CERVICAL CANCER

Identical HPV DNA integration sites have been found in vaginal or vulvar and cervical samples of lesions from patients with a prior history of high grade CIN or cervical cancer. This suggests that dysplastic lesions in the female lower genital tract may emerge as monoclonal lesions from a transformed cell population derived from the cervix (2).

Unfortunately there is no screening test for VIN. VIN lesions are often multiple and show high recurrence rate. The risk for progression is significant and may be even higher than that of cervical intraepithelial neoplasia (CIN) 2/3. High grade VIN is treated by surgery. Surgical treatment is often disfiguring and mutilating, in addition, the disease burden of genital warts is enormous (3).

HPV Virus-like particle vaccines

HPV virus-like particles (VLP) were discovered approximately 20 years ago, and this discovery rapidly led to the development of prophylactic VLP vaccines. Currently two prophylactic vaccines are available. Quadrivalent vaccine (Gardasil, Merck) is targeted against HPV 6/11/16/18. The bivalent vaccine (Cervarix, GlaxoSmithKline) is targeted against HPV16/18. (Figure 1) These vaccines have different adjuvants. Clinical phase III efficacy trials have been performed in 13-14 countries in four continents among 15-26 year old women (4-10). The quadrivalent HPV vaccine has also been studied in women aged 24-45 years with no history of genital warts or cervical disease (11).
Highlights of the global phase III efficacy trials

Multinational phase III trials of a quadrivalent HPV L1 VLP vaccine were conducted in the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II trials which enrolled more than 17,000 women aged 15-26 years. The impact of the prophylactic quadrivalent vaccine on all HPV-associated genital disease was studied in a population that approximates sexually naive women, so called “negative to 14 types” population and in a mixed population of HPV exposed and HPV unexposed women, so called intention to treat group. Vaccine or placebo was given at day one, month two and month six. The average follow-up was 3.6 years. In the “negative to 14 HPV types” population vaccination was up to 100% effective in reducing HPV16/18 related high grade cervical, vulvar and vaginal lesions and HPV6/11 related genital warts. Reduction in disease end points irrespective of causal HPV type in the “negative to 14 types” population was 42.9% for CIN2, 43.0% for CIN3, 82.8% for genital warts and 77.1% for VIN2/3 or VaIN2/3.

In the “intention to treat” population vaccination also reduced disease end-points related to the vaccine HPV types. Reduction irrespective of causal HPV type in the “intention to treat” population were lower. Pap abnormalities, colposcopy procedures and cervical definitive therapies reduced 20%-40% in both populations, and generally more in the “negative to 14 types” population.

A multinational phase III trial of the bivalent HPV16/18 AS04 adjuvanted vaccine, the Papilloma TRIal against Cancer In young Adults (PATRICIA) trial, was performed among 18,644 15-25 year old women vaccinated at months 0, 1, and 6. The total vaccinated cohort (TVC) included all women receiving at least one vaccine dose regardless of their baseline HPV status, representing general population of sexually active young women. The TVC naive population included women with normal cytology and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV16/18, approximating the primary target population for organised vaccination programs (that is young women before sexual debut).

The mean follow-up was 34.9 months after the third dose. Vaccine efficacy against CIN2+ associated with HPV16/18 was 92.9% in the primary analysis and 98.1% in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncogenic types. Vaccine efficacy against CIN2+ irrespective of HPV type in lesions was 30.4% in the TVC and 70.2% in the TVC naive. Corresponding values against CIN3+ were 33.4% n the TVC and 87.0% in the TVC naive. The bivalent vaccine also substantially reduced colposcopy referrals and cervical excision procedures in both the TVC and TVC naive. (Figure 2)

The quadrivalent HPV vaccine has been efficacious in women aged 24-45 years not infected with the relevant HPV types at enrolment. The efficacy against disease or infection related to HPV16/18 was 83.1% in the per protocol population but only 22.6% in the intention-to-treat population since infection and disease were often present at baseline. No vaccine related serious adverse events were recorded.

