Why Consider Human Papillomavirus Vaccination in Older Women?

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Abstract
Preventive human papillomavirus (HPV) L1 vaccines are safe and efficient to prevent infection and lesions of vaccine-specific HPV types in women from 15 to 26 years, but also in older age groups. Clearly, public health funds are to be spent to organize programs for vaccination of young adolescents. Immunobridging studies and clinical trials have shown that HPV vaccines generate significantly higher plasma antibodies than following natural infections in women up to 55 years and prevent up to 90.5\% (95\% CI 73.7–97.5) vaccine-specific HPV infections and lesions in women aged 24–45 years who are HPV DNA-negative at the time of vaccination. However, data from clinical trials with HPV L1 vaccines in older women (older than 25 years) are still scarce compared to the amount of evidence from trials in women younger than 26 years. Information from large population-based studies indicates that older women remain at risk of infection by high-risk HPV and the risk of persistent high-risk HPV infection is significantly higher than in young women, leading to a higher risk of progressing disease and carcinoma. The natural history of HPV infection remains enigmatic as we do not know if the immune mechanisms that clear the HPV infection offer prolonged protection. On the contrary, some data indicate that seroconversion after a natural infection only partially protects against re-infection. Given the large proportions of adult men and women that change sexual partners, the protective effects of HPV L1 vaccines may offer an extra benefit against HPV-related genital diseases within a much shorter time period than after vaccination of prepubertal adolescents.

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Introduction

Cervical cancer is a common cancer in developing and developed countries. The implementation of cervical cytology screening programs has reduced the incidence of and mortality from cervical cancer. In countries with high coverage rates of cervical screening, death from cervical cancer has become relatively uncommon when compared to earlier figures or to other countries without effective screening programs. Nevertheless, mortality

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and morbidity rates of cervical cancer cannot be reduced to zero by screening alone.

Human papillomaviruses (HPV) are the major cause of cervical cancer. The development of two HPV vaccines, the bivalent HPV 16/18 Cervarix® (GlaxoSmith-Kline) and the quadrivalent HPV 6/11/16/18 Gardasil® (Merck, MSD Sanofi Pasteur) were designed to prevent HPV type 16 and 18 infections. Both infections are spread easily through genital contact and worldwide both HPV types are responsible for about 70% of cervical cancer cases, 50% of high-grade precancerous lesions and 25% of low-grade lesions. Gardasil is designed also to prevent HPV type 6 and 11 infections that cause the majority of genital warts in men and women and about 10% of low-grade lesions of the cervix.

National regulatory agencies have approved the use of both HPV vaccines based on safety and efficacy data, while public health agencies have included health economic calculations.

Public health money is spent mainly for the implementation of vaccination programs in very young adolescent women before the first sexual contact as immunogenicity, efficacy and safety data of HPV vaccine trials show maximal prevention of HPV vaccine type infections and lesions in women not currently infected with the vaccine-specific HPV types at the time of vaccination.

Available scientific data already offer various arguments to positively advise HPV vaccination in sexual active women, even at older age.

**Effects of HPV L1 VLP Vaccines**

The Future I trial, a randomized, placebo-controlled double-blind trial with the quadrivalent HPV 6/11/16/18 vaccine included 5,455 women between the ages of 16 and 24 years followed for an average of 3 years after the first dose [1]. In the intention-to-treat group, including women with prevalent infection or disease caused by HPV vaccine type or non-vaccine type, vaccination reduced the rate of any vulvar or vaginal or perineal lesions regardless of the causal HPV type by 34% (95% CI 15–49) and the rate of cervical lesions regardless of causal HPV type by 20% (95% CI 8–31). In the per-protocol population (negative for HPV16 or HPV18 infection during the vaccination period), vaccine efficacy was 100%. In this study population, 14.3% of the women were DNA-positive for one or more vaccine types.

In the Future II trial, 20,583 women aged 16–26 years were randomized to receive the quadrivalent vaccine, the HPV16 VLP vaccine or placebo. The mean follow-up was 3 years after the first dose [2]. In the intention-to-treat group vaccine efficacy was 44% (95% CI 31–55) in preventing HPV16/18-related CIN2/3, adenocarcinoma in situ (AIS) or cervical cancer.

