Sundhedsstyrelsen

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- a health technology assessment - Summary

2007

Health Technology Assessment 2007; 9(1)

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C: National Board of Health, Danish Centre for Health Technology Assessment

URL: http://www.sst.dk

Keywords: HTA, health technology assessment, HPV, human papillomavirus, vaccination, vaccine, cervical cancer, cancer

Language: Danish with an English summary
Format: pdf
Version: 1,0
Version date: 30. April 2007

Published by: National Board of Health, May 2007

Category: Advisory

Design: National Board of Health and Schultz Grafisk
Layout: Schultz Grafisk

Electronic ISBN: 978-87-7676-496-6
Electronic ISBN: 1399 2481

The report should be referred as follows:

Reduction in the risk of cervical cancer by vaccination against human papillomavirus (HPV) - a health technology assessment
Copenhagen:
National Board of Health, Danish Centre for Health Technology Assessment, 2007
Series Name 2007; 9(1)

Series Title: Health Technology Assessment
Series Editorial Board: Finn Børlum Kristensen, Mogens Hørder, Leiv Bakketeig
Series Editorial Manager: Stig Ejdrup Andersen

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Preface

Cervical cancer strikes more than 400 women annually in Denmark, and approximately 175 of these women die from the disease. Despite the introduction of a nation wide screening programme, Denmark has one of the highest incidences and mortalities of cervical cancer in the EU. Cervical cancer starts as cell changes without symptoms and develops gradually over many years. Infection with certain types of human papillomavirus (HPV) is a prerequisite for the development of cervical cancer. Presently, two different vaccines against HPV have been tested, one of which has been licensed in Denmark; and the other vaccine is expected to be licensed during 2007. These new vaccines provide a potential for reducing the risk of cervical cancer by vaccination. This has led to a health technology assessment (HTA) regarding this option.

This HTA report concerns the reduction in the risk of cervical cancer by vaccination and illustrates status about HPV infection, cervical cancer and the vaccines. The effect of the vaccines on the frequency of HPV 16 and 18 infections, cell changes as well as cervical cancer is assessed in different vaccination scenarios, and the health and economic aspects are estimated. In addition, other prerequisites and consequences of introducing the HPV vaccination in Denmark are investigated, including a possible implementation of HPV vaccination in the Danish childhood immunisation programme. Finally, ethical aspects of HPV vaccination are investigated together with attitudes to and acceptance of HPV vaccination among parents and young people in Denmark.

The presentation in this report is based on systematic literature reviews within the areas of technology, personal aspect, ethical issues, organisation and economy in connection with HPV vaccination. Furthermore, register data have been used and original data have been collected in the form of four focus group discussions taking place in connection with the personal aspect as well as our own economic analysis based on a mathematical simulation model of HPV infection.

The report is published by the Danish Centre for Health Technology Assessment (DACEHTA) and is the result of an intensive effort by an interdisciplinary project group. The project was started as a result of a need for establishing an evidence base and a need for wider clarification within this field. Prior to publication, the report has been through an external peer-review from relevant experts.

The target group of the report is political, administrative and professional decision makers at a national level who are involved in deciding on the use of HPV vaccination in connection with the reduction in the risk of cervical cancer. DACEHTA would like to thank all project group members as well as others who have contributed to the report, for their extensive work.

Danish Centre for Health Technology Assessment
May 2007
Finn Børlum Kristensen
Director

Summary

Background and purpose

Within the last 15 years it has been demonstrated that infection with certain types of human papillomavirus (HPV) is a prerequisite for developing cervical cancer. Only a small proportion of the women who are infected with oncogenic HPV types during life will develop cervical cancer or its precursors. There are more than 100 different types of HPV of which around 40 especially infect the mucous membranes in and around the genital organs and the anus. At least 12 of these HPV types are oncogenic. Especially HPV 16 and 18 are dominant (those with the highest risk) since they can be detected in approximately 70% of women with cervical cancer.

