

REVIEW

Effectiveness of preventive human papillomavirus vaccination

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Summary: Infection with human papillomavirus (HPV) is one of the major preventable causes of cancer world-wide. Rapid increase in cervical cancer incidence also in some western countries with cervical cancer screening programmes is probably due to increase in background exposure to HPV in the young. HPV vaccines are in clinical trials and the results have been promising, but due to assortative transmission of the infection and multiple HPV types the effect of large-scale immunization on their spread will vary between different populations and by HPV type. Thus, it is difficult to predict the effect of vaccination on cancer incidence on the basis of efficacy trials only. In the following evaluation of population level, effectiveness of vaccination on cervical cancer incidence (1) and HPV prevalence (2) by combined cluster/individually randomized trials (1) and cluster/community randomized trials (2) are described.

Keywords: cervical cancer, cost-effectiveness, human papillomavirus, population biology, vaccination

Population biology of cervical cancer and HPV infection

A sharp peak in the incidence of cervical cancer occurred in Iceland during the 1980s¹. Increasing incidence was found especially among fertile-aged women. In Finland and some other European countries (Israel, Slovakia, Slovenia, United Kingdom) the incidence of cervical cancer has also increased during the late 1980s and/or 1990s^{2,3}. In Finland, the predicted incidence for 1998–2002 was 2.2/100,000 women years⁴, but by 1995–1999 the incidence was already 4.2. The increase has been most prominent among women aged 35–39 years (4.1 in 1985 and 7.7 in 1999)⁵. However, low participation rate in the organized mass screening for cervical cancer does not explain it².

Profound increase in background exposure to the oncogenic human papillomaviruses (HPVs), accounting for more than 80% of the population attributable fraction (PAF) of cervical cancer^{6,7}, is a sizeable explanation for the above-mentioned changes. With HPV one is dealing with the most widespread and certainly the oldest sexually transmitted infection in humans⁸, with long periods of stable endemic prevalence in the sexually active population^{9,10}. Thus, common determinants of infection's reproductive rate:

transmission probability (β), duration of infectiousness (D) and contact rate (c)¹¹ are being applied to a totally different context than in the case of epidemics caused by new agents such as human immunodeficiency virus (HIV).

Phylogenetic studies suggest that the biology of HPVs has remained basically the same for over 200,000 years¹². It is, therefore, unlikely that biological changes, which would have increased the transmission probability or duration of infectiousness of the virus, would have taken place abruptly. High endemic prevalence of, e.g. HPV16, and assortative transmission of the virus together result in relatively low proportions of susceptible individuals in the sexually active population. This means that in a stable population like Finland rapid changes in HPV epidemiology cannot result simply from changes in the contact rate within that population. On the other hand, there are good data showing that decrease in the age of sexual debut from 18.9 to 16.6 has over the last 25 years¹³ disclosed one new, susceptible female birth cohort to HPV per decade. This is an ongoing trend in the younger birth cohorts (Table 1).

Verification of corresponding changes over time in the incidence of oncogenic HPVs at the population level is difficult because of lack of population-based biological sample banks suitable for HPV DNA or antibody analyses. So far, the only relevant data stem from the Finnish Maternity Cohort, a repository of sera originally collected at the first trimester from >98% of pregnant Finnish women for screening of congenital infections¹⁴. To define rates of seroconversions we identified

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Table 1. Relative proportions of Finnish adolescents, who have had their sexual debut at the ages of 14–16, by gender, education and calendar year (www.stakes.fi/kouluterveys)

Year	14 years		15 years		16 years [§]		16 years*	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
1998	12%	14%	21%	28%	n.a.	n.a.	40%	52%
1999	12%	15%	22%	29%	26%	37%	37%	52%
2000	19%	19%	29%	34%	31%	41%	43%	56%
2001	17%	19%	29%	36%	30%	43%	42%	59%
2002	17%	18%	27%	34%	30%	41%	44%	57%

