

Sound implementation of human papillomavirus vaccination as a community-randomized trial

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To be (most) effective, the very efficacious vaccines against oncogenic human papillomaviruses have to be implemented into national vaccination programs. Inferences from mathematical modeling studies can be made as to the most effective vaccination strategy in an ideal world. In addition, the best strategies can be evaluated against each other in community randomized trials. Results of such trials can hopefully guide vaccination implementation, which naturally varies owing to country-specific differences in economics, values (cultural and religious) and health policy.

Safe & efficacious vaccines against oncogenic human papillomaviruses exist

The first two vaccines against oncogenic human papillomavirus (HPV) types 16 and 18 have been licensed in most western countries [1]. The basis for the licensure was the excellent vaccine efficacy (VE) against infections with the HPV types 16/18 and/or 6/11/16/18, including, for example, persistent infections and associated high-grade squamous intraepithelial lesions, which are precursors of cervical cancer. Interim efficacy results of the two Phase III trials with the two substances (Cervarix[®] and Gardasil[®]) have had overlapping confidence intervals [2,3]. In addition, adverse effects have been comparable in the vaccine and control arms in both trials. Ongoing Nordic long-term follow-up trials involving, in total, 22,000 Finnish girls (originally aged 16–19 years) and approximately the same number of Scandinavian young women (originally aged 18–23 years) [4] will eventually document the long-term safety of the vaccines and whether they are efficacious against invasive cervical cancer. However, it is already important to plan the future as if the vaccines were also highly efficacious against cervical cancer and HPV-associated vulvar and vaginal cancers.

How not to use the HPV vaccines, from the public health point of view

It is likely that in the beginning, HPV vaccines will be used and administered opportunistically; for example, the new HPV vaccines will be paid for by customers and their use will resemble the use of vaccines related to traveling (e.g., vaccines against hepatitis A virus [HAV]). However, the HPV vaccines are prophylactic and have no therapeutic impact. Hence, at the individual level, people already infected with HPV 16 do not

benefit from HPV 16 vaccination; for them, benefit from the HPV 18 component of the vaccine is notable mainly because HPV 18-associated cervical adenocarcinoma is not detected by cytological screening. It is possible that, in the long-run, these individuals would benefit from vaccination-gained immunity because the antibody levels induced by natural infection gradually decrease [5] and may provide only partial protection against re-infection. However, after the age of 25 years, for example, after the incidence peak of HPV 16/18 infections, the benefit is marginal. Hence, average middle-aged individuals who are not yet infected with HPV have little benefit from purchasing the HPV vaccine because of the low probability of acquiring primary infection with genital HPVs [6]. Finally, even if highly efficacious at the individual level, opportunistic use of the prophylactic HPV vaccines will not yield high effectiveness at the population level.

Purchasing either one of the expensive HPV vaccines for one's own child or children (under the age of 19 years) provides the benefit of high VE, but only at the individual level. The beneficial and free effects of herd immunity will probably be marginal if the vaccine coverage of the opportunistic HPV vaccination is low. It is likely that delivery of (even subsidized) HPV vaccines in affluent societies, for example, in Finland, through pharmacies for opportunistic use will yield low vaccine coverage and low effectiveness.

On the other hand, even organized vaccination programs for girls only may not be enough for eradication of the oncogenic HPVs. The vaccine coverage of any program will never be 100%, and the lower the vaccine coverage in females, the more beneficial vaccinating boys additionally will be. Eradication of rubella only

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after both girls and boys were vaccinated in the Nordic countries is a good example of the significance of herd immunity [7,8]. In common sexually transmitted infections, such as HPV infections, the herd immunity is even stronger because of the assortative (like with like) nature of sexual behavior.

How the HPV vaccines should be implemented at the population level

The full impact of HPV vaccination can be obtained if the vaccine is administered for each birth cohort in early adolescents (both boys and girls) before they enter sexually active life, for example, when they start junior high school at the age of 12–13 years. Mathematical models based on comprehensive data and validated assumptions on sexual behavior, and the occurrence of HPV 16 infections during the last 20 years, indicate that 50–70% vaccine coverage in girls and boys helps to protect 70–85% of the new birth cohorts from HPV 16 infection [9,10]. With the normal 90% coverage of the Nordic national vaccination programs, HPV 16 infection will be almost eradicated according to the models. The models also predict that little additional effectiveness (in terms of reduction of the cervical neoplasia burden) will be gained by vaccinating individuals older than 18 years of age [11].