A second intention-to-treat analysis noted 18% (95% CI 7–29) reduction in the overall rate of CIN2/3 of AIS due to any HPV type. In the per-protocol group, vaccine efficacy was 99% (95% CI 93–100) in prevention of HPV16/18-related CIN2/3, AIS or cervical cancer. Women who were currently infected at the time of vaccination with either HPV16 or HPV18 (DNA-positive) were not protected against cervical lesions by the relevant HPV type, but were still fully protected against cervical lesions caused by the vaccine types that these women were not infected with at the time of vaccination. In the presence of HPV16 or HPV18 antibodies in the serum, but in the absence of HPV in the cervical smear at the time of vaccination, the natural antibody was boosted by the vaccination and no HPV vaccine type-related cervical lesions were found during follow-up [3]. Enrolment in the study was limited to women with a lifetime number of 0 to 4 sexual partners. About 21% of the enrolled women had virological evidence (DNA-positive) of HPV16 or HPV18 infection at baseline. No clear evidence of protection was noted against HPV16- or HPV18-related disease in women who were DNA-positive at baseline.

Recently, the combined results from four phase II and phase III clinical trials with the quadrivalent vaccine in a 4-year follow-up period were presented for the per-protocol population (16–26 years). In this study population, Gardasil prevented 100% of HPV16/18-related CIN2 (95% CI 95–100), 97% of HPV16/18-related CIN 3 (95% CI 88–100) and 100% of HPV16/18-related AIS (95% CI 33–100) [4].

In the Future III trial, 3,800 women between the ages of 24 and 45 years were randomized to be vaccinated with Gardasil or placebo [5]. After a median follow-up of 26 months, the vaccine efficacy of Gardasil in the prevention of vaccine type-related infection alone and disease alone (cervical intraepithelial neoplasia and external genital lesions) in the per-protocol efficacy cohort (not currently infected at the time of vaccination) was 92.6% (95% CI 76.9–98.8) and 92.4% (95% CI 49.6–99.8), respectively. Of this sexually active study population 67% were serum-negative and DNA-negative to all four HPV vaccine types. None of them were infected with all four HPV vaccine types, less than 1% was infected with three vaccine types and 1% with two vaccine types [5]. Antibody titers main-
These preliminary data indicate that even in older women the frequencies were also higher for Cervarix in all age groups. Rates for anti-HPV16 and anti-HPV18 antibodies in cervicovaginal secretions were 2.3- to 4.8-fold higher for HPV16 and 6.8- to 9.1-fold higher for HPV18, respectively, than those elicited after natural infection. Antibody levels in sera at months 7, 12 and 18 in the 46- to 55-year-old group were higher or in the same order of magnitude as antibody levels for HPV16 and HPV18 achieved at months 40–50 in women 15–25 years of age. The correlations between serum and cervicovaginal secretion anti-HPV16 and anti-HPV18 antibody titers by age at month 24 were equal in all age groups, ranging from 0.73 to 0.90 for HPV16 and 0.82 to 0.93 for HPV18.

The safety and immunogenicity of the bivalent adjuvant HPV16/18 vaccine Cervarix was studied in women aged 15–55 years. The mean age of the total vaccinated cohort was 35 years. These data show that Cervarix is well tolerated and safe. 100% seropositivity was achieved 1 month after the third dose in all age groups. There was a high correlation between HPV16 and HPV18 antibody levels in cervicovaginal secretions and sera. An age-dependent decrease in antibody levels in serum was observed with increasing age. However, absolute values were high in all age groups. Peak antibody levels in the oldest age group of 46–55-years-old women were still 84- and 57-fold higher for HPV16 and HPV18, respectively, than those elicited after natural infection. Antibody levels in sera at months 7, 12 and 18 in the 46- to 55-year-old group were higher or in the same order of magnitude as antibody levels for HPV16 and HPV18 achieved at months 40–50 in women 15–25 years of age. The correlations between serum and cervicovaginal secretion anti-HPV16 and anti-HPV18 antibody titers by age at month 24 were equal in all age groups, ranging from 0.73 to 0.90 for HPV16 and 0.82 to 0.93 for HPV18.

