/

Int J Cancer (2024)



How to make the most of of a powerful intervention?

Coverage	(♀)
UK&Sweden	85%
Australia	73%
Finland	70%
Germany	<50%
France	<30%

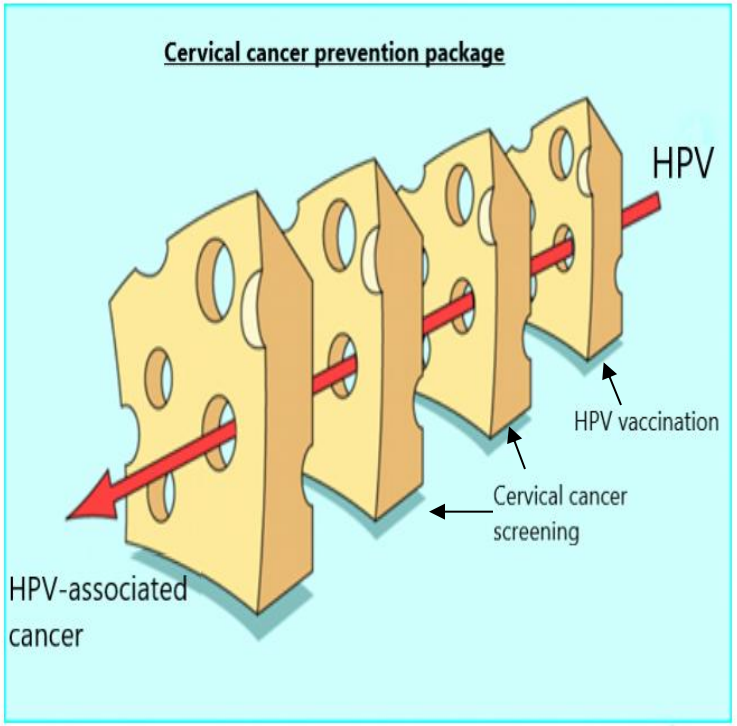
Marginalization destroys impact of public health policy

WHICH STRATEGY?

Unvaccinated marginalized women

Swiss cheese model

HPV unvaccinated ♀ are more likely to be screening non-attenders (Kreusch 2018)

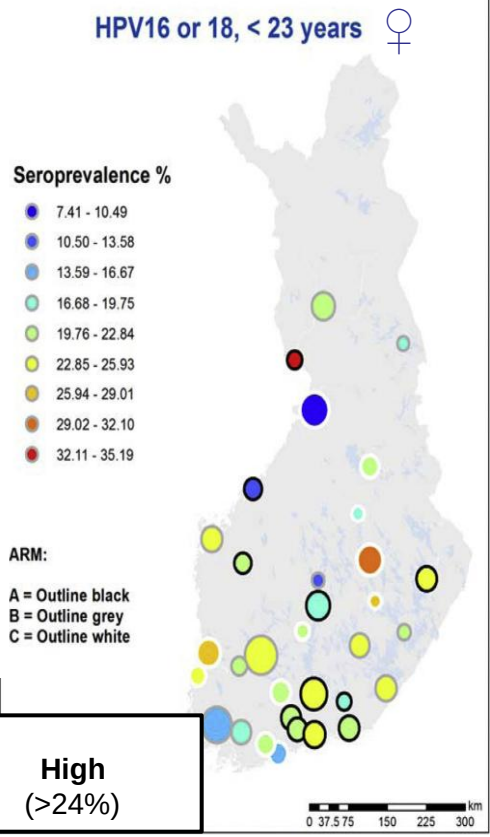


(Reason 2000, amended)

Community-randomised implementation trial

School-based **gender-ntrl** vs. **girls-only** **HPV** vaccination

(2007-2014)



1. Study population
   92-95 birth cohorts

2. Stratification by
   HPV16/18 sero-
   prevalence in ♀

3. Randomization to
   intervention arms

4. Invited/**consented**
   early adolescents

33 Communities (80.272 feasible invitees)

- **Low** (<20.5%)
- **Intermediate** (20.5-24%)
- **High** (>24%)

- **A) Gender-ntrl arm** (11 communities)
  - 12243/ **6468**
  - 12463/ **2734**
- **B) Girls-only arm** (11 communities)
  - 14,570/ **7364**
  - 15,460/ **4885**
- **C) Control* arm** (11 communities)
  - 12,607/ **6682**
  - 12,929/ **4042**