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**Table 1: Preventive HPV Vaccines**

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Cervarix ®</th>
<th>Gardasil ®</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV Type</td>
<td>HPV-16 and HPV-18 VLP L1 capsid component</td>
<td>HPV-6/11/16/18/VLP L1 capsid component</td>
</tr>
<tr>
<td>Concentration</td>
<td>20 μg HPV 16 20 μg HPV 18</td>
<td>20 μg HPV 6 20 μg HPV 11 20 μg HPV 16 20 μg HPV 18</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>AS04: 500 μg Aluminium Hydroxide 50 μg 3-O-desacyl-4’-monophosphoryl lipid A</td>
<td>Alum: 225 μg Aluminium Amorphous Aluminium Hydroxyphosphate Sulfate AAHS</td>
</tr>
<tr>
<td>Age Range*</td>
<td>15-25 years</td>
<td>15-26 years</td>
</tr>
</tbody>
</table>

*Phase III efficacy trials*
WHO SHOULD AND WHO SHOULD NOT BE VACCINATED AGAINST HUMAN PAPILLOMAVIRUS INFECTION?

**Vaccine Control Vaccine efficacy P-value**

<table>
<thead>
<tr>
<th></th>
<th>Vaccine n</th>
<th>Control n</th>
<th>Vaccine efficacy % (96.1% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVC naïve*</td>
<td>CIN2+</td>
<td>33</td>
<td>70.2 (54.7-80.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CIN3+</td>
<td>3</td>
<td>87.0 (54.9-97.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TVC**</td>
<td>CIN2+</td>
<td>224</td>
<td>30.4 (16.4-42.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>CIN3+</td>
<td>77</td>
<td>33.4 (9.1-51.5)</td>
<td>0.0058</td>
</tr>
<tr>
<td></td>
<td></td>
<td>322</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>116</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Vaccine N=5449; Control N=5436; **Vaccine N=8667; Control N=8682

**TCV** All women who received ≥1 dose of study vaccine; Case counting began the day after 1st vaccination

**TVC naïve** Received ≥1 dose of study vaccine; Normal cytology at Month 1; HPV DNA negative for all oncogenic types at Month 0; Seronegative for HPV-16/18 at Month 0; Case counting began the day after 1st vaccination

**Cross protection**

L1 of HPV16/18 share homology with other high-risk types. Therefore antibodies to HPV16/18 L1 VLPs may be able to neutralise virions of related types. This cross-protection may increase the impact of the vaccines. In the phylogenetic tree of papillomaviruses HPV31 is relatively closely related to HPV16, and HPV45 is closely related to HPV18. HPV45 and 31 are the next important cancer related HPV types after HPV16/18. It should be noted however that most of this cross protection was based on protection against HPV 31, not HPV 45 (12-13). In the FUTURE trials cross protection against HPV31/45 related high grade CIN was 58.7%.

Cross protection against five most common high risk types was 32.5% and against 10 most common high risk types again 32.5%. Cross protection by the bivalent vaccine against HPV31/45 related CIN2+ was 100%, and against HPV31/33/45/52/58 related high grade CIN 68.2% and against 10 most common high risk HPV types related CIN2+ was 68.4%.

In the bivalent vaccine trial vaccine efficacy was approximately 37% against CIN2+ lesions associated exclusively with non-vaccine HPV types. Globally 70% of cervical cancer is estimated to be caused by HPV16/18 with the remaining 30% caused by other oncogenic HPV types. Thus, this analysis suggests that cross protective efficacy of the bivalent vaccine could represent 11%-16% additional protection against cervical cancer that is greater than the protection provided by vaccine efficacy against HPV16/18 (9).

**Safety**

Both quadrivalent vaccine and the bivalent vaccine have been proven to be safe with no significant safety signals based on the large global multinational randomised efficacy trials. This applies to serious adverse events, medically significant conditions, new onset autoimmune diseases, and pregnancy outcomes. Post-licensure surveillance is ongoing. (Figure 3)

HPV positivity did not increase local or general symptoms after vaccination. Similarly there is no evidence that vaccination affects the progression of pre-existing lesions.

**Additional findings from clinical trials**

Among women positive for 1-3 HPV vaccine types before vaccination the quadrivalent HPV vaccine protected against cervical neoplasia caused by remaining types (14). This supports vaccination of the general population without pre-screening. Vaccination also induces robust immune memory (15). These findings suggest that efficacy of the quadrivalent vaccine will be long lasting. The role of immune memory in the context of vaccine efficacy is not fully understood.

Natural HPV infection induced antibodies may not provide complete protection over time. However, the immune response to the HPV vaccines may prevent reinfection or reactivation of disease with vaccine HPV types (16). Women who have been treated for CIN continue to be at increased risk of cervical cancer. Results with the quadrivalent vaccine suggest that vaccinated women who had definitive therapy for CIN had significantly decreased risk for new cervical disease after definitive therapy (17).

