Monitoring of Human Papillomavirus vaccination

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Why HPV surveillance and why is HPV special?

Incubation time from infection to cancer is decades.

- **First ever prophylactic vaccines approved with "prevention of cancer" as indication. Basis: Solid clinical endpoint (CIN2/3) + post-licensure requirement for long-term follow-up.**
- **Evaluation of whether the program works or should be improved cannot wait for cancer endpoints.**

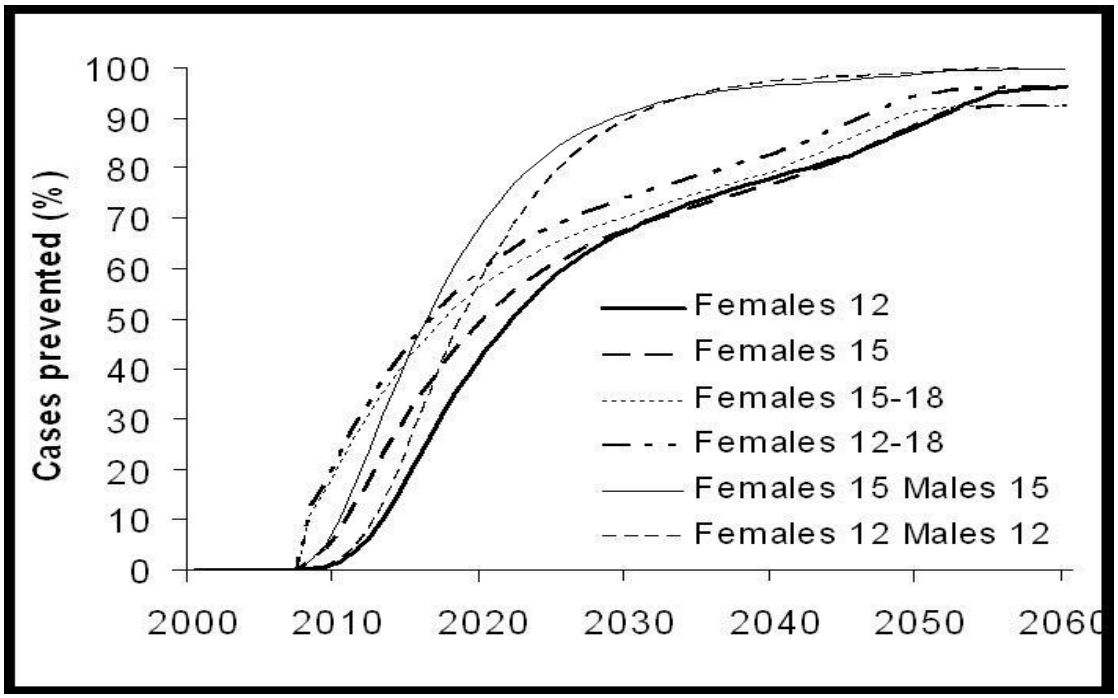
Infection is asymptomatic.

- **Standard clinical case reporting systems not possible for oncogenic HPV. Surveillance based on laboratory testing required.**

Many HPV types.

- **Requests for monitoring against type replacement**

Modelled demands on HPV eradication:
High Coverage, Catch-up and Both sex vaccination
(Swedish Natl Board of Health & Welfare 2007; Vaccine 2008)