*HBV vaccination

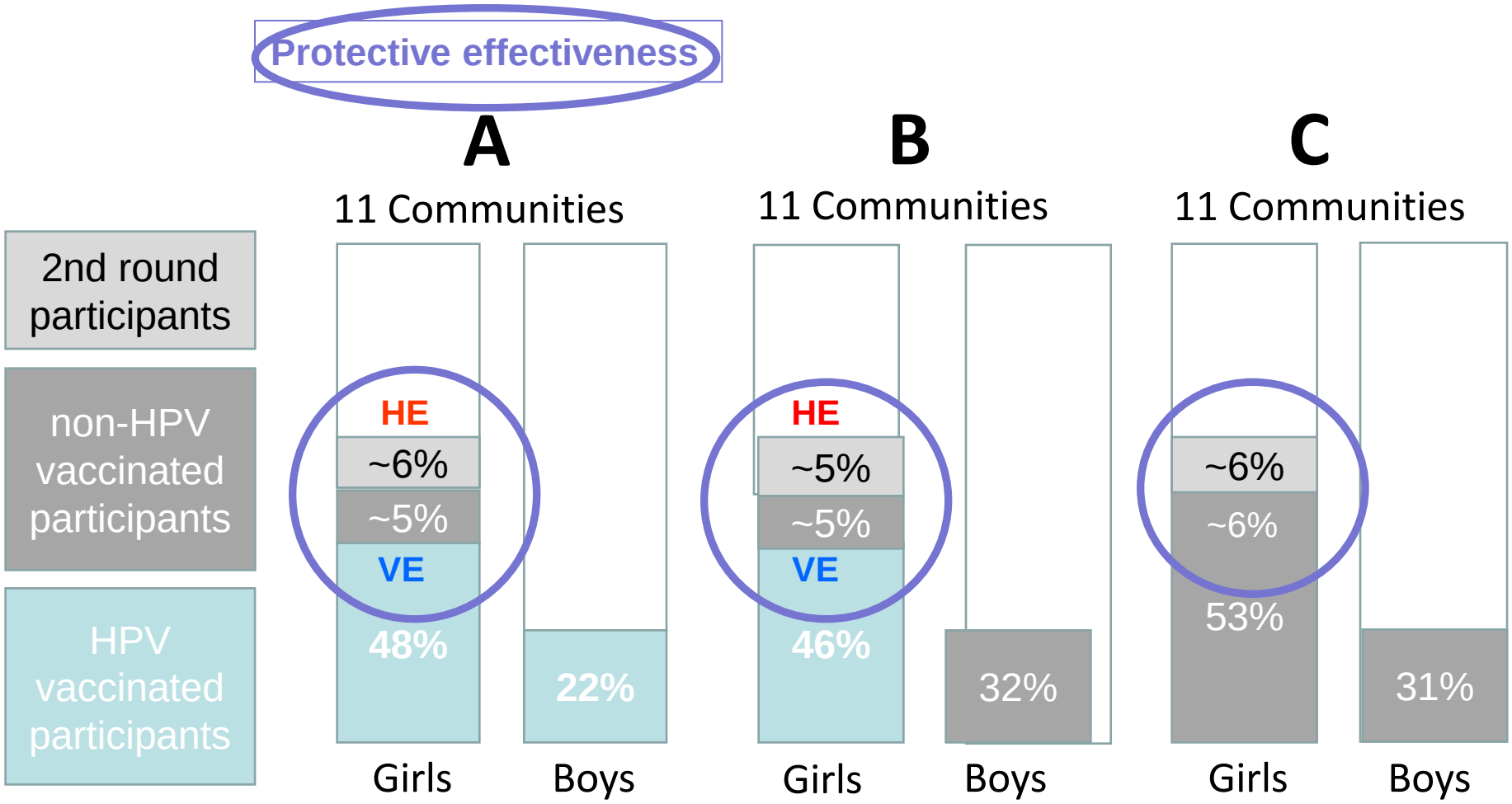
Vaccine (2015)

Community-randomized trial on the impact of implementing different HPV vaccination policies

- 33 communities (11 communities/arm)
  A-arm: gender-neutral (HPV16/18 vaccination)
  B-arm: girls-only (HPV16/18 vaccination)
  C-arm: control (HBV vaccination)
- 4 birth-cohorts invited (80 272 eligible subjects)
  1992/93 in 2007/08, 1994/95 in 2008/09
- **enrolled** **vaccinees**
  1992/93 born **16 000**
  1994/95 born **16 200**
  total **32 200**
- **vaccination coverage** **52% girls / 29% boys**
- **objectives** **Reduction of HPV prevalence in vaccinated ♀ (Vaccine efficacy)**
  Reduction of HPV prevalence in unvaccinated ♀ (Herd effect)
  Reduction of HPV prevalence in all ♀ (Overall impact = Protective effectiveness)