Risk of HPV Infection according to Age

The age-specific HPV DNA prevalence is correlated with sexual activity and in some populations reaches low levels at old ages. In other populations however, there is no decrease as the curve rises again in middle age or never substantially falls. Indeed some studies have reported a second peak in later life and this is most pronounced in developing countries. In Australia, 12% of men and 6% of women aged 30–39 years report more than one partner in the previous year.
Age stratification of HPV prevalence has indicated the highest rates in young women under 25 years of age, decreasing rates from 30 years of age and a second peak of prevalence in women older than 45 years of age [20]. The increased prevalence of high-risk HPV infections in elderly women found in population-based studies may be explained by a higher rate of viral persistence and lower rate of HPV clearance. Selection of an integrated viral clone may take place and drives the HPV infection towards progressing disease, high-grade CIN or invasive carcinoma [21]. Older women between 40 and 50 years of age who were followed up for the development of cervical neoplasia show a significantly higher proportion of persistent HPV infections than younger women between 22 and 32 years old [22]. The relative risk for development of high-grade CIN is three times higher in high-risk HPV-positive older women than in younger women. Prolonged persistent infection increases the risk of progression to invasive carcinoma.

Clearly, the minority of partnerships is life-long and concurrent partnerships are not uncommon [23]. New sexual partners can continue with age, with 17% for men and 11% of women aged 35–44 in the United Kingdom [24]. National figures on legal divorces are therefore merely an underestimation of ending or changing sexual relationships.

Risk of Acquiring HPV16 or HPV18 Infection

The recently published data of the interim analysis of a large phase III randomized controlled trial on the efficacy of the bivalent HPV vaccine Cervarix show that 93% of the study population between 15 and 25 years were DNA-negative for HPV16 or HPV18 at the time of vaccination [8]. Only 1 in 1,000 of the women in the phase II and III trials with the quadrivalent vaccine had either serological or DNA evidence of exposure to all four HPV types 6, 11, 16 and 18, meaning that most sexually active young women still receive some benefit from vaccination.

In the Future III trial with the quadrivalent vaccine in women aged 24–45 years, about one third (33.2%) were positive for HPV types 6, 11, 16 or 18 at baseline by serological or DNA testing [5]. However, only 7.9% were infected with a vaccine HPV type at baseline as determined by DNA testing alone. 90% of the women enrolled in the study were susceptible to three or four vaccine HPV types and 67% were naive via DNA testing and serology to all four vaccine HPV types.

Therefore, these sexually active older women can be considered as candidates for primary prevention of HPV infection with the available HPV vaccines. These vaccines are very efficient in preventing HPV vaccine type-related CIN when the vaccinated woman is DNA-
negative for the HPV vaccine types at the time of vaccination.

Epidemiological data from the United Kingdom have shown that approximately 96% of women between the age of 21 and 51 do not have current HPV16 or HPV18 infection [25]. Older women of 51 years of age who are DNA-negative at baseline have the highest risk (21.3%) of acquiring a cervical HPV infection during a 3-year period compared to younger age groups (21 years – 15.2% and 41 years – 13.3%).

In young women with a mean age of 19 years, the 1-year cumulative incidence of first HPV infection was 28.5% and increased to almost 50% by 3 years [26]. The risk increased when the first partner was sexually experienced.

Although cumulative lifetime exposure to HPV might be as high as 80%, lifetime exposure to HPV16 or HPV18 may be much lower. The prevalence of serum antibodies to HPV16 ranges from 8 to 17% and for HPV18 from 3 to 15% [27]. Evidence for infection with both HPV16 and HPV18 is relatively uncommon. In vaccine trials, combined infections with HPV16 and HPV18 were encountered only in about 1% of the women. As much of the rationale for vaccinating older women depends on understanding whether a HPV infection is acquired via sexual activity or the re-emergence of an earlier latent infection, interesting epidemiological data have been gathered from the Ludwig-McGill cohort study [28]. In women aged 40 or older new HPV infection episodes with the same or new types are associated with new partners, which suggests that HPV exposures and infection could be prevented by HPV vaccination.

**Natural Immunity against HPV**

Among women with incident HPV infections 59, 51 and 68% seroconvert for HPV16, HPV18 or HPV6, respectively, within 18 months [29]. Whether these antibodies are protective is not known. A population-based cohort study of 7,046 women in Costa Rica studied the association between baseline seroreactivity to HPV16, HPV18 and HPV31 capsids and the risk of subsequent infection at follow-up visits 5–7 years later [30]. Immunity by these antibodies against subsequent infection was not observed. It can be stated that even after a previous infection women remain at risk of a subsequent infection with the same or a related HPV type. These data confirm the results of earlier data from a 2.9-year follow-up study on concurrent and subsequent genital HPV infections in 518 women (18–20 years) [31]. The risk of acquiring a specific HPV type was not substantially decreased among those with prior infection with a phylogenetically related type.