*Technical school students

[§]College students

women with a minimum of two pregnancies (paired sera) within five years. These women were divided into different cells according to three-year intervals in expected age and calendar-time at the time of possible seroconversion. Sub-samples of up to 400 women, altogether 8000 women, were selected randomly for each cell and antibodies to HPV6/11 and 16 were analysed by standard enzyme-linked immunosorbent assay (with a sensitivity of 50 to 65%). We found a highly significant increase in HPV16 incidence throughout the 1980s and 1990s accompanied by a recent outbreak of HPV16 epidemic among adolescent (15–19 year old) women in the 1990s¹⁵. HPV16 seroprevalences appeared to be stable among fertile-aged Nordic women during the 1980s^{10,15}. However, a significant increase in the HPV16 seroprevalences could be identified over a longer period of time (between 1960s and 1980s in Sweden, between 1980s and 1990s in Finland)^{10,15}. It is likely that the decrease in the age at sexual debut exposed gradually increasing numbers of susceptible adolescents to the oncogenic HPVs, and is eventually resulting in a considerable increase (even epidemic outbreaks) of HPV16 prevalence in the new sexually active birth cohorts¹⁵. It is also possible that specific biological phenomena such as vulnerability of immature cervical transformation zone in the adolescent females might have indirectly increased the transmission probability of the virus or duration of infectiousness after acquisition of the virus, but this remains to be shown.

It is likely that conventional cervical cancer prediction models for the western countries mostly considering the effects of demographic transition and epidemiological transition of the disease prove unsatisfactory. Future predictions on the incidence of cervical cancer should also consider probable changes in the risk environment and the widening gap in health problems and health needs across social classes^{16,17}. Secondary preventive measures like cytological or HPV screening do not change the risk environment and are flawed by the increasing social and economic inequality, which result in low participation rates among women who would have benefited most from the screening. It is likely that their achievements, most notable in Finland with

up to 80% decrease in cervical cancer incidence between 1965 and 1990¹⁸ cannot be repeated even if proper treatment facilities were available. Thus, we will consider the long-term efficacy and effectiveness of HPV vaccination as the only opportunity for global control of cervical cancer.

Long term efficacy of preventive HPV vaccination

In our previous review we considered the pros and cons of HPV vaccination using virus-like particle (VLP) or DNA vaccines comprising the major viral capsid protein (L1) alone, as compared to using chimeric VLPs into which different early proteins or genes of the virus (E2 and/or E7) have been introduced¹⁹. Besides excellent immunogenicity the plain HPV L1 VLP vaccines have shown minimal adverse effects as compared to placebo in phase I and II trials^{20,21}. In the first phase III trial with the Merck HPV16 vaccine 2392 young women were vaccinated using the conventional three-dose intramuscular (i.m.) regimen with either HPV16 VLP vaccine or placebo. During an average of two years' follow-up the vaccine gave 91% protection against infection with HPV16 (as defined by polymerase chain reaction positivity), and 100% protection against persistent HPV16 positivity²¹. Despite a notable drop-out rate, 1533 individuals were eligible for the final analysis, and the fact that follow-up time in this study was relatively short it may well mark 'the beginning of the end for cervical cancer'²².

A number of clinical phase III trials (Merck's quadrivalent HPV6/11/16/18 VLP vaccine, Glaxo-SmithKline's bivalent HPV 16/18 vaccine, National Institutes of Health's bivalent HPV16/18 vaccine) have just started or are about to start. They will provide important information on the efficacy of the VLP vaccines against HPV infections, and against associated premalignant cervical and anogenital lesions. Limited licensure (based on efficacy against HPV 16/18 infection) of the HPV VLP vaccines will be the major immediate benefit of these trials. Since the mode of action of the HPV VLP vaccines is the induction of high-titre

type-restricted neutralizing antibodies²³ it is self-evident that the VLP type combination of the once commercialized vaccines should meet the HPV type distribution in the target area. VLPs for new HPV types are in the manufacturers' portfolios.

Phase III enrolment/vaccine administration will take 1–2 years, after which the vaccinees will be followed for three to five years by HPV testing, Papanicolaou smears and colposcopy. In the Nordic countries they can then be referred to the existing organized mass screening programmes, which have been proven effective against cervical cancer¹⁸. This is an ethically sound alternative to vaccinating placebo arm in the end of a successful phase III trial, which at its best can prove efficacy of the vaccine against HPV (vaccine types only) positive cervical intraepithelial neoplasia (CIN) 2/3. At least in Finland, where HPV vaccination will seriously be considered for the national vaccination programme, data on the efficacy of the vaccine against the hard end points (carcinoma *in situ*, CIS) not likely to regress spontaneously is considered of pivotal importance.