Int J Cancer (2018, 2019)

Community-randomized trial design and analysis



- Birth cohorts 1992-95
- HPV status at age 18

J Infect Dis (2020)

Cervical HPV typing (incident infections)

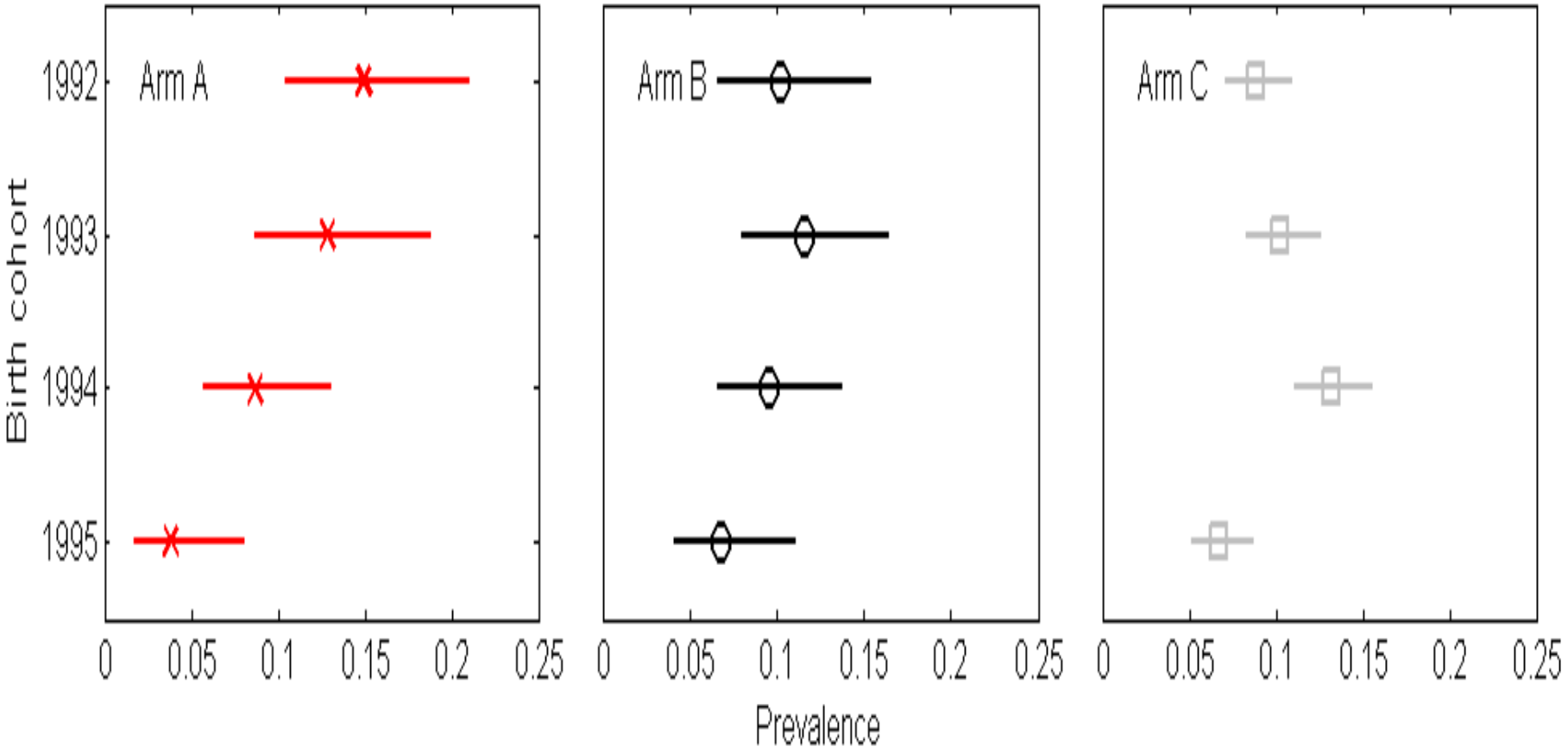
modified general primer
PCR → MALDI-TOF
mass spectrometry

HPV DNA typing

Prevalence of
HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59/66

(Söderlund 2008, 2009)