The realisation that infection with oncogenic HPV types, like HPV 16 and 18, is a prerequisite for cervical cancer prepared the way for the development of vaccines against cervical cancer. In 2006, the first vaccine against HPV was licensed in Denmark and the licensure of a second vaccine is expected during 2007. These vaccines make it possible to improve the prevention of cervical cancer. Furthermore, there will be a potential to prevent certain other - rarer - cancer forms that are also the result of an HPV infection. In addition, one of the two vaccines makes it possible to prevent a large proportion of venereal warts - a common and troublesome, but benign disease.

There are, however, unsolved questions about the use of the HPV vaccine. Amongst others, this is related to the vaccines themselves being so new that there is still no practical experience from the use of the vaccines in prevention programmes. The public attitude to and acceptance of HPV vaccination, the optimum planning and organisation of a vaccination programme and an assessment of the total effect in terms of public health are thus partly still unanswered questions. So far the vaccines have been assessed in studies with a maximum follow-up of up to five years which is a relatively short period of time when it is known that it takes approximately 20 years on average from exposure to oncogenic HPV type to possible development of cervical cancer.

This report is a health technology assessment. It forms part of the basis for the decision of whether and how HPV vaccination may be introduced in Denmark, including whether HPV vaccination should possibly be introduced in the childhood immunisation programme or in another publicly financed prevention programme. This report primarily focuses on the effect of cervical cancer and its preliminary stages. This is partly due to the fact that it is the most frequent cancer form associated with HPV infection and partly due to the fact that this is the cancer form which has especially been in focus in the scientific studies available.

An interdisciplinary project group established in the autumn of 2006 was commissioned to:

- Investigate the prerequisites for and consequences of introducing the HPV vaccination in Denmark, including a possible implementation of HPV vaccination in the Danish childhood immunisation programme in different scenarios.
- Analyse circumstances of HPV infection, cervical cancer and the appropriate vaccines (the technology).
- Investigate and analyse parents' and young peoples' attitude to and acceptance of HPV vaccination based on focus group discussions.
- Focus on ethical aspects of HPV vaccination.

- Assess how to organise an HPV vaccination programme.
- Determine the vaccines' effect on the frequency of HPV 16 and 18 infection, cell changes as well as cervical cancer in different vaccination scenarios.
- Perform a health economic assessment of an HPV vaccination programme.

Overall assessment and conclusions

It has been demonstrated with great certainty that both the existing vaccines protect efficiently against persistent infection with the HPV types at which they are aimed. Since HPV infection is a prerequisite for cervical cancer, it is thus likely that there will be an effect of at least the same order of magnitude for both regarding the risk of cervical cancer. This has been confirmed by the studies that have used cell changes of the type CIN 2/3 as their endpoint. It is important to stress that the published studies have a follow-up period of maximum five years and thus, it is impossible to predict of the duration of the protection, just as the actual degree of protection against cervical cancer can only be calculated in many years' time. There is a theoretical possibility that the use of HPV vaccination will only postpone the natural HPV infection for a number of years, after which the vaccine recipients again run the risk of infection. However, this is estimated to be not especially likely. It cannot be completely dismissed that it will be necessary to supplement a possible HPV vaccination programme with a booster vaccination some years after the primary vaccination series. The published studies furthermore have the limitation that the vaccine has been used only for specially selected population groups. It concerns especially women in the age group 16-23 years with a lifetime history of fewer than five sexual partners.

- HPV vaccines are well tolerated by the recipients and so far no serious adverse reactions attributable to the use of the vaccine have been demonstrated.

The vaccine is approved for use together with other vaccines, including that for the prevention of measles, mumps and rubella (MMR), which is currently given in the second dose at the age of 12 years. The Danish parents and young people taking part in the focus groups stated that the optimum would be to vaccinate at the age of 12 years, as the children had to see the doctor anyway in connection with the second MMR vaccination. Other reasons for this vaccination age are that the children in this age group are old enough to understand the vaccination, and that it is likely that they have not yet had their sexual debut. This may mean that there is a likelihood of an increase in the number of recipients, if the vaccine is given at this age.

There have been no studies of vaccine interaction during co-administration with the MMR vaccination. The National Board of Health has recommended the second MMR dose moved to the age of 4 years. If this is carried out considerations of an interaction with MMR vaccination are less relevant; however, it may still be a good idea to aim at the age of 12 years as the time of vaccination.