If/when the enrolment for the phase III trials is population based, randomization both by birth cohort and individual basis together with long-term follow-up, based on country wide cancer registries, it will eventually provide data on the protective efficacy of preventive HPV VLP vaccine against CIS and invasive cervical cancer (ICC)^{24,25}. It is important that a reference cohort of young women, who would have participated in vaccination had it been offered to their birth cohort, will be enrolled to estimate the indirect (intervention) and total (vaccination+intervention) effects of vaccination on both the HPV incidence rate ratios and the cumulative incidence rate ratios of CIS+ICC²⁶ (Table 2). Approximately 5000 adolescent female vaccinees and 7500 referents need to be enrolled to have a power of 80% for the CIS+ICC end-point assuming total vaccine efficacy against CIS+ICC of 70% and a 15-year cumulative incidence rate of 0.65%.

Finally, it is of utmost importance to understand that the impact of vaccination on CIS+ICC incidence must be evaluated now before the population gets 'contaminated' with the licensed vaccines²⁷. The phase III HPV vaccination trials in some Nordic countries will be performed in a population-based fashion and in the context of mass screening. This means that there is no obligation to vaccinate the placebo arms. Besides, after the phase III trial, i.e. three to five years of sexually active life, vaccination of the placebo arm is barely beneficial^{25,28}.

Effectiveness of preventive vaccination

If phase III trials are successful and followed by linkage of the cohorts of vaccinees and reference groups with the country wide cancer registries the following questions should be addressed: (1) Does large-scale vaccination result in reduced HPV prevalence in a naive adolescent population? (2) What is the optimal combination of preventive vaccination and different screening activities? (3) Is there a need for booster immunizations and what is the optimal timing of booster immunization? (4) What is the cost-effectiveness of a nation-wide HPV vaccination programme? Again the time-window when data for limited licensure of the VLP vaccines are available, but the licensure is pending should be exploited to find unbiased answers to these questions by running phase IV trials in an 'uncontaminated' population.

(1) Does large-scale vaccination result in reduced HPV prevalence? Eradication of HPV from the core groups may be equally difficult as eradication of hepatitis B virus or any other sexually transmitted virus. The difficulties range from the identification of the individuals at risk to their inaccessibility and low compliance²⁹. However, at the same time the assortative spread of sexually transmitted diseases, i.e. those with multiple sex partners have contacts with others with multiple sex partners and *vice*

Table 2. Basic concepts: main outcome measure, equations, definitions and impact of phase III HPV vaccination trials (amended from Halloran *et al.*²⁶)

Outcome measure	Equation	Definition	Impact
Vaccine efficacy: VE = 1 – relative risk	$1 - \frac{IR^* \text{ HPV vac.}}{IR \text{ placebo}}$	Direct protective efficacy against infection	Can the individual be protected against the infection?
	$1 - \frac{IR \text{ placebo}}{IR \text{ unvac.}}$	Indirect protective efficacy against infection	Impact of improved health conscience
	$1 - \frac{IR/CI^{\S} \text{ HPV vac.}}{IR/CI \text{ unvac.}}$	Total protective efficacy against infection/cervical cancer	Can the individual be protected against both the infection and cervical cancer?
	$1 - \frac{f \text{ CI HPV vac.} + (1-f) \text{ CI placebo}}{CI \text{ unvac.}}$	Total protective efficacy against cervical cancer	Can the population be protected against cervical cancer?

*IR = incidence rate, §CI = cumulative incidence rate, f = relative proportion

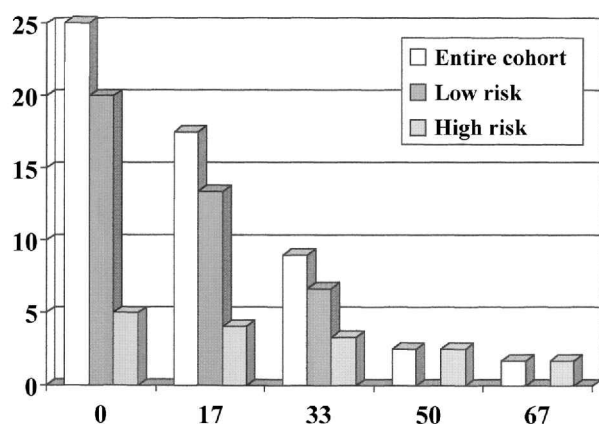


Figure 1. Theoretical reduction of human papillomavirus (HPV) type 16 prevalence among initially 11–13 year old adolescents by vaccine coverage assuming 100% vaccine efficacy and booster frequency of 5–10 years. y-axis=expected HPV prevalence (%) at the age of 20, x-axis=vaccine coverage (%)