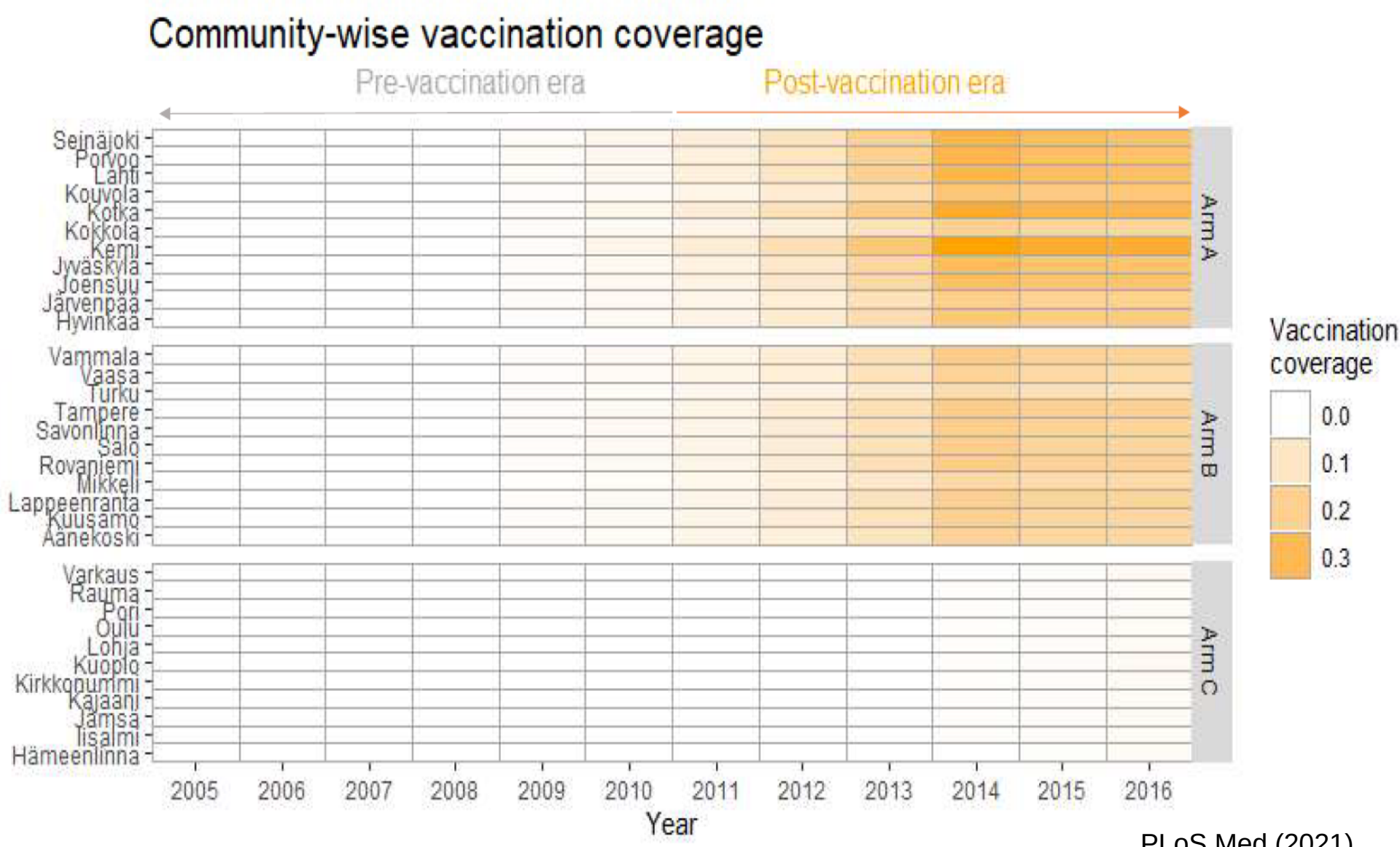
Fig. Herd effect - HPV18/31/33 prevalence reduction in non-HPV vaccinated 18 year-old females by birth cohort and vaccination strategy



Arm A [p for trend 0.0005], Arm B) [p for trend 0.092]

J Infect Dis (2020)

Fig. HPV16/18 serosurvey of pre/post -vaccination era in <23 year-old unvaccinated female residents of the 33 communities