The existing vaccine is approved for both women and men, but there is as yet only little experience with using the vaccine in men and the efficacy of the vaccine has not been determined for boys and young men.

The rationale for possibly offering the vaccination to boys/men is that this may contribute to reducing HPV transmission and thus in the longer term maximise the effectiveness of the vaccination programme on cervical cancer. In addition, the vaccination would prevent a proportion of cases of penile and anal cancer caused by HPV infection. Furthermore, the approved 4-valent vaccine will have an effect on venereal warts. This may be an additional reason for offering the vaccination to boys/men. The parents and young people taking part in the focus groups find that both sexes should be vaccinated.

- An introduction of the HPV vaccination into the vaccination programme would be an innovation that will naturally lead to a number of questions and public debate.

Generally, in the public at large, in the families of the target group and in the health service there will be a need for obtaining information and discussing attitudes to vaccination. If the programme is to become a success it is important to meet this need and for society and health service to actively support the implementation. This can be done using active call for vaccination notifications possibly with the use of new technology, e.g. text reminders. As it is probably the most vulnerable girls/women who will not be fully vaccinated it is especially important to include an organisation capable of reaching such groups.

Speaking *against introducing* HPV vaccination as a free offer of prevention it is:

- That HPV vaccination is a new technology, the long-term effects of which are not yet known, and there is no experience from using vaccination in large prevention programmes. Thus the total net effectiveness in terms of public health is not yet established.
- That heavy expenses are associated with a general offer of vaccination. Naturally, these expenses depend on the price at which a vaccine can be purchased and on how such a vaccination offer is organised.
- Also, the fact that an offer already exists today - via the screening programme - which can prevent most cases of cervical cancer could speak against introducing HPV vaccination. The screenings have resulted in more than a halving of the number of cases of cervical cancer during the last 40 years.

Speaking *for an introduction* is:

- That the first vaccine has been approved as safe and efficient.
- That disease burden and expenses due to cervical cancer and the associated interventions as part of the screening programme (follow-up after cell changes and conisation) are quite significant.
- The health gain from vaccinating a large proportion of girls in the age group around 10 - 12 years will be significant. In addition to this the participation in the screening programme is not 100%, due amongst other things to the programme requiring repeated examinations and to the uncertainties in connection with examinations and follow-up after the detection of possible cell changes. Participation in the existing screening programme is socially lopsided, and a well-structured vaccination programme could be a more "democratic" offer if it is made available uniformly across demographic and social groups. Even with complete backing of the screening programme there will still be occurrences of cervical cancer.

If vaccinated women choose not to participate in the screening programme against cervical cancer, cancer cases will develop from HPV types that are not covered by vaccination, and which could have been discovered had they participated. The beneficial effect of the vaccination is thus significantly reduced or eliminated. Consequently it is paramount that the screening programme against cervical cancer continues in its present form for the time being. Vaccinated women should be informed of the importance of continuing in this programme.

Depending on the selection of vaccine and target group, the use of HPV vaccination might potentially lead to a reduction in other HPV-related diseases, including cancer of the vagina, vulva, anus and penis as well as venereal warts and respiratory papillomatosis.

It should be stressed that the present lack of knowledge about the duration of the protection of the vaccine, occurrence of rare adverse effects as well as net effectiveness in terms of the public health will only be known in years to come. To document this more closely will probably require large population studies. This HTA presents existing research-based knowledge. Analyses and assessments point out both circumstances speaking for and circumstances speaking against the introduction of a vaccination programme.

- The basis for the decision to which this HTA contributes is thus vitiated by uncertainties, and it will probably not be possible to solve the still unanswered questions within a short time frame.

Technology

The technology is described based on the published clinical studies identified during the literature review.

HPV is a virus that is mainly transmitted through sexual contact. The use of condoms has however shown no significant and important protective effect on infection.

The lifetime risk of being infected with HPV is very high as the majority of people have had an HPV infection at some point in life, and it is the oncogenic types that are dominant. Contrary to this, the lifetime risk of cervical cancer is around 1%. This difference is due to the fact that most HPV infections are cleared spontaneously and only persist in a small group of women.

