General Childhood Vaccination Against HPV 16 and 18 Aimed at Preventing Cervical Cancer

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Summary and Conclusions

SBU's appraisal of the evidence

Vaccination against viral infections is a relatively new principle for cancer prevention. Vaccines against human papilloma virus (HPV) are aimed at preventing cervical cancer. Current vaccines target HPV types 16 and 18 and not all cervical cancer-associated HPV types.

- In young women[1] showing no signs of past or current HPV 16 or 18 infection at the onset of the study, vaccination provided over 90% protection against high-grade cervical intraepithelial neoplasias (CIN) positive for HPV 16 or 18[2] (Evidence Grade 1)*. These study results currently offer the closest estimate of the expected preventive effect of vaccinating children.
- After vaccination, children initially developed an immune response that was equal or superior to that achieved in young women after vaccination[2] (Evidence Grade 2)*.
- The effect of general childhood vaccination against HPV 16 and 18 on future morbidity and mortality from cervical cancer in Sweden is not yet known. One estimate shows that nearly half of the cervical cancer cases would not be prevented by general childhood vaccination against HPV 16 and 18. Therefore organized cervical cancer screening programs would need to continue.
- The effect of general childhood vaccination against HPV 16 and 18 on the willingness of vaccinated women to participate in organized screening programs would need to be determined.
- Scientific evidence on the cost-effectiveness of general childhood vaccination against HPV 16 and 18, in combination with organized cervical cancer screening programs, is uncertain and therefore found to be insufficient. Whether or not vaccine against HPV 16 and 18 should be included in the Swedish general vaccination program is a policy issue that concerns, among other things, the level of uncertainty that the public can accept regarding positive and negative effects when allocating resources. Introducing such a program would require organized, systematic followup of the outcomes and cost-effectiveness of all preventive interventions against cervical cancer.

1 *Aged 15 to 26 years.*

2 *The conclusions are based on studies of both vaccines, ie, Gardasil and Cervarix.*

* *Criteria for Evidence Grading SBU's Conclusions, see page 3.*

TECHNOLOGY AND TARGET GROUP Two vaccines against HPV are approved for use in Europe, Gardasil and Cervarix. They target two HPV types associated with cervical cancer, HPV 16 and 18. This report assesses the benefits, risks, and costs of general childhood vaccination against HPV 16 and 18.

Infection of the cervix by one or more HPVs is a prerequisite for cervical cancer. These infections are usually asymptomatic and most of them regress spontaneously. They can however persist and develop into cellular changes. These persistent cellular changes can in some women progress to cancer. Over 100 HPV types have been identified, 18 of which are high-risk or potentially high-risk types for cervical cancer. The time lapse from infection with HPV to fully developed cancer can be very long, often more than 20 years.

The incidence of cervical cancer and mortality from the disease are highest in some developing countries and lowest in Western Europe, North America, and Japan. The incidence in Sweden has decreased by over 60% in the past 40 years. Cervical cancer is currently the 15th most common type of cancer among Swedish women. Introduction of organized cervical cancer screening programs is one reason behind the reduced incidence. These programs enable early detection and treatment of cellular changes, before they become at risk for developing into cancer. Nevertheless, around 450 women in Sweden are diagnosed with cervical cancer annually, and approximately 150 women die of the disease per year. Hence, preventive interventions can be further improved.

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PATIENT BENEFIT *Can general childhood vaccination against HPV 16 and 18 prevent high-grade cervical intraepithelial neoplasias (CIN)?* There are no study results of the capacity of the vaccines to prevent cellular changes after childhood vaccination. However, vaccination of young women (average age: 20 years) has been assessed. Study results are available on young women who had normal pap smears before study onset and were without signs of past or current HPV 16 or 18 infections at study onset. These results currently offer the closest estimate of the expected preventive effect of vaccinating children.

The findings indicated over 90% protection against high-grade CIN positive for HPV 16 or 18. The average followup time was 3 years at most. Hence, the vaccines' protective effects were assessed during a short time after they had been administered. This situation differs from one where children are vaccinated several years prior to their sexual debut, ie, where the protective effects must remain for a longer period than that shown by available data.

Do children develop an immune response after vaccination against HPV 16 and 18 equivalent to that found in young women after vaccination? Studies have addressed the percentage of individuals who develop antibodies against HPV 16 or 18 and the antibody levels in these individuals after vaccination.