Strategy evaluation

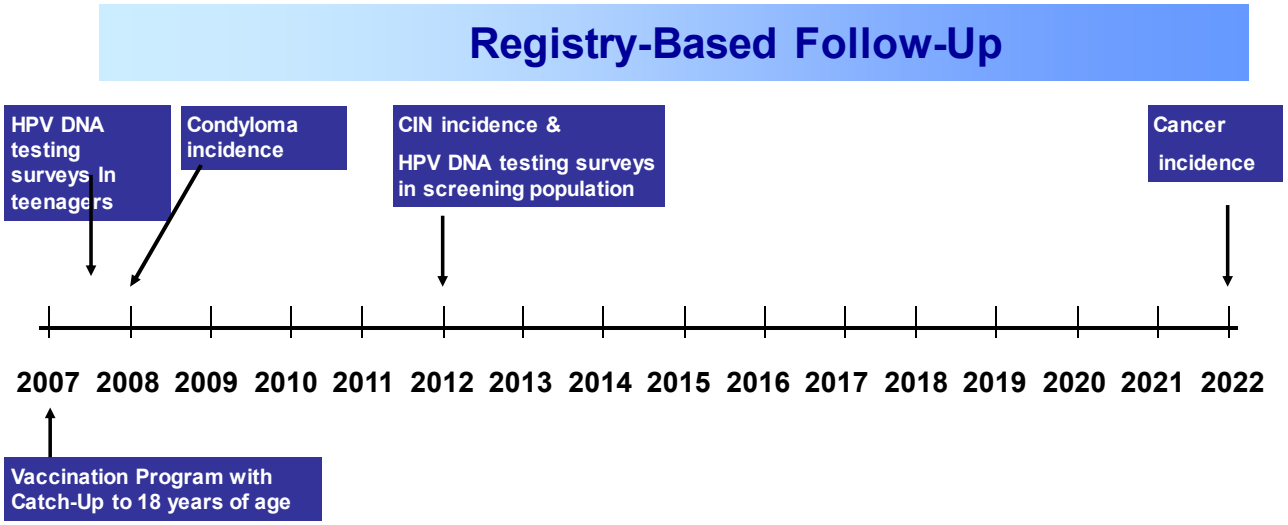
Different countries that use different vaccination strategies should have comparable evaluation systems - rapid accumulation of data on which strategy works best.

Exact strategy choice probably less important than using comparable evaluation systems!

Early evaluation components:

1. An HPV Vaccination Registry (determines coverage; enables registry linkages)
2. Condyloma Surveillance with HPV typing
3. Quality-assured HPV testing and typing in the target age groups (e.g. anonymised Chlamydia screening samples or cervical screening samples)

Early and late evaluation possibilities: When can we start to see effects?



Laboratory testing will have a key role in monitoring/evaluation.

The 2006 launch of the **WHO Global HPV LabNet** was significant news for HPV vaccination monitoring/evaluation.

Mission: To contribute to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact, through enhancing, state-of-the-art and internationally comparable laboratory analyses.

Support 1) the introduction of HPV vaccines and 2) surveillance of disease and infection.

Works e.g. by establishing quality criteria, international standards & proficiency panels & piloting surveillance systems.

World Health Organization

GLOBAL HPV LABNET

Assigned tasks for WHO global reference lab

*Design pilot projects to gain practical experience of how to follow-up the effects of HPV vaccination programs in a practical and (cost-)efficient manner.
-Condyloma reporting and typing in sentinel clinics
-Monitoring of sexually active youth groups by anonymised testing of Chlamydia screening samples
-Typing of all HPV-associated cancer in the country

Pilot high throughput system for monitoring of HPV vaccination effectiveness

Swedish HPV-vaccination policy:

- **Organised vaccination 11-18 year old girls since january 2012**
- **HPV vaccines subsidised for 13-17 year-old girls since 2007.**

Available infrastructural options for monitoring of HPV vaccination:

1) Cervical screening:

- **Screening begins at age 23, vaccination effect not measurable until several years later.**
- **No information regarding sex-specific changes of the HPV prevalence.**

2) *Chlamydia trachomatis* testing programme

- **High coverage among sexually active teenagers**
- **More rapid evaluation of HPV vaccination impact among both sexes**

Chlamydia trachomatis testing program

Chlamydia trachomatis **testing program in southern Sweden:**

- **Testing is free of charge. Promoted at youth clinics, STD clinics, OC prescription as well as by internet and media.**
- **~80 000 samples collected/year (pop. ~1.2 million inhabitants).**
- **>50% of participants in the ages 14-24.**
- **Primarily urine & vaginal swabs.**
- **One single lab performs all *Chlamydia trachomatis* testing.**

Aims

- **Development of a cost-effective monitoring strategy that**

  i) exploits an existing sampling infrastructure that covers a majority of the target population.

  ii) can perform large-scale HPV genotyping at a reasonable cost.

