Human papillomavirus (HPV) vaccination for the prevention of HPV 16/18 induced cervical cancer and its precursors

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Introduction
Cervical cancer is the second most common cancer in women worldwide. Since the implementation of organised screening programs in the 1970s, incidence and mortality of cervical carcinoma in Germany decreased considerably. Currently, about 6,200 women annually are affected by cervical cancer in Germany. The mortality rate is 2.8 cases per 100,000 women; fatal cases of women with cervical carcinoma constitute 1.7 % of all death cases due to cancer.

Human papillomavirus (HPV) represents the most frequently sexually transmitted pathogen. The frequency of HPV infections in young women under the age of 30 is particularly high and declines afterwards. A HPV infection is asymptomatic at first but can already be transmitted at this stage. A persistent infection with the human papillomavirus is deemed to be a causal factor initiating the process in developing cervical carcinoma. Over 100 different HPV types have been identified so far, whereof about 15 increase the risk of a cervical cancer (high-risk types). The HPV genotypes 16 and 18 are of particular importance as they are related with approximately 70 % of all cases of cervical carcinoma.

Two vaccines against HPV 16 and HPV 18 came to the market in 2006/2007. The German Standing Vaccination Committee (STIKO) at the Robert Koch Institute recommends vaccination of girls between 12 and 17 years of age, preferably before first sexual contact.

Objectives

Medical question
To analyse whether HPV vaccination is effective with regard to the reduction of cervical cancer and precursors of cervical carcinoma (CIN), respectively?

Economic questions
Does HPV vaccination represent a cost-effective alternative or supplement to present screening practice? Are there any differences concerning cost-effectiveness between the two available vaccines? Should HPV vaccination be recommended from a health economic point of view? If so, which recommendations can be conveyed with respect to a (re)organization of the German vaccination strategy?

Ethical/social/legal questions
Which ethical, social and legal implications have to be considered?

Methods
A systematic literature search has been conducted including all relevant English and German publications since 2000. Two independent experts reviewed the identified literature with regard to relevance for the posed
study questions randomized controlled trials (RCT) looking at the effectiveness of HPV vaccination for the prevention of cervical carcinoma and its precursors - cervical intraepithelial neoplasia - have been identified. In addition, health economic models were identified to address the health economic research questions. To assure comparability of results of identified international model analyses, reported values were adapted to the price level in 2007 also converting all currencies into Euro. In addition, two specific German models - which were provided by the manufacturers - are included as well. Quality assessment of medical and economic literature was assured by application of general assessment standards for the systematic and critical appraisal of scientific studies.

Results

Based on the selected key words, the systematic literature search resulted in 289 medical, 627 economic, and 108 ethical/legal references. Further economic publications were provided by the manufacturers or identified by conducting a formal search in data bases of international HTA-organizations as well as a result of reference scanning. As a result of that process, this report considers nine medical, 24 economic and 19 ethical/social/legal sources. The nine medical sources are based on six clinical trials and three follow-up studies. All trials are prospective randomized-controlled studies. One of the six studies used a monovalent serum against HPV 16, two studies used a bivalent serum against HPV 16 and 18 and three studies used a tetravalent serum against HPV 6, 11, 16, and 18 (HPV 6 and 11 are not considered as high-risk types, but are associated with the development of genital warts). The observational period of the incorporated studies comprises 15 to 60 months, with an overall sample size of 39,866 women between 15 to 25 years of age.

Vaccine efficacy in prevention of CIN 2 or higher lesions in HPV 16 or HPV 18 negative women, who received all vaccination doses, ranges between 98 % and 100 %. Side effects of the vaccination are mainly associated with injection site reactions (redness, turgor, pain). No significant differences concerning serious complications between the vaccination- and the placebo-groups were reported.