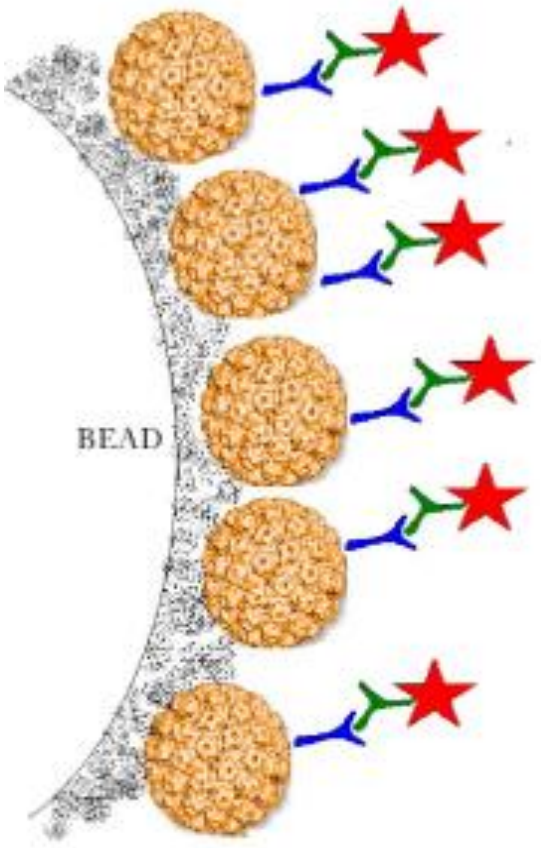


PLoS Med (2021)

HPV-seroprevalence (cumulative incidence)

→Multiplexed heparin-bound HPV pseudo-virion assay

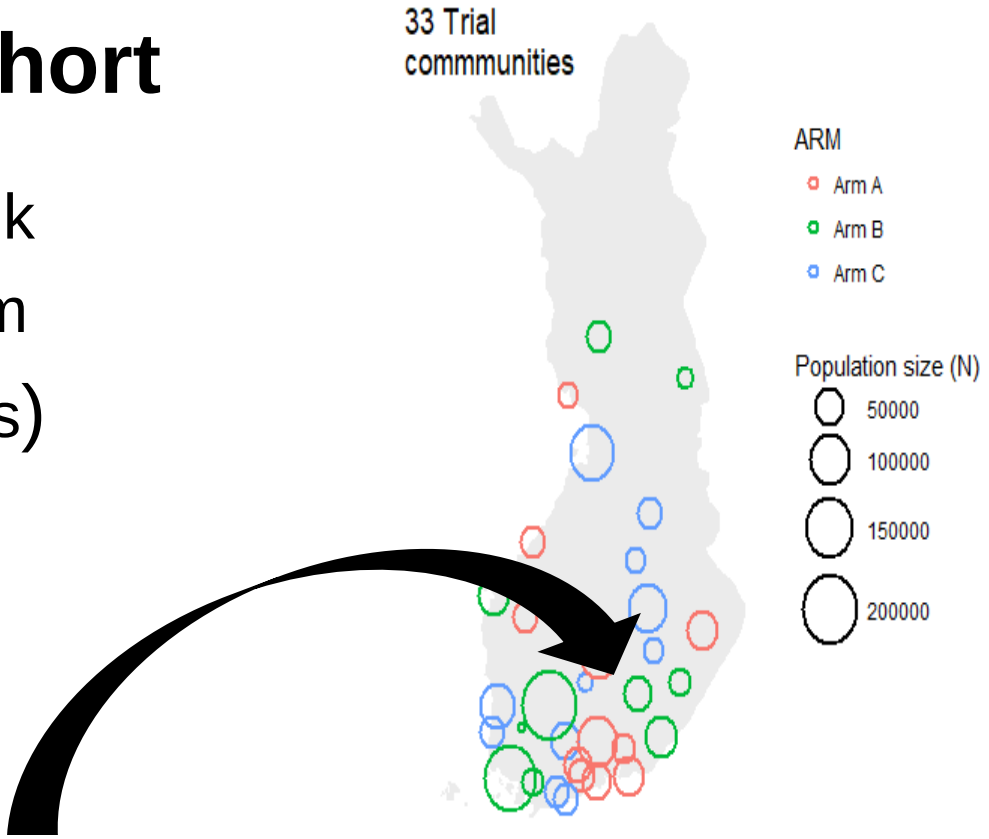
→ Serum antibodies to HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59/66/68/73



(Faust 2012, 2013)

Finnish Maternity Cohort

- population-based serum bank
- 96% of pregnant women from 1983-2016 (2 million samples)