**Should HPV vaccine be given to men?**

In October 2009 the FDA approved the use of the quadrivalent vaccine in boys and men aged 9-26 years for the prevention of genital warts (18). Additional data are expected to be forthcoming on the efficacy of the quadrivalent vaccine to prevent anal intraepithelial neoplasia on homosexual men. In general, the vaccine may work as well in boys as in girls since both vaccines are effective in preventing infection with the vaccine HPV types in women naïve to these types. The vaccines are probably effective in boys as well.

**Figure 2: Overall Vaccine Efficacy Against CIN2+ and CIN3+ irrespective of HPV type in the lesion**

**Figure 3**
The benefit may be firstly reduction of HPV associated disease burden in boys and men and secondly prevention of HPV transmission to women. Mathematical modelling has demonstrated that if vaccine coverage in women remains low vaccination of boys is important for so called herd immunity which then ultimately may lead to eradication of the high-risk vaccine HPV types (19).

However, if vaccine coverage in girls is more than 70%, the added value from the population point of view may be relatively small. This also means that the cost effectiveness of so called catch-up vaccination programs is limited and achievement of major public health takes longer time. As with HPV transmission from women to men it has not yet been proven that male vaccination would reduce transmission of HPV from men to women.

In addition cost-effectiveness analysis of including boys in an HPV vaccination program seems to exceed conventional thresholds of cost-effectiveness (20). It should be emphasised however, that vaccination eradicated rubella only after both genders were vaccinated. The same situation may hold for HPV as well.

HPV vaccination – reason for caution

The disease end-point in the efficacy trials has been high grade cervical, vulvar or vaginal pre-cancer, not cancer (21). High grade pre-cancer can be considered a valid surrogate marker for cancer, and it is usually managed by surgery. The question whether the current vaccines ultimately prevent cancer and death can be answered in just a few years by linking the large registries of vaccines and cancer registries in countries with high-quality cancer registries such as Scandinavian countries. If the vaccines are effective against high grade pre-cancer it is more than likely that vaccination will prevent cancer as well.

Another open question is the duration of protection against HPV infection. Antibody levels seem to plateau and stay well above the levels induced by natural HPV infection for at least 8 years. We do not know yet whether booster vaccination is needed. Most likely, the vaccination will also change screening practices. In the vaccine era HPV DNA testing will be undoubtedly introduced in primary screening.

One important question is also so called type replacement. This means that if vaccination eradicates HPV16/18 is it then possible that other high-risk types fill the so called ecological niche. However HPV is a stable DNA virus so that such type replacement is highly unlikely to happen in any foreseeable future. However, it is difficult to predict the likelihood of HPV type replacement following implementation of HPV vaccination programs. A competitive advantage for specific high risk HPV types over other genital HPV types in the unvaccinated population is possible and this certainly warrants further studies and monitoring or post marketing surveillance following universal mass vaccination programs. Many remaining questions will be answered based on the ongoing community randomised controlled phase IV trial in Finland among 35,000 12-15 year old females and males enrolled from 33 communities.

HPV disease burden beyond cervical and other anogenital cancers

HPV has also been linked to oropharyngeal cancers and cancers of the oral cavity. Head and neck cancer is the sixth most common cancer worldwide with approximately 640,000 new cases per year. The incidence is increasing rapidly as reported from Sweden, United States and United Kingdom. The incidence of these oropharyngeal squamous cell carcinomas seems to be accounted for by rising HPV related carcinomas.
Sexual transmission of HPV primarily through orogenital intercourse might be the reason for the increase in incidence. For instance, a pooled analyses of eight multinational observational studies comparing more than 5,600 cases of head and neck cancer and more than 6,000 found that the risk of developing oropharyngeal carcinoma was associated with the history of six or more lifetime sexual partners, four or more lifetime oral sex partners and an earlier age at first sexual intercourse. Thus, HPV vaccination programs may also affect the incidence of HPV related oropharyngeal carcinomas which is an important added value or bonus effect to be considered in modelling exercises of vaccination programs or cost-effectiveness calculations.

CONCLUSIONS

Current prophylactic HPV vaccines are highly effective against high grade cervical pre-cancer that is related to the vaccine HPV types or irrespective of HPV type in HPV naive target populations. HPV vaccines should therefore be given before sexual debut for maximum benefit. The vaccines show significant cross-protection against other nonvaccine HPV types. This extended protection provides added value which is most relevant to the full public health impact of the vaccines and in particular so called catch-up vaccination in the general population of sexually active young women. The vaccines demonstrate favourable safety profile and no association with adverse pregnancy outcome. Ongoing surveillance and monitoring HPV vaccination programs remains important.

REFERENCES