Mathematical models can also be used to design the most feasible effectiveness (Phase IV) studies in order to find the best vaccination strategy at the community level. Usually the variation between trial communities for a given exposure is assumed to be 50%. However, if the baseline variability in HPV 16/18 prevalence between the communities is reduced by stratification according to existing data [12], the power of any community-randomized trial in assessing the effectiveness of different vaccination strategies is remarkably increased (Table 1). It is important to note that this is true both for models assuming ‘take’ type of protection (vaccine protects against all challenges or not at all) and ‘degree’ type of

protection (vaccine protects against a fraction of challenges). This distinction does affect the modeling; however, for simplicity, the calculations presented here have been performed using the previous take type model only.

The optimal vaccination age, appropriate vaccine coverage, and whether both girls and boys need to be vaccinated to reach maximal effectiveness, as defined by HPV prevalence reduction, can be explored in a community randomized intervention study [13,14]. In the community randomized approach, direct comparisons of effectiveness can be performed between communities where girls only are vaccinated versus communities where both girls and boys are vaccinated (Table 1). If vaccination induces (probably mostly theoretical [15]) changes in sexual behavior, these do not easily jeopardize the feasibility of these studies (Table 2). Moreover, the power even increases by increasing sexual activity in studies comparing the effectiveness of vaccinating girls versus vaccinating girls and boys (Table 2). This is because the reduction of transmission probability by vaccinating boys is more important the more sexual risk-taking behavior is assumed to take place.

Paradoxically, the herd-immunity effect, which follows from reducing the fraction of susceptible people by vaccination and reducing the transmission probability among those vaccinated, can be assessed only among those who are unvaccinated [16]. In moderate (30–70%) coverage conditions (among girls and boys), breaking the chains of transmission by vaccinating both girls and boys is assumed to also have a notable impact among unvaccinated people in the (more or less) homogeneously behaving general population (Figure 1). However, using a take type of vaccine at the population level, the benefits of herd immunity seem to occur only through vaccination of both genders (Garnett *et al.* Unpublished Data). Finally, owing to the assortative nature of sexual (risk-taking) activity, HPV infection will eventually be concentrated among the highest

Table 1. The power of community randomized trials to assess significant reduction in HPV 16/18 prevalence among adolescents in 7 years by different CV in community HPV 16/18 prevalence*.

Coverage (%)	Design	CV 0.5 (%)	CV 0.2 (%)	CV 0.1 (%)
70	F+ & M+ vs F- & M-	73	100	100
70	F+ & M- vs F- & M+	50	99	100
70	F+ & M+ vs F+ & M-	13	34	51

*Assuming 420 adolescents/community & eight communities/arm ($\alpha 0.05$).
CV: Coefficient of variation; F: Female; HPV: Human papillomavirus; M: Male.

Table 2. The power of two different types of community randomized trials to assess significant reduction in HPV 16/18 prevalence among adolescents in 7 years*.

Coverage (%)	Design	CV 0.15 (%)	25% increase in sex CV 0.15 activity (%)	CV 0.10 (%)	25% increase in sex CV 0.10 activity (%)
30	F ⁺ & M ⁺ vs F ⁻ & M ⁻	83	14	94	18
	F ⁺ & M ⁺ vs F ⁺ & M ⁻	14	15	18	19
40	F ⁺ & M ⁺ vs F ⁻ & M ⁻	9	49	100	64
	F ⁺ & M ⁺ vs F ⁺ & M ⁻	21	22	21	29
50	F ⁺ & M ⁺ vs F ⁻ & M ⁻	100	84	100	94
	F ⁺ & M ⁺ vs F ⁺ & M ⁻	28	31	36	40
60	F ⁺ & M ⁺ vs F ⁻ & M ⁻	100	98	100	100
	F ⁺ & M ⁺ vs F ⁺ & M ⁻	36	40	44	51
70	F ⁺ & M ⁺ vs F ⁻ & M ⁻	100	100	100	100
	F ⁺ & M ⁺ vs F ⁺ & M ⁻	43	49	52	60
80	F ⁺ & M ⁺ vs F ⁻ & M ⁻	100	100	100	100
	F ⁺ & M ⁺ vs F ⁺ & M ⁻	61	69	70	79