versa, favours herd immunity in the general population³⁰. In simple theoretical models this results in effective reduction of HPV prevalence in the general population. However, it is even more important to understand the difference between expected HPV prevalence after five to 10 years of sexually active life without vaccination and the eventually reduced HPV prevalence with vaccination. Theoretically 65% to 85% eventual reduction from the expected HPV16 prevalence can be obtained with an HPV16 VLP vaccine showing 100% vaccine efficacy against HPV16²¹ infection with vaccination coverage of 50% (Figure 1).

Half of sexually transmitted HPV infections are obtained within three years after sexual debut²⁸. In the US, HPV infection incidence peaks at the age of 19 and declines rapidly thereafter³¹. Due to earlier onset of sexually active life in Finland the peak may come one year earlier^{32–34}. On the other hand, the coverage of the Finnish vaccination programme at age 15 is >95% compared to 70% in the US³⁵. Thus, a significant reduction of HPV prevalence in new birth cohorts entering sexually active life is worth pursuing in Finland. Young girls and boys could be vaccinated before sexual debut at the age of 11–13 by a phase IV trial with a licensable/licensed HPV vaccine or with a beneficial hepatitis B vaccine. Fourteen to 16-year-old adolescents could serve as the reference population. In order to obtain all the possible information about the vaccination of both sexes randomization should be by communities matched for HPV prevalence as follows: (A) HPV girls and HPV boys, (B) HPV girls and hepatitis B virus (HBV) boys, (C) HBV girls and HBV boys (Table 3)^{30,36,37}.

(2) What is the optimal combination of preventive vaccination and different screening activities? Effect on rare end-points (CIS+ICC) could be assessed in the phase IV trial if communities with >3000 female vaccinees are considered eligible. It

is important to note that data for CIS will emerge from the long-term follow-up of phase III trials several years earlier but for the ICC end-point large randomized phase IV trials may well be the only chance for obtaining sound efficacy data²⁴. If the population attributable fraction of cervical cancer for the different HPV types included in the vaccine exceeds 80%^{5,6} its efficacy against CIS+ICC probably overrides the best results ever obtained by the organized cytological mass screening. The effect of primary (once in a life-time) HPV screening³⁸ at the age of 30 to 35 years could be evaluated in this context against conventional (every two to five years) cytological screening programme on the top of HPV vaccination.

(3) Is there a need for booster immunizations and what is the optimal timing for boosting? This deserves most serious attention. The neutralizing HPV antibody levels resulting from the three-dose i.m. regimen are very high but are likely to wane over time. It is important to note that HPV VLP vaccine is technically similar to the HBV vaccine, which has an efficacy of 95% against chronic infection^{39,40}. Comparison with protection against sexual transmission of hepatitis B after childhood immunization, however, indicates that boosters are likely to be needed at least at 10-year intervals. While the vaccine efficacy (VE) against chronic hepatitis B was still reasonably good (88%), VE against transient (sexually transmitted) infection 10 to 15 years after immunization was low (65%, with the lower confidence limit of 56%)⁴¹. Moreover, chronic hepatitis B is not directly comparable with chronic HPV infection because the target tissue/cells are readily available in the latter and persistent HPV infection does not require systemic

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

Assumptions: (1) Most HPV infections are acquired within 5 years after sexual debut and within ± 3 birth cohorts, (2) 12 to 15 year old adolescents are randomized by birth-cohort for HPV or hepatitis B virus vaccine arms, 16 to 17 year old adolescents serve as a reference cohort, (3) communities have >1000 adolescents in the target birth-cohorts, (4) expected HPV prevalence at the age of 20 years can vary between 15% to 35%, (5) vaccine efficacy (VE) against HPV infection can vary between 85% to 95%, (6) vaccine coverage within an arm is >95%, (7) $\alpha=0.05$, $1-\beta=0.9$. An example: 14 communities per arm would yield 90% power for the demonstration of 75% eventual reduction of HPV prevalence by the age of 20, assuming that the subjects have sexual contacts in the ± 3 birth cohorts of the same population, 50% of which is vaccinated against HPV, VE of 95%, expected HPV prevalence of 25% in unvaccinated 20 year old individuals and population mixing of 20%.

infection/viraemia against which the neutralizing antibodies are extremely efficient.