All 24 economic publications are based on health economic modeling. 16 studies use Markov-models. Seven studies are based on transmission models, which allow for a consideration of herd immunity effects. One publication uses a simple incidence-based population model. Results of base case scenarios in the identified health economic modeling analyses range from approximately 3,000 Euro to 40,000 Euro per additional quality-adjusted life year (QALY) and approximately 9,000 Euro to 65,000 Euro per additional life year (LYG), respectively. When productivity losses are included in the analyses, incremental cost-effectiveness ratios (ICER) range from approximately 1,000 Euro to 51,000 Euro per life-year saved. Variations of the duration of protection as well as the discounting rate were identified as the primary influencing factors of cost-effectiveness results.

Discussion

The included studies show that both available HPV vaccines are effective in preventing HPV 16 and HPV 18 infections and probable resulting pre-malignant lesions of the cervix. The maximum observational period of five years poses an important limitation of the evidence from clinical trials. Therefore, questions concerning the duration of the protection or a possible later need of repeating the vaccination cannot be answered currently.
With regard to side effects, the vaccination can be considered as secure. Nevertheless, the number of cases within the clinical studies is not sufficient to determine the occurrence of rarely occurring (severe) adverse events in a reliable way.

The age of the study participants ranges from 15 to 25 and therefore exceeds the age of the target group for HPV vaccination in Germany, which is currently recommended to take place between twelve to 17 years of age. However, immune response to a vaccination and the profile of side effects in younger subjects at the age of nine to 15 seem to be similar to older subjects.

A reduction in the incidence and induced mortality through cervical cancer in Germany is not only depending on the vaccine's clinical efficacy. Effects of the new technology on the overall participation rate in screening programs and the resulting vaccination rate and immunization status are also important factors.

Although almost all of the 24 health economic models based their base case analysis on almost identical research questions, the variability of results is considerable. Nevertheless, the vast majority finds a cost-effectiveness ratio under a threshold of 50,000 Euro per additional QALY. The application of transmission models resulted in lower (better) cost-effectiveness ratios compared to the findings by Markov-models. This highly likely is due to the consideration of herd immunity effects. Studies that focus on the quadrivalent vaccine usually yielded lower (better) cost-effectiveness ratios compared to models, which evaluated the bivalent vaccine. Duration of protection can be considered as the major influencing factor within all studies.

Ethical/social/legal aspects

The 19 ethical/social/legal sources contain six studies dealing with the acceptance of the HPV vaccination, one narrative review of the vaccination's acceptance, and twelve comments about different ethical/social/legal aspects of the HPV vaccination. The transferability of specific aspects of the discussion – such as the availability of vaccination for persons without insurance coverage or the call for a compulsive vaccination program – into the German context is limited. However, one finding might be that parental acceptance of the vaccination is of great importance. As underage girls are the target group and the pathogen is sexually transmitted, a negative attitude might emerge among more conservative groups in the population. This is partly confirmed by the results of the incorporated studies: although the acceptance of the vaccination is high throughout all population groups, there are higher rates of renunciation in special parts of the population such as ethnic minorities or religious groups. As no study has been conducted in Germany, it is unclear to what extent the results are transferable to the German context. Experience with other vaccination programs showed, that not all population groups will participate equally in vaccination programs.

Conclusion

Implementation of HPV vaccination might lead to a reduction of cervical cancer in immunized women. However, uptake of immunization should be accompanied by further studies in order to assess long-term effectiveness and safety aiming at an optimization of possible implementation processes.

The effects of the HPV vaccination on population level depend on the vaccination rate and the consequences on already existing early detection programs. By taking appropriate action high vaccination rates and high participation rates in the screening programs for cervical carcinoma have to be achieved to yield optimal benefits. School-based immunization schemes or an invitation system might constitute an appropriate approach.
Regarding the long-term cost-effectiveness of HPV vaccination, German and international studies suggest that under the assumption of lifelong protection there is a high probability that the cost-effectiveness ratio of the HPV vaccination falls under a threshold of 50,000 Euro per QALY. As the cost-effectiveness ratio of the HPV vaccination significantly depends on the duration of the protective benefit as one of the not completely answered questions, a concluding verdict on the cost-effectiveness in the German setting is not possible. Hence, risk-sharing-agreements between third-party payers and manufacturers would pose an option to balance the consequences of uncertainty towards the duration of protection on cost-effectiveness.