Sub-sample of 8022 unvaccinated women <23 yrs of age

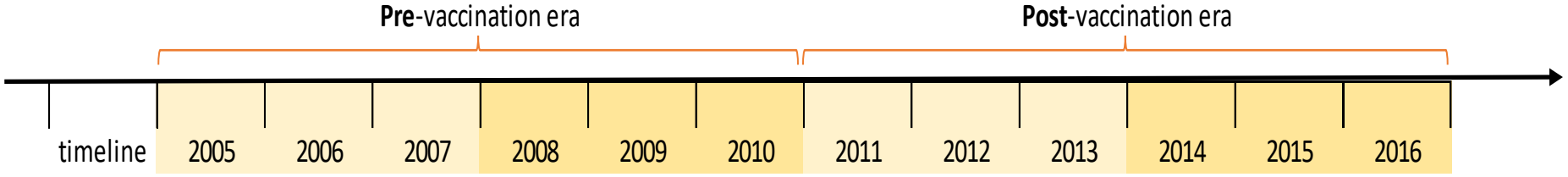


Table. Post- vs. pre-vac HPV seroprevalence ratios (PR) in <23 yr-old unvaccinated women of (A) gender-ntrl, (B) girls-only, and (C) control communities

	Post- vs. Pre-vaccination era		
	PR (95% CI) accounting for random error & systematic error		
HPV type	Arm A (N= 1247 vs. 1322)	Arm B (N= 1158 vs. 1289)	Arm C (N=1211 vs. 1304)
16	0.64 (0.10-0.85)	1.19 (0.98-3.50)	1.07 (0.89-1.81)
18	0.72 (0.22-0.96)	0.89 (0.41-1.11)	0.79 (0.22-1.03)
16/18	0.65 (0.09-0.84)	0.92 (0.42-1.06)	0.84 (0.24-1.01)

PLoS Med (2021)

Fig. Overall impact (HPV18/31/33/35 prevalence reduction) of gender-ntrl HPV vaccination (○) vs HBV vaccination (◊) vaccination between 2007-10 as measured in female birth cohorts 1992/93 (**a**) and 1994/95 (**b**) at age 18 in 2010/11 and 2012/13.