The results showed that, compared to young women, children (average age: 12 years) initially develop significantly higher antibody levels after vaccination. The longest followup times in studies including vaccination of children were 18 months for Gardasil and 7 months for Cervarix. The most common side effects reported after vaccination were local reactions at the injection site, eg, pain, redness, and swelling.

Can general childhood vaccination against HPV 16 and 18 reduce future morbidity and mortality from cervical cancer in Sweden? High-grade CIN can progress to cancer and is therefore considered an acceptable surrogate endpoint for cervical cancer. The studies have primarily analyzed the effects on high-grade CIN positive for HPV 16 or 18.

The percentage of morbidity in cervical cancer that could be prevented through a general vaccination program depends on, among other things, the prevalence of HPV 16 and 18 in cellular changes and in cervical cancer. The HPV types in cervical cancer are however not routinely identified. In some cancer cases, HPV 16 and/or 18 appear concurrently with other oncogenic HPV types. It is not known whether vaccination against HPV 16 and 18 would be able to prevent these cases. It is estimated that just over half of the cases of cervical cancer could be prevented under the following assumptions: vaccination against HPV 16 and 18 would have an effect on 60% of cervical cancer cases; the vaccines offer a protective effect of 90%; and participation in the vaccination program is 95%.

The effect that a nation-wide, general vaccination program would have on morbidity and mortality from cervical cancer is not yet known.

RESEARCH GAPS Followups exceeding 5.5 years are not available for the vaccines' capacity to protect against HPV 16 and 18 infections. The need for booster doses to achieve lifelong protection has not been established. Cervarix contains a relatively new adjuvant, and no results from long-term followups are available after vaccination of children.

The antibody level mediating protection against infection with HPV 16 and 18 is not yet known. Nor has a standardized method been established to measure antibody levels after HPV vaccination.

A rigorous, systematic followup is required to assess the effects of general vaccination against HPV 16 and 18. For example, the willingness of vaccinated women to participate in organized screening programs would need to be monitored.

ECONOMIC ASPECTS *Is general childhood vaccination against HPV 16 and 18 in combination with organized cervical cancer screening programs cost-effective in Sweden?* The estimated annual cost for general vaccination against HPV 16 and 18, of girls in Sweden, is approximately 200 million Swedish kronor (SEK). With a booster dose, the cost would be just over SEK 260 million. A vaccination program also including boys would double these costs.

Several health economic model studies have analyzed the costs for HPV vaccination of girls aged 12 years. The estimated cost per life-year saved varies from less than SEK 100 000 to just over SEK 450 000, under the assumption that vaccinated girls will participate in cervical cancer screening programs. The relationship between cost and effect is influenced by several factors, among others, the price of the vaccine and the percentage of cancer cases that could be prevented by vaccination. All studies assumed the latter to be 70%. This assumption did not vary in any of these studies. The percentage of cancer cases that could be prevented by vaccination against HPV 16 and 18 might be lower. Hence, all of the model studies might have overestimated the effects of a general childhood vaccination.

Vaccine price is also a decisive factor in assessing cost-effectiveness. A lower price increases the probability that a general childhood vaccination would be considered cost-effective in relation to an alternative use of these healthcare resources.

ETHICAL ASPECTS Cervical cancer is a serious disease. One could therefore argue that an intervention that might prevent some of these cases is motivated. On the other hand it may be seen as unethical to commit resources for an intervention whose effect on future morbidity and mortality is unknown. This issue is further complicated by the fact that the potential effects on morbidity and mortality will not be known for several decades.

Criteria for Evidence Grading SBU's Conclusions

Evidence Grade 1 – Strong Scientific Evidence. The conclusion is corroborated by at least two independent studies with high quality and internal validity, or a good systematic overview.

Evidence Grade 2 – Moderately Strong Scientific Evidence. The conclusion is corroborated by one study with high quality and internal validity, and at least two studies with medium quality and internal validity.

Evidence Grade 3 – Limited Scientific Evidence. The conclusion is corroborated by at least two studies with medium quality and internal validity.

Insufficient Scientific Evidence – No conclusions can be drawn when there are not any studies that meet the criteria for quality and internal validity.

Contradictory Scientific Evidence – No conclusions can be drawn when there are studies with the same quality and internal validity whose findings contradict each other.

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The complete report is available only in Swedish.