Persistent HPV infection of the cells of the cervix uteri can cause cell changes, which may be a precursor of cancer. Cell changes can develop into cervical cancer and annually more than 400 women are diagnosed with cervical cancer. The treatment often results in infertility and frequently leads to complications from surgery and/or radiation. Annually, approximately 175 die of the disease. Furthermore, the preliminary stages of cervical cancer represent a significant disease burden. Every year 14,800 have an abnormal smear at the screening and these are to be resolved regarding cell changes. Annually, conisation is performed on just over 5,000 Danish women as a result of cell changes in the cervix uteri. Men can be carriers of HPV and may develop rarer forms of cancer as well as venereal warts.

Cervical cancer is prevented through a screening programme that aims at detecting and removing precursors to and early stages of cancer. At the screening an ordinary gynaecological examination with a smear is performed. In Denmark, the first screenings of cer-

vical cancer were introduced at the beginning of the 1960s. From 1989 the screening programme was more systematically introduced. The screenings have resulted in a significant reduction in the number of diagnosed cases of cervical cancer. However, Denmark still has one of the highest incidences of cervical cancer in the EU. The uptake of the screening aimed at women in the age group 23-60 years varies between regions and is on average around 70%. Even with an optimum organisation and complete participation in the screening programme it will not be possible to detect and prevent all cases of cervical cancer in time.

Vaccines

One vaccine has now been licensed in Denmark and another vaccine is expected to be on the market during 2007. Both vaccines comprise a protein that forms virus-like particles which together with an adjuvant can trigger an immune response. This immune response has turned out to be much larger than for a natural HPV infection. Since virus-like particles do not contain genome (DNA), they cannot infect the recipient of the vaccine. This is contrary to vaccines produced from a living, but weakened virus. Thus, the recipients will not be infected with HPV due to the vaccination.

As already mentioned, the vaccines have been tested in studies with a maximum follow-up period of approximately 5 years. Consequently, it has not yet been possible to estimate how well the vaccines protect against the development of cancer. However, it has been shown that the vaccines protect against cell changes of the type CIN 2/3, which is a preliminary stage of cervical cancer. These cell changes have been acknowledged by WHO and the FDA (United States Food and Drug Administration) as a valid indicator for the protection against cancer which develops later in life. Both vaccines efficiently protect women without any previous HPV infection against persistent infection with the HPV types present in the vaccine. Overall, the available data suggest that the vaccines are very efficient and that they will protect well against disease caused by the specific HPV types in the vaccine.

Both vaccines must been administered in three doses within 6-12 months. Since the vaccines are preventive the effect is best utilised if they are administered prior to the sexual debut.

Both vaccines often result in local reactions like redness, swelling and pain at the injection site, and temporary systemic reactions like fever and malaise are also seen rather frequently, i.e. in approximately 10%. No serious adverse reactions as a result of the vaccines have been observed so far. However, experience is limited regarding the use of the vaccines in very large population studies and over a long time. Consequently, it is not yet possible to exclude very rare and serious reactions, nor non-specific effects.

Even though the vaccines are produced based on identical principles there are some very important differences:

- The now authorised vaccine (Gardasil®) is aimed at four HPV types (6, 11, 16 and 18) and will thus potentially be able to protect approximately 70% of the cervical cancer cases as well as some of the other HPV-related cancer forms in genital organs and anus, but also a large proportion of venereal warts. Venereal warts is a very common and troublesome but benign disease, 90% of which is caused by HPV 6 and 11. The vaccine is authorised for persons in the age group 9-26 years.

- The second vaccine which is expected to be approved in 2007 (Cervarix®) is aimed at HPV 16 and 18. It differs from the 4-valent vaccine by containing another adjuvant (adjuvant system). It has been demonstrated that this leads to a better and longer lasting immune response than the traditional alum adjuvant, which is used in the 4-valent vaccine as well as in many other vaccines. Whether the use of this new adjuvant implies that this vaccine, over time, will protect more efficiently against HPV 16 and 18 is unknown, as it is unknown whether the new adjuvant may lead to the vaccine being tolerated less well by the recipients and to an increase in the number of rare adverse reactions.