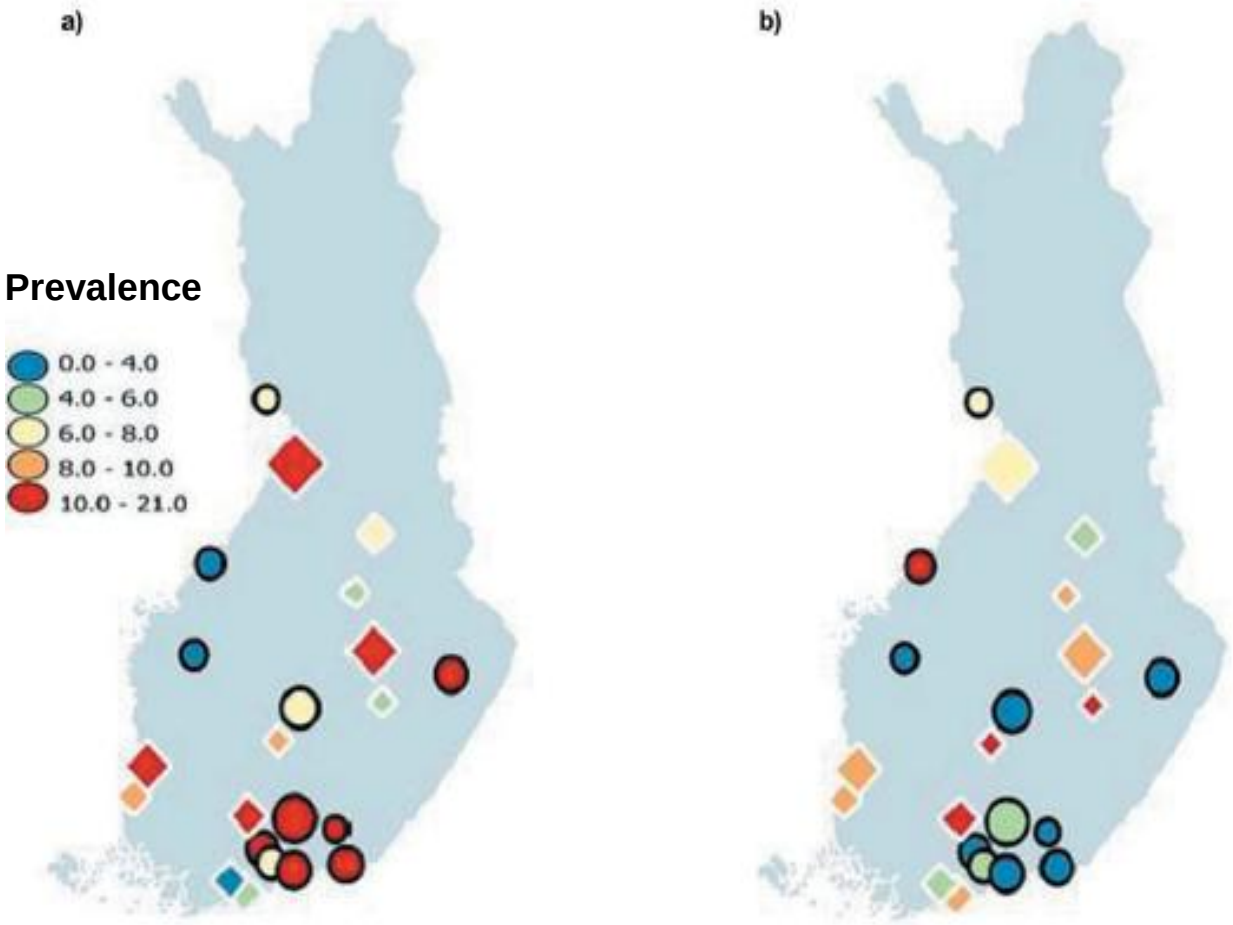


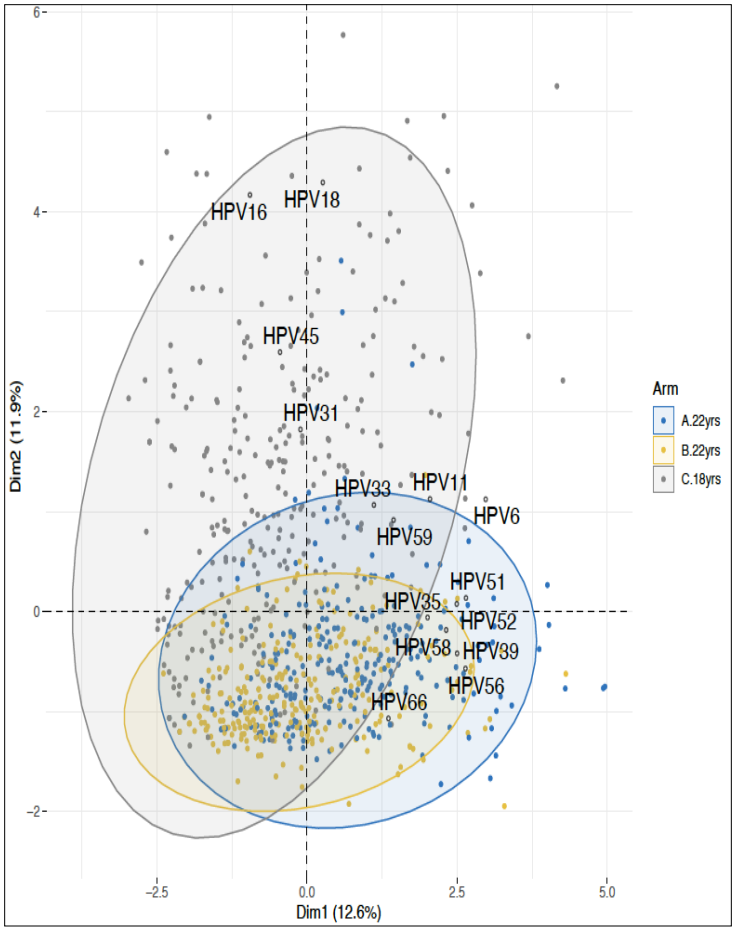
TABLE 1 The number[a] of vaccinated birth cohorts needed to eliminate human papillomavirus (HPV) (95% reduction of the life-time HPV) from post-vaccination birth cohorts as compared to the pre-vaccination birth cohorts by vaccine efficacy (VE), vaccination coverage and strategy (gender-neutral/girls-only), and targeted HPV types.

		Coverage of vaccination strategy							
		95%		90%		75%		50%	
HPV type	VE	Girls and boys	Girls	Girls and boys	Girls	Girls and boys	Girls	Girls and boys	Girls
HPV16	95%	7	24	9	NA	19	NA	NA	NA
HPV18	95%	3	6	5	9	8	NA	NA	NA
HPV31/33/45/52/58	95%	2	3	3	5	6	11	13	NA
	80%	6	9	6	10	8	31	21	NA
	50%	13	NA	14	NA	34	NA	NA	NA
HPV (faster clearance types)	95%	1	1	2	3	5	7	8	12
	80%	4	6	5	6	6	9	9	16
	50%	8	12	8	13	10	18	15	NA

[a]Computed by a transmission model adjusted to Finland (https://doi.org/10.1371/journal.pone.0072088).