- **Establishment of a baseline HPV prevalence in the sampled population.**

Establishing the baseline prevalence

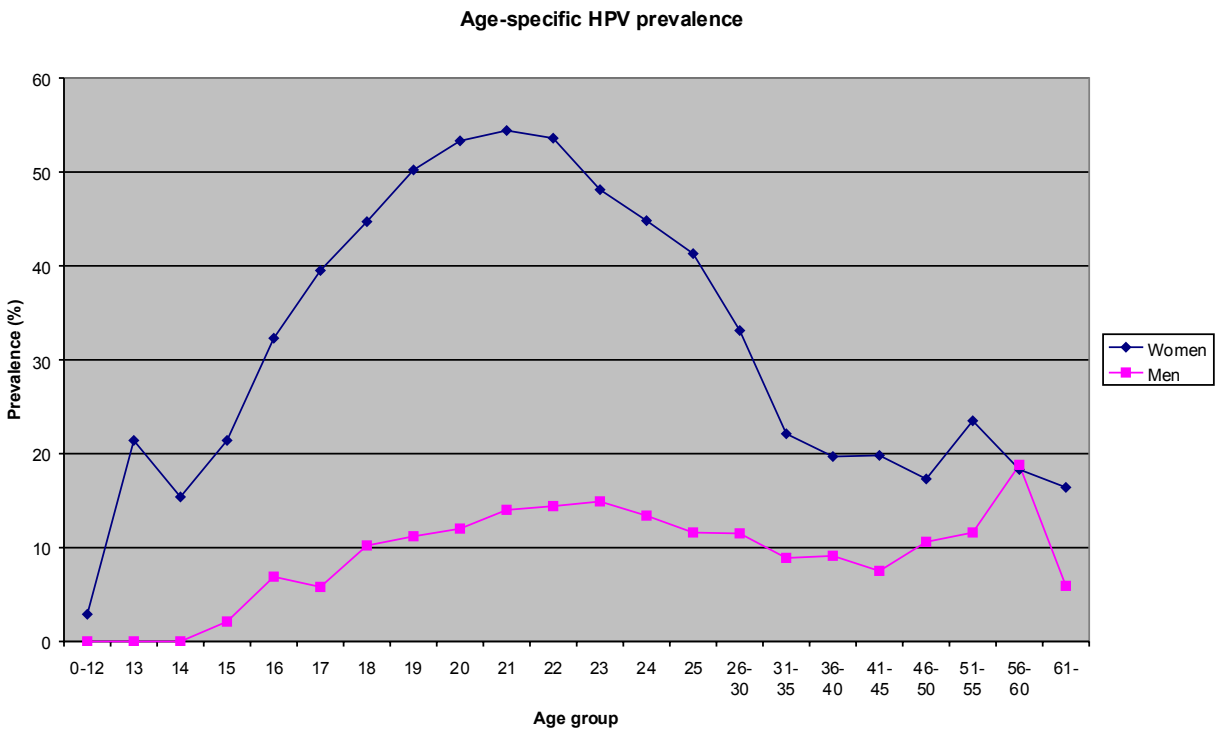
- **Low vaccine coverage among 13-17 year-old girls (7% to 18%) during 2008**
- **HPV DNA analysis of all samples collected March-November 2008. Anonymised samples. IRB support for testing without consent.**
- **Mass Spectrometry testing for type-specific baseline prevalence for 14 oncogenic and 2 benign HPV types: HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.**

Establishing the baseline prevalence

HPV DNA analysis:

- **PCR followed by MALDI-TOF mass spectrometry (Söderlund-Strand et al, Clin Chem 2008).**
- **Semi-automated, high-throughput system.**
- **Cost for consumables ~2,2 euro/sample.**
- **Proficient in the 2010 WHO HPV LabNet proficiency panel.**
- **Quality control: Consistent use of HPV DNA plasmid combinations in each run.**