More than 2,000 young women were recently tested with a pseudovirion-based neutralizing antibody assay to test functionally relevant neutralizing HPV antibodies [32]. This study shows that most women seroconvert after their first sexual intercourse and test positive for HPV16 or HPV18 at the level of the uterine cervix. But the 12-month cumulative seroconversion rate was only 51.4%. Seropositivity for HPV may be a transient phenomenon.

**HPV Vaccine Efficacy in HPV-Seropositive Women**

In the recent phase III randomized controlled trial with the bivalent vaccine, 18,644 women were enrolled between 15 and 25 years of age, including women with prevalent HPV infection and low-grade cytological abnormalities [8]. Only 21% of the study population showed evidence of current or past HPV16 or HPV18 infection (seropositive and/or DNA-positive), leaving up to 80% of these women vulnerable to HPV16 or HPV18 infection. Analogous data were found in the phase III trial with the quadrivalent vaccine.

For both HPV vaccines complete vaccine efficacy for HPV16 and HPV18 has been reported for both virgins and sexually active women older than 15 years of age when the woman is HPV-negative (DNA-negative) at the time of vaccination (up to the third dose at 6 months) independent of the natural HPV plasma antibody level at that moment. Vaccination of women with evidence of a prevalent vaccine-targeted HPV infection does not lead to an increase of adverse events and appears to be safe based on the data of phase II and phase III trials of both HPV vaccines. Obviously, vaccination has no therapeutic effect on these vaccine-targeted HPV infections. The results of a recent combined analysis using a combination of a preceding HPV infection and HPV DNA in CIN2 and CIN3 biopsies provide evidence that the bivalent HPV vaccine will contribute significant cervical cancer protection beyond the unexposed, naive population [33].

Local and systemic antibody responses play a significant role in the prevention of precancerous lesions. Neutralizing antibodies are considered in a publication of the World Health Organisation ‘to be the major basis for protection by VLP-based vaccines in humans’ (http://www.who.int/reproductive-health/publications/hpvvaccines_
Experimental data indicate that these serum antibodies are sufficient to afford protection. These neutralizing antibodies are not produced locally, but transudate from the serum to the cervical mucosa at sufficient levels to neutralize the virus before it enters the basal cell of the epithelium. High levels of HPV16 and HPV18 antibodies in serum and cervicovaginal secretions for at least 24 months following vaccination with the bivalent HPV vaccine in females aged 25–55 years have been shown [34].

**Conclusions**

Based on the presented data, we conclude that most adult and sexual active women may benefit from HPV vaccination. Although published efficacy data on the prevention of HPV16/18-related cervical lesions by vaccination in older women above 26 years of age are limited to one published study with the quadrivalent HPV vaccine with a 26-month follow-up, at least 90.5% (95% CI 73.7–97.5) vaccine efficacy against vaccine HPV types infections or disease has been reported. Published immunogenicity and safety data on the bivalent HPV vaccine in women up to 55 years show an impressive robust and persistent immune response that predicts a long-lasting protection against infection and disease by HPV16 and HPV18 and phylogenetically related HPV types. Therefore, HPV vaccination in older women should not be argued against as these women have equal risks of acquiring HPV infection via new sexual relationships compared to younger women. The protective effects may be seen much more rapidly in screening and cancer registries than after vaccination of young adolescents.

In clinical practice, the individual risk for HPV16/18 infection remains difficult to estimate, but HPV vaccination has no definite contraindication depending on age and remains safe at older age, even when being seropositive for one or more of the vaccine HPV types. Furthermore, these older women should be offered regular cervical screening. It is clear that most countries will not refund the cost of HPV vaccination in this older age group because cost-effectiveness calculations may not give the same convincing data as in the adolescent virginal age group. Women will need to pay for the HPV vaccines and by doing so, they will experience a potential individual benefit. This also creates an ethical problem as prevention of disease becomes dependent on individual initiative and financial resources.

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