HPV Vaccination – Where Are We Now?

Arne Wikström
Dept. of Dermatovenereology
Karolinska University Hospital Solna
SE-171 76 Stockholm, Sweden
E-mail: arne.vikstrom@karolinska.se

In United States, the quadrivalent HPV vaccine Gardasil® produced by Merck, was introduced on the market as early as June, and in the European Community in October of last year. This vaccine contains the HPV types 6, 11, 16 and 18. A bivalent HPV vaccine with HPV 16 and 18; Cervarix®; is marketed by GlaxoSmithKline and will be on the market later this year. We now have a few months of experience of Gardasil®. Many questions remain unanswered. This short review will hopefully provide some background to the issues currently discussed in the HPV vaccination field.

Clinical and subclinical human papillomavirus (HPV) infection is probably the most common sexually transmitted infection (STI) in the world, affecting a high number of individuals during their lifetime. More than 100 different HPV types have been detected, of which about 40 have tropism for the anogenital tract. Between 12–18 HPV types are regarded as "high-risk" (oncogenic) HPV types (1). The rest of the genital HPV types are "low-risk" or benign types. Of these, HPV 6 and 11 are most commonly found in benign lesions such as condylomas. Genital HPV infection can be prevented to an extent by using condoms, reducing the number of partners and delaying the start of sexual activity.

During the last 20 years, an etiological relationship between a number of anogenital cancers and HPV has been demonstrated. The most important among these malignancies is cervical cancer, which is (after breast cancer) the second most common cause of death in cancer among women worldwide, despite the implementation of screening programs using cervical cytology. In developing countries, where no such programs exist, the problem is even bigger.

In 2002 it was estimated that 493,000 women worldwide were diagnosed with cervical cancer, and 274,000 died from it (1). Cervical dysplasia is even more common. HPV DNA is detected in more than 99% of both cervical cancer and dysplasia. The two most common HPV types in dysplastic lesions are HPV 16 and 18, found in about 70% of squamous cell carcinomas (2). Contributing risk factors for cancer development are smoking, immunosuppressive diseases such as HIV infection, genetic factors, parity, oral contraceptive use and other STI:s such as chlamydia (3). High-risk HPV:s have also been found in other genital cancers, such as vulvar, anal and penile cancers, as well as in oropharyngeal carcinomas. In men who have sex with men (MSM), the risk of anal cancer is 30 times increased compared with heterosexual males (4). The risk of anal cancer in MSM is the same as the risk of cervical cancer in women without cytological screening.

The current HPV vaccines (Gardasil®, Cervarix®) are developed from non-infectious virus-like particles (VLP:s) of L1, the major capsid protein. The quadrivalent vaccine is produced in yeast, whereas the bivalent vaccine is produced using an insect cell culture system. The recombinant L1 proteins self-assemble into VLP:s structurally similar to natural virions but are not infectious since they lack infectious DNA. It was initially shown that immunization with L1 VLP:s could protect against viral challenges with cottontail rabbit papillomavirus (CRPV), canine oral papillomavirus (COPV) and bovine papilloma virus (BPV) (5, 6, 7).

Routine vaccination programs have had a great impact on reducing the prevalence of a number of infectious diseases. The HPV vaccine trials have

shown overwhelmingly positive results. Both vaccines have been demonstrated to be highly efficacious, highly immunogenic and very safe, with almost no unfavourable side effects, most of them occurring at the injection site (8, 9). HPV vaccines may be the most effective tools to prevent HPV infection and HPV associated disease. A successful collaboration between the academic field and commercial companies has enabled the development of the vaccines.

Topics that are under lively discussion at the moment are: whether both females and males should be included in vaccination programs, the durability of the immune response and of course the economic aspects. The target population for prophylactic vaccination will probably be adolescent girls. Whether or not males should be included in the vaccination programs has been debated. HPV 6- and 11-induced genital warts represent a big clinical problem among both women and men. Diseases associated with HPV 16 and 18 are much less frequent in men than in women, but HPV-associated anal, penile and oropharyngeal cancers exist. Apart from preventing disease in males, inclusion of males might be good for reducing the HPV load in the society. Rubella is a good example of a successful vaccination where both sexes are included. A significant reduction in the disease was not seen until boys were included in the vaccine program. Whether or not the vaccines also protect against other HPV types has been discussed, and there is data indicating some cross-protection (9). In Sweden, to be able to follow the vaccinated individuals in the future, after their consent, they will be registered in a national vaccine registry, Svevac. This registry can later be compared with the national cancer registry. It will take many years to answer a lot of the questions.

The HPV vaccines are prophylactic, so the vaccines should be given before the adolescents are exposed to genital HPV:s, i.e. before the onset of any sexual activity. The average age of first intercourse varies between different countries, but generally the ages of 9–13 years have been discussed as appropriate for the introduction of HPV vaccines. Studies about the parents' attitudes and willingness to vaccinate their prepubertal daughters have been performed. Most were pro-vaccination and happy to able to protect their daughters from cervical cancer, but some feared that it might lead to risky behaviours (10, 11). The acceptance of vaccination in the society will probably be high, and will hopefully not be a problem.

It is important to remember that we still do not know whether vaccination will be beneficial for persons already exposed to the HPV types vaccinated against. However, in the phase-III trial of the quadrivalent vaccine where more than 90% non-virgins with a sexual history of 1–4 life-time partners included, 82% were not seropositive for any of the four HPV-types included, and very few were seropositive for all types (12). Therefore, many women in the age of 16–23 would probably benefit from a "catch-up" vaccination. Also many patients outside the studied group, 9–26 years of age, will ask for vaccination. Of course, the vaccine is better for a 27-year-old with one life-time partner than for a 17-year-old reporting 10 life-time-partners. Individual counselling is of crucial importance, since it is very difficult to set up general guidelines. However, the effectiveness is not known for females over the age of 26 or for men. Trials of women over 26 years (both quadrivalent and bivalent vaccines) and of heterosexual men as well as MSM (quadrivalent vaccine) are underway. For men, we still only have immune response and safety data, but we do not know the efficacy yet. The phase-II and phase-III trials have not shown any adverse events in those already infected, so the risks of vaccinating this group is probably not large. Still, vaccination is costly for the individual, so from an ethical point of view, vaccination of the right target group is important.

Education will be needed for many clinicians who will be asked by patients and parents about the vaccines, namely gynecologists, dermatovenereologists, general practitioners, midwives and staff in the youth clinics, as well as school nurses. The vaccine is now offered by many vaccination centers mostly dealing with travel vaccines. Their staff generally do not have any knowledge in the HPV field and will also need to be updated. We have already experienced, that hospital clinics, as well as youth clinics with high compe-

tence in the field unfortunately do not have enough resources to offer vaccination. Therefore other operators working with this are necessary. The introduction of the vaccines will probably evolve gradually, and there will be large differences between different countries in the vaccination policies.

Conflicts of interest

I have been an investigator in the Merck, Gardasil® trial.

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