Collected urine/vaginal samples (estimated number of unique subjects)			Inhabitants in Skåne 2008-11-01		Estimation of % tested	
Age, years	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
0-12	70 (55)	57 (44)	82586	87789	0.067	0.050
13	14 (11)	1 (1)	6782	7258	0.016	0.014
14	130 (101)	15 (12)	7227	7595	1.4	0.016
15	565 (441)	47 (37)	7647	7837	5.8	0.47
16	983 (767)	202 (158)	7811	8384	9.8	1.9
17	1717 (1339)	327 (255)	7983	8503	16.8	3.0
18	2319 (1809)	548 (427)	8284	8497	21.8	5.0
19	2301 (1795)	704 (549)	7808	8261	**23.0**	6.6
20	2247 (1753)	766 (597)	8083	8077	21.7	7.4
21	2054 (1602)	767 (598)	7850	7762	20.4	7.7
22	2043 (1594)	794 (619)	8002	7863	20.0	**7.9**
23	1857 (1449)	743 (580)	7943	7795	18.2	7.4
24	1575 (1229)	649 (506)	7888	7832	15.6	6.5
25	1423 (1110)	586 (457)	7643	7872	14.5	5.8
26-30	6011 (4689)	2170 (1693)	38862	40067	12.1	4.2
31-35	3839 (2994)	1125 (878)	39788	41643	7.5	2.1
36-40	2192 (1710)	616 (480)	40526	41742	4.2	1.1
41-45	1067 (832)	372 (290)	42727	44256	1.9	0.7
46-50	468 (365)	208 (162)	37411	38144	1.0	0.4
51-55	196 (153)	147 (115)	36744	37119	0.4	0.3
56-60	93 (73)	101 (79)	38374	37927	0.2	0.2
61+	73 (57)	102 (80)	154379	127875	0.037	0.063
Total	33237 (25925)	11047 (8617)	612348	600098	4.2	1.4



HPV type-specific results from the analysis of 44284 samples collected during March-November 2008.

Gender	HPV6	HPV11	HPV16	HPV18	HPV31	HPV33	HPV35	HPV39
% HPV+ women (95% CI)	4.1 (3.9-4.3)	0.88 (0.78-0.98)	9.9 (9.6-10.2)	5.1 (4.9-5.3)	5.2 (5.0-5.4)	2.4 (2.2-2.6)	1.6 (1.5-1.7)	3.7 (3.5-3.9)
% HPV+ men (95% CI)	1.7 (1.5-1.9)	0.43 (0.031-0.055)	2.1 (1.8-2.4)	1.4 (1.2-1.6)	1.3 (1.1-1.5)	0.51 (0.38-0.64)	0.24 (0.15-0.33)	0.60 (0.46-0.74)

Gender	HPV45	HPV51	HPV52	HPV56	HPV58	HPV59	HPV66	HPV68
% HPV+ women (95% CI)	3.2 (3.0-3.4)	6.0 (5.7-6.3)	4.7 (4.5-4.9)	4.0 (3.8-4.2)	2.5 (2.3-2.7)	2.6 (2.4-2.8)	5.1 (4.9-5.3)	0.89 (0.79-0.99)
% HPV+ men (95% CI)	0.92 (0.74-1.1)	1.7 (1.5-1.9)	0.74 (0.58-0.90)	0.67 (0.52-0.82)	0.48 (0.35-0.61)	0.41 (0.29-0.53)	1.4 (1.2-1.6)	0.14 (0.070-0.21)

Type-specific prevalence in March-April in comparison to September-November among girls aged 15-18

HPV	March-April (%)	September-November (%)	P-value
6	98 (6.4)	83 (5.3)	0.18
11	9 (0.6)	16 (1.0)	0.18
16	150 (9.8)	188 (11.9)	0.053
18	89 (5.8)	96 (6.1)	0.73
31	72 (4.7)	86 (5.4)	0.33
33	40 (2.6)	47 (3.0)	0.52
35	19 (1.2)	10 (0.6)	0.08
39	54 (3.5)	58 (3.7)	0.81
45	29 (1.9)	37 (2.3)	0.38
51	121 (7.9)	142 (9.0)	0.26
52	62 (4.0)	57 (3.6)	0.54
56	53 (3.4)	56 (3.5)	0.88
58	32 (2.1)	38 (2.4)	0.54
59	39 (2.5)	45 (2.8)	0.59
66	104 (6.8)	112 (7.1)	0.72
68	5 (0.3)	7 (0.4)	0.59

Conclusions

- **A high throughput HPV monitoring system was established and validated using HPV genotyping of all 44284 samples from the Chlamydia testing program in Southern Sweden, March-November 2008.**
- **Maximum attendance among 19 year old girls – 23% of all girls resident in the region.**
- **Large number of observations also down to 15 year old girls.**
- **The HPV prevalences peaked at 54.4% at age 21 among women, and at 14.9% at age 23 among men.**
- **The most common HPV types in the population was HPV 16 followed by 51 and 31 for women and HPV16, 6 and 51 for men.**
- **Prevalence of the different HPV types did not change appreciably among women aged 15-18 (vaccination target group) during the sampling period.**

World Health Organization

GLOBAL HPV LABNET

Assigned tasks for WHO global reference lab

*Proficiency Testing

-HPV DNA proficiency panel.