The vaccines cover, as mentioned, both HPV 16 and 18, which collectively are associated with 70% of all cervical cancer cases; thus 30% are not covered. With the existing vaccines it will still be necessary to continue the screening programmes unchanged. If vaccinated women choose not to participate in the screening programme against cervical cancer, some of these women will be at risk of developing cancer from HPV types not covered by the vaccine. Since these cases will only be detected late the beneficial effect of the vaccination programme may be significantly reduced or possibly eliminated.
As this concerns new vaccines there is no experience from their net effectiveness on the public health when used in vaccination programmes. The efficacy of vaccines has been demonstrated for up to five years after the vaccination but any requirement for a booster dose at a later time, e.g. 10-20 years after the primary vaccination series, has not yet been established.

The personal aspect

Initially a literature review was undertaken to illustrate the attitude to and acceptance of the possibility of vaccination against cervical cancer. The review showed that the majority of studies of the attitude to and acceptance of HPV vaccinations against cervical cancer is from the USA and a few are from United Kingdom and Australia. The attitude to HPV vaccination is considered to be context dependent, e.g. based on the population's sexual morality, conceptions of health and disease as well as the organisation and financing of the health service. Consequently, it was decided to carry out a Danish study with a qualitative approach to the problem. This was done as focus group discussions with parents of children in the age groups 9-10, 11-12, 13-17 years as well as young people in the age group 18-22 years. This summary is based on the focus group discussions.
The participating parents and young people were positive towards vaccination that can prevent serious diseases. However, especially the parents need a large amount of reassurance and confidence that a vaccine has been adequately well-tested and does not lead to serious adverse reactions.

The focus group participants were predominantly positive towards a cervical cancer vaccine. However, the request for vaccination is not without reservations. Many parents experience a dilemma because, on the one hand, they feel that they ought to have their children vaccinated since they have the opportunity, but on the other hand, the vaccine is so new that they are worried about the adverse reactions in the longer term. There was a large need for more knowledge about HPV vaccination among the participants. The young people want to be vaccinated against HPV, but doubt that they will actually do it if they have to pay for it themselves. The financial question is very important for Danish parents and young people, and the majority think that the HPV vaccination should be made part of the childhood immunisation programme. There is an explicit request for equal access to this vaccination.

Most participants suggest the age of 12 years as the best time for the HPV vaccination. You are then certain to reach the children before their sexual debut and the children are old enough to understand the significance of the vaccination. It is important for the parents to be able to talk to the children about the vaccination and state the reasons for the necessity. The parents of teenagers also want to have their children vaccinated despite the possibility that they may already have been infected with HPV.

The fact that HPV is sexually transmitted incidentally has no significance for the Danish parents and young people in the study. On the contrary, several participants find that it is essential that there is less focus on the sexual aspect than on the fact that HPV infection may lead to cervical cancer. The mode of infection means that all participants think that the vaccination should be given to both girls and boys.

Ethical assessment

A literature review was carried out to illustrate the ethical aspects. The ethical assessment is made in relation to respect for autonomy, not inflicting damage, beneficence and fairness. Provided that cervical cancer screening is continued the introduction of HPV vaccination prior to the sexual debut would strengthen the prevention of a serious and in many cases terminal disease which hits many women. So far the HPV vaccination has not shown to cause known serious adverse reactions. However, there is the reservation that there is no experience from using the vaccines in large programmes, and for that reason there is still uncertainty about very rare adverse reactions and non-specific effects. Based on the principle of autonomy it is important to emphasise the limited experience with HPV vaccination and to emphasise that knowledge of modes of transmission and connection between HPV and cervical cancer is ensured via thorough information. Such information is an important part of the basis for an independent and responsible way of life. Since it is a serious disease that is prevented, it appears justified - from a point of ethical fairness - to ensure economic equal access to the vaccination.

Organisational aspects

A literature review forms the basis for the analysis of the organisational aspects. These aspects concern the best possible implementation of the HPV vaccination. The HPV vaccination must comply with the same requirements that apply to other vaccinations as regards equipment, observation and storage of the vaccine. As the vaccination should preferably be given before the sexual debut the time of vaccination will probably be at the age of 9-12 years. In order to ensure that persons above the age of 12 years can be vaccinated, in the case of a possible implementation of a national vaccination programme, a so-called catch-up programme may be implemented. A catch-up programme means that, when implementing a programme, a number of age groups above the vaccination age will be offered the vaccine for a given period, e.g. during 1-2 years. This would partly accelerate the time of a so-called herd immunity and partly accelerate the time at which the effect of the vaccination programme can be seen among the population.