HPV is phylogenetically a very stable virus¹². However, complete coverage of all oncogenic HPV types by a multivalent vaccine may not be necessary for two reasons: (A) Data on the oncogenicity of all the 20 'oncogenic' HPV types is variable⁴², and far from complete. For instance, after control for multiple comparisons in the International Agency for Research on Cancer series statistically significant odds ratios are obtained for HPV types 16, 18, 31, 33, 35, 45, 52, 58 and 59. Moreover some of these types (HPV33, 35 and 59) are found in less than 1.5% of cervical cancers⁴², and proportions of these and other rare HPV types in cervical cancer cases and controls are close to what one could await by chance. (B) Prospective data suggest that there exists cross-reactive (cell-mediated) immunity that may keep the oncogenic non-vaccine types under control due to naturally occurring boosting by the benign non-vaccine included types^{43,44}. Time will prove whether one of these types has the biological properties to fill in, or even expand, the ecological niches created by vaccinating against the most prevalent types^{30,45}. Meanwhile, it is most important to monitor for breakthrough infections through established country-wide surveillance systems and establish such a surveillance if not existent.

(4) What is the cost-effectiveness of a nation wide HPV vaccination programme? A number of deterministic models on the impact of preventive vaccination on HPV prevalence, cervical cancer incidence and the resulting cost-effectiveness have recently been published^{35,45,46}. These models are largely based on US or Nordic data on epidemiology of HPV, associated diseases, screening and treatment^{31,46}. Simplifying assumptions about (A) the agent, e.g., HPV types do not change over time or interfere with each other, (B) the population, e.g., it divides into a number of sexual activity groups of infinitive size defined only by differences in rate of sex partner change, (C) the natural history of cervical neoplasia, e.g., transition probability matrices for different steps of HPV pathogenesis, (D) the vaccine, e.g., different modes of vaccine failure and booster requirement, (E) screening, e.g., low efficacy opportunistic screening *vs* high efficacy organized screening are their very nature⁴⁷. The models are, of course, established to raise new and important questions, and emerging data verifies or falsifies their validity. Hopefully more reliable models will be generated, but important pieces of information may already be available.

Assuming 90% vaccine coverage, VE of 75% and 10-year duration of immunity HPV vaccination of both sexes would reduce the endemic prevalence of a specific HPV type by 45% as compared to 30% of vaccinating women alone⁴⁵. The impact was reported to be stable under a broad range of assumptions. All the models up to date agree that vaccinating high risk groups is not effective in the

case of such a wide spread agent as HPV^{35,45,46}. Resurgence of oncogenic HPV types not included into the vaccine may indeed be an issue, as in one model 60% reduction of incident infections of oncogenic HPV types by the vaccination resulted in only 46% and 47% reduction of CIS and ICC due to the resurgence⁴⁵. As discussed above, the seemingly stable endemic epidemiological situation leaves little room for the impact of (changes in) contact rate if new immunologically naive birth-cohorts do not become exposed to the oncogenic HPVs. We know that they do, and the impact of rapidly declining age at sexual debut needs to be considered in the models urgently.

Cost-effectiveness analysis of HPV vaccination assuming VE of 75% against the oncogenic HPV types predict that the vaccination would have comparable effectiveness to common childhood vaccines like the measles, mumps and rubella or pertussis vaccine. It would improve the life expectancy of 12-year-old girls by 2.8 days or 4.0 quality adjusted life days at a cost of \$250 relative to current practice³⁵; 113,000 cases with squamous intraepithelial lesion (SIL), 3300 cases with ICC and 1300 deaths from ICC would be prevented in the US³⁵. Unfortunately, this model does not consider the impact of herd immunity, perhaps because the authors assume relative low vaccine coverage of 70% among the 12-year-old girls. If the best case impact of herd immunity is assumed such that the prevalence of the major oncogenic HPV types would be reduced by e.g., 85% at the population level 160,000 cases with SIL, 6600 cases with cervical cancer and 2600 deaths from cervical cancer would be prevented in the US by vaccinating one birth-cohort of 12-year-old girls and boys.

In conclusion, HPV vaccination shows great promise for the control of cervical cancer in developing countries. As for the developed countries, those protected by a rational HPV vaccination programme would be the women not likely to participate in any kind of screening activities.

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