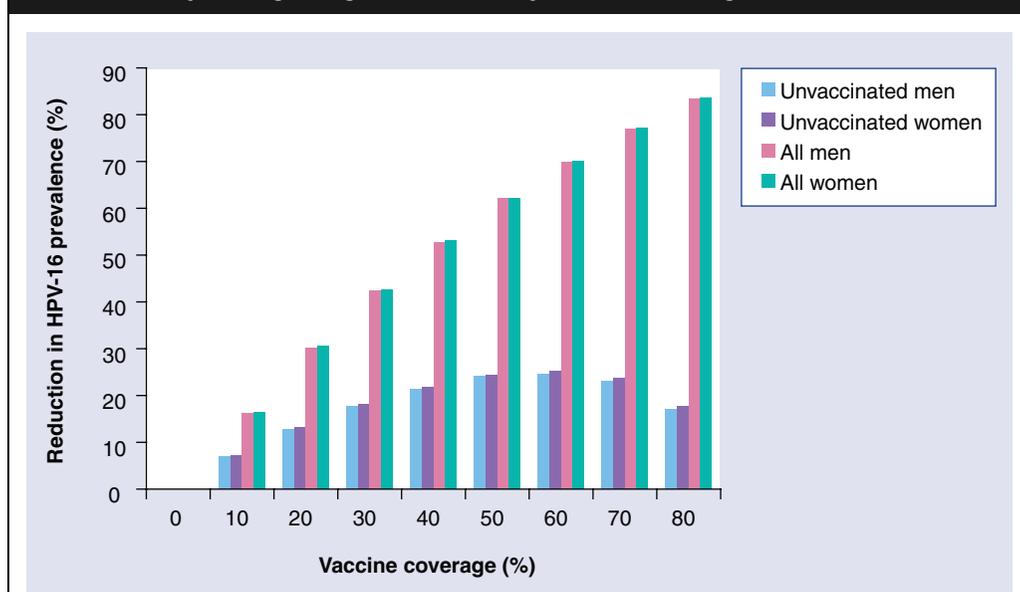
*Assuming different HPV vaccine coverage, 420 adolescents/community and eight communities/arm (α 0.05). CV: Coefficient of variation; F: Female; HPV: Human papillomavirus; M: Male.

activity groups from whom eradication will be difficult even with a ‘take’-type of vaccine [17]. Immigration of, for example, sex workers, may further complicate the situation.

In Finland, the National Public Health Institute has started a community randomized trial in 33 towns, which also have a relatively high occurrence of genital HPV infections [12]. Dur-

ing the term 2007–2008, adolescents aged 14 and 15 years have been vaccinated against HPV types 16/18. During the terms 2008–2010, adolescents aged 15 and 12 years will be vaccinated with the same vaccine. At the age of 18 years, a crossover vaccination will be organized to provide the participants (up to 90%) with all the envisioned health benefits. From 2010 onwards

Figure 1. Impact of herd immunity on HPV 16 prevalence after vaccinating both early adolescent boys and girls against HPV-16 by vaccine coverage.



HPV-16: Human papillomavirus type 16.

reduction of HPV 16/18 (and other oncogenic HPV) DNA prevalence will be evaluated among 18 year olds in conjunction with *Chlamydia trachomatis* screening by comparing oncogenic HPV prevalence in communities where early adolescent girls only or both girls and boys have been vaccinated against HPV 16/18, with oncogenic HPV prevalence in communities, where both boys and girls have received the hepatitis B virus (HBV) vaccine. Direct comparison between the two HPV vaccination strategies will also be performed. Furthermore, the effectiveness of the different vaccination strategies among both vaccinated and unvaccinated individuals will be evaluated.

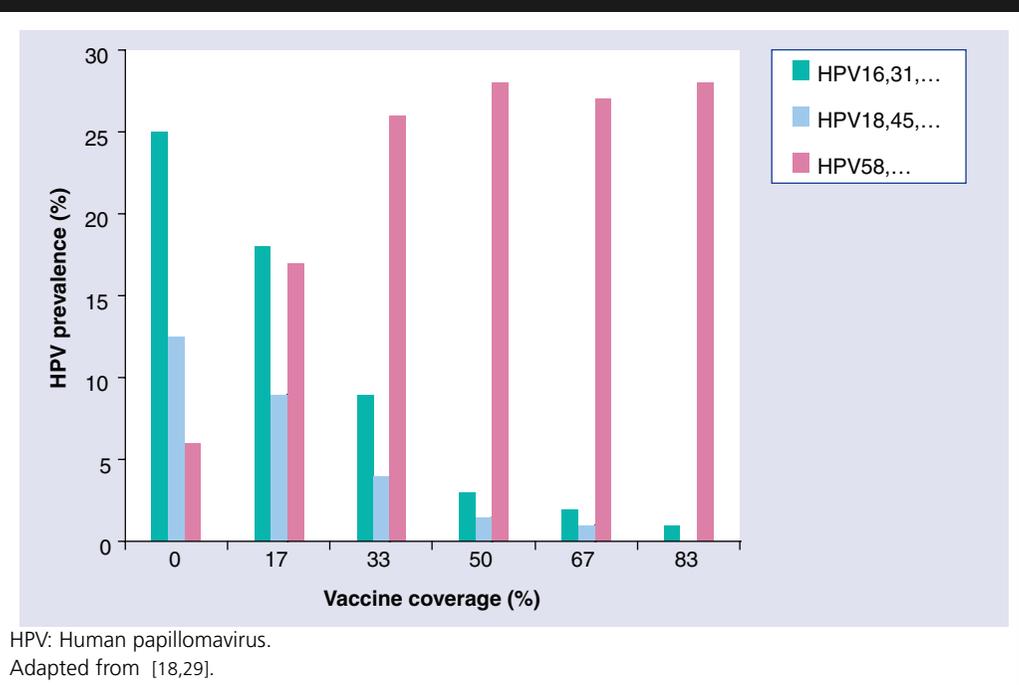
Monitoring vaccination safety at the population level: the issue of type replacement