-HPV serology proficiency panel.

*International Standards

-HPV DNA: Large plasmidprep defining amount of HPV DNA (copy number traceable to biological standard)

-HPV antibodies: Large serum bleed defining an International Unit of antibodies

WHO HPV Serology International Proficiency studies

- HPV serology used as endpoint for:
  - →"Bridging studies" showing that vaccines are equally immunogenic for children (girls and boys) as for adolescents.
  - →Validating different vaccine batches by immunogenicity
  - →Studies on mode of administration, phase IV studies et c
  - →Earliest endpoint for evaluating new vaccines
- Serology established as correlate of protection only for animals.
- WHO international proficiency program for HPV serology (Eklund et al, Vaccine 2012) likely to significantly facilitate HPV vaccinology.

HPV DNA genotyping proficency panels

- Accurate and internationally comparable HPV DNA genotyping is essential for evaluation of a) HPV vaccines and b) vaccination programs.
  - →Use of virological endpoints (HPV persistence) will allow more rapid and efficient vaccine trials
  - →HPV DNA testing used to determine inclusion into trials strongly affects efficacy estimates
  - →Global evaluation of HPV vaccination programs will need comparable methodology
- Internationally standardised evaluation of different HPV DNA typing methods, as performed in different laboratories.

WHO HPV DNA Genotyping
Proficiency Panels

- Traceable to international standard preparation of DNA with defined amount (International Unit) to allow reproducibility of panels over time - necessary to compare quality over time.

- Should be able to detect multiple infections.
- High capacity to detect typing error.
- Should be possible to use with all known HPV DNA tests.
- HPV types: 14 high risk types and 2 low risk types.

- Issued once per year (Eklund et al, JCM 2010)

Post vaccination surveillance: Three ambition levels

- Low: Coverage and safety.
- Medium: Effectiveness surveillance systems.
  - HPV DNA testing (in teenager surveys or in cervical screening program);
  - Immunogenicity;
  - Monitoring of HPV-associated diseases.
- High: Registry-based follow-up systems

WHO Strategic Advisory Group of Experts. Meeting of the immunization Strategic Advisory Group of Experts, November 2008 – conclusions and recommendations. Weekly Epidemiological Record 2009;84:1–16. Available from: https://www.who.int/wer/2009/wer8401_02.pdf

Registry-based long-term follow-up

Exploiting the Nordic advantage of population-based registries and biobanks

- Basis: PIN-identifiable HPV vaccination registry.
- Followed-up over several decades of all subjects who have received the vaccine.
- Data on disease endpoints, health care resource utilization and any possible side effects are accrued using registry linkages with population-based health data registries.
- Cases of disease (e.g. CINII+) are retrieved from smear and tissue biobanks for HPV typing.
- Linkage with population-based serum biobanking system to determine antibody levels

Registry-based follow-up

- Long term effects and duration of protection
- Real life documentation of the health care cost benefits, for example, reductions in the use of Smears/Biopsies/Colposcopies/Cancer treatments
- Reliable evaluation of any possible late side effects.
- Long term data on persistence over time of the level and functional activity of the vaccine-induced HPV antibodies (search for correlates of immunity).
  -Will booster vaccination be required?
  -Is there really a protection against HPV types not included in the vaccine and for how long does it last?
  -Will there be type replacement or escape mutants?

Summary

Internationally standardised laboratory testing and global reporting systems will be important for HPV surveillance

- Early evaluation of effectiveness (HPV testing surveys; condyloma surveillance).
- Medium term evaluation (HPV typing of cases of HPV-associated diseases)

Internationally standardised laboratory testing and global reporting systems will be important for HPV vaccine development & implementation

-Second generation vaccines will arrive faster, be less expensive and trials for different vaccines will be possible to compare