Int J Cancer (2025)

Community-level distribution of oncogenic HPVs 8 years post-vaccination



Differential distribution of HPVs between communities ($P < 0.001$) using both Bray-Curtis and Jaccard distances

Gender-ntrl (blue HPV33/39/51/52/56/59)
Girls-only vaccinated (yellow)
Control communities (grey)

Cell Host & Microbes (2023)

Conclusions

- Vaccination provides protection against invasive HPV-cancers
- Moderate coverage gender-neutral HPV vaccination provides superb herd effect and protective effectiveness in <5 yrs and probable eradication of pivotal hrHPVs within the next 15-30 yrs
- Low oncogenicity hrHPV types replace vaccine HPV types in ecological niche vacated following gender-neutral vaccination

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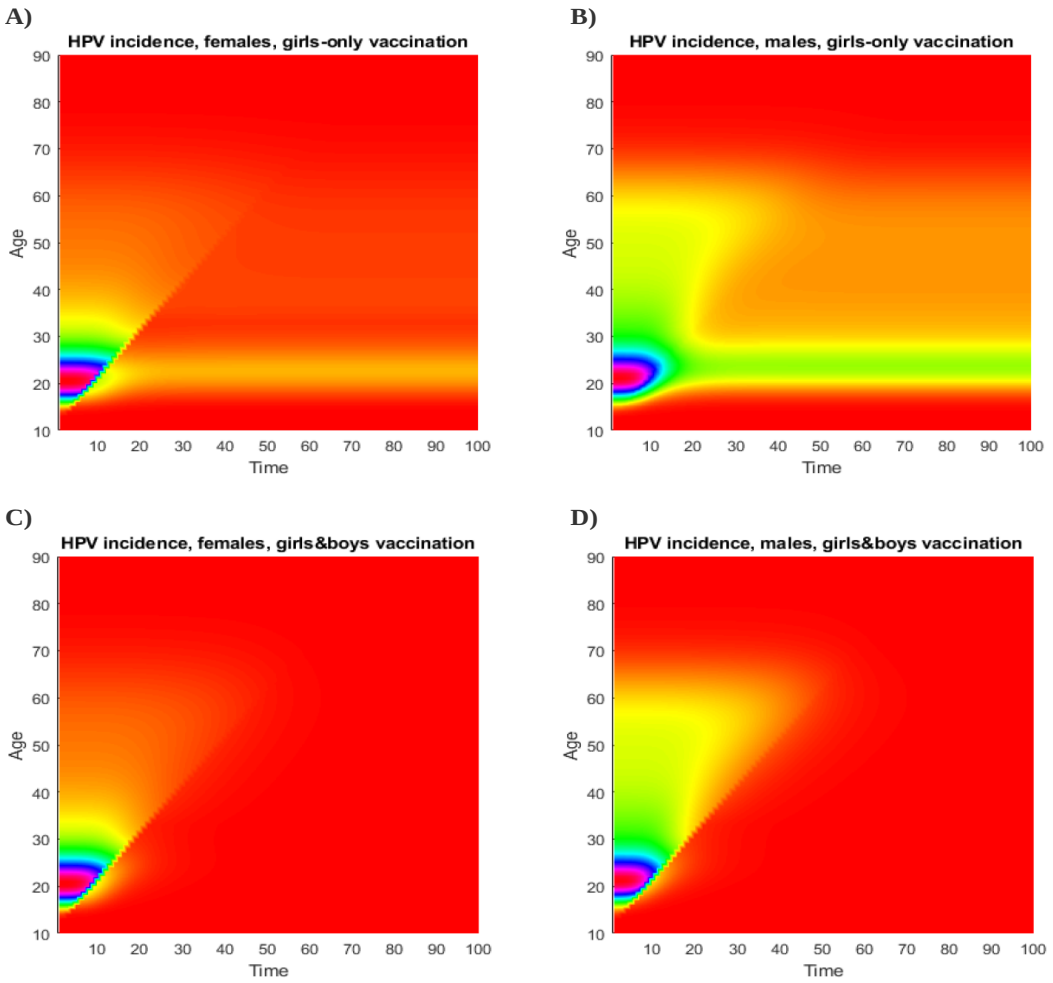
Ville Pimenoff	(Oulu University)
Simopekka Vänskä	(Finnish Institute for Health&Welfare)



Gender-neutral vaccination - the eradication strategy

Exp Rev Vaccines (2022)