Replacement of vaccine-targeted microorganisms by related serotypes or strains of the same micro-organism was predicted by Marc Lipsitch in 1997 [18]. The theoretical assumptions have been proven correct in the context of pneumococcal vaccination [19,20]. There are gross biological differences between colonizing bacteria and simple DNA viruses such as the HPVs causing mucosal infections; however, the possibility that vaccine-induced high antibody levels would create an ecological niche that in the worst-case

scenario (Figure 2) would be fulfilled by another (immunologically distinct) type of the same microorganism warrants consideration.

With the advent of increasingly sensitive PCR techniques, the occurrence of multiple HPV infections seems to be common [6]. There is some evidence of competition between oncogenic HPV types [6,21], but population-based studies are missing. In a community randomized trial setting with high vaccine coverage, it will be possible to monitor whether replacement of HPV 16/18 by new high-risk HPV types not included in the vaccine occurs. This is possible because in geographically distinct communities where either HPV 16/18 or HBV vaccines are being used, very low or practically no opportunistic HPV 16/18 vaccination occurs concomitantly with the trial. In the ongoing Finnish Phase IV trial, more adolescents at the enrolment (baseline) Phase (12–15 years of age) or at the screening (crossover) Phase (18 years of age) will be protected against both HPV and HBV infections through baseline and crossover vaccinations than following any opportunistic vaccination, which makes the approach ethically sound [3]. Eventually, the community randomized trial enables evaluation of both the population-level safety and the effectiveness of the different HPV vaccination strategies modeled in the above-mentioned studies [9,10] for implementation into the national vaccination program.

Figure 2. Models for oncogenic human papillomavirus prevalence reduction and resurgence of new human papillomaviruses by vaccine coverage.



Conclusion & future perspective

Irrespective of societal values, promoting the sexual health of the adolescents is one of the major contributions any society can provide. In addition to the beneficial issues associated with HPV vaccination, there may also be unwanted, albeit unlikely, consequences, such as an increase in the occurrence of other sexually transmitted infections owing to relaxed sexual behavior. However, the time will never be right for (monitored or evaluable, i.e., randomized) implementation of the most effective new HPV vaccine if potential harms are given priority. Evaluable implementation in the context of a community randomized trial allows evidence-based decisions on the implementation process, and how to integrate HPV vaccination and mass screening for cervical cancer [22].

Ongoing HPV and cervical cancer epidemics [12,23] can not be ultimately controlled without vaccination. However, the promising cross-reactivity of HPV vaccines, and inclusion of relevant oncogenic HPV types in the vaccines, will be critical. Primary HPV DNA screening [24] will be especially important for the vaccinated population should vaccinated women be less willing to attend organized screening for cervical cancer [15]. The

possibility of once or twice in a lifetime screening in the vaccination era needs to be evaluated.

Finally, there are promising vaccines emerging against comparable common sexually transmitted infections with severe sequelae, for example, Epstein–Barr virus, causing mononucleosis and Hodgkin’s lymphoma [25,26]; and herpes simplex virus type 2 causing genital herpes and neonatal herpes [26,27]. A combined vaccine against sexually transmitted infections of the young is the next goal.

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Executive summary

- Vaccines against the major human papillomavirus (HPV) types that cause genital infections are safe and efficacious.
- Opportunistic use of HPV vaccines (outside vaccination programs) will only benefit the individual receiving the vaccine.
- Sexual activity and risk-taking behavior are assortative; for example, individuals with a low number of previous partners tend to have partners who also have a low number of previous partners.
- Herd immunity from reducing the amount of susceptible people and reducing transmissibility has an especially strong impact for vaccines against sexually transmitted infections.
- Community-randomized trials bear the opportunity to verify the effectiveness of modeled vaccination strategies.
- Community-randomized trials also yield high enough vaccination coverage to assess population-level safety, for example, type replacement following implementation of a given vaccination strategy.

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