There are four general target group scenarios for a vaccination programme with the HPV vaccination:

- girls of a certain age, e.g. 12 years
- girls and boys of a certain age
- girls of a certain age, including a catch-up programme
- girls and boys of a certain age, including a catch-up programme

At present, the vaccinations in the childhood immunisation programmes are given at the ages of 3, 5, 12 and 15 months as well as at the ages of 5 and 12 years. The vaccine at the age of 12 years is the second MMR vaccination. It is recommended to move this vaccination to the age of 4 years.

The vaccinations of the childhood immunisation programme are offered free of charge to the citizens, as the vaccines are paid for by the state and the vaccination fee is paid by the regional councils. If the HPV vaccination is also implemented in a national vaccination programme this will imply almost an additional 100,000 consultations annually if only girls are vaccinated and twice as many if boys are vaccinated as well. In principle, a vaccination programme may be financed in three ways: complete user fee, partial user fee and complete payment by public financial sources. Even today, an HPV vaccination is available for a user fee. With a reimbursement it will be possible to introduce a partial user fee. The introduction in the childhood immunisation programme will correspond to complete payment of the costs by public finances.

If the vaccination is introduced in the childhood immunisation programme the general practitioners will administer the vaccinations according to the current legislation. On average, it will amount to 27-55 additional consultations per general practitioner per year per vaccinated year group, which will not cause any problems according to the Organisation of General Practitioners (Praktiserende Lægers Organisation, PLO) and the Danish College of General Practitioners (Dansk Selskab for Almen Medicin, DSAM).
It is an advantage if it is the general practitioners who administer the HPV vaccination. They are familiar with and in contact with their patients and it will be possible to ask questions before the possible participation in the vaccination programme as well as questions which may arise afterwards. As the vaccine does not cover all oncogenic HPV types it is particularly important to inform the patients that the vaccine does not afford 100% protection against cervical cancer. It is still necessary that vaccinated girls/women follow the screening programme for cervical cancer when they reach the relevant age. The general practitioners are responsible for the screening programme and it will thus be a disadvantage in terms of knowledge to spread vaccination over several professional groups.

Alternatively the vaccinations could be administered by private vaccination clinics, health care centres, via the health care schemes at the schools or "mobile" schemes in gymnasiums, village halls or vaccination buses.

As it is important to get all three vaccinations within the given period of time it may be necessary to establish a reminder scheme to ensure that as many as possible will complete all three vaccinations.

In order to gather information about those who have been vaccinated and those who have not, as well as knowledge about all administered vaccinations, a register should be established as soon as possible in order to register personal identity, vaccination dates, type of product, batch/lot number and general practitioner/vaccinator. This is important in order to be able to evaluate the effect of the vaccine on cervical cancer and other cell changes in the long term. Vaccinations in the childhood immunisation programme are already today registered via the vaccination fee on a personal level but the registration does not include the product name and lot number. Furthermore, those who contact the general practitioner themselves and pay for the vaccination are not registered. A natural solution is to establish this registration in connection with the payment of vaccinations as a double registration can thereby be avoided. This register should, however, also inclu-

de vaccines paid for by the patient. Another possibility is to link the solution with www.sundhed.dk, which is meant to be a common access to the health service for both citizens and health care providers.

Health economical analysis

The economic analysis consisted of a review of the existing literature in the area and an independent economic analysis. The latter was carried out by means of a mathematical simulation model of the HPV infection in different vaccination scenarios; a so-called subject-based simulation model. The result of these simulations was subsequently used for the actual economic analysis. The analysis includes an estimate of the costs and effects of cervical cancer in the form of life benefit when introducing a vaccine against HPV 16 and 18. The analyses were carried out as results from foreign economic analyses are not adequate in a Danish context due to for instance varying treatment practices and levels of costs.

The simulation models showed that the frequency of HPV 16 and 18 will decrease a few years after the introduction of the vaccination and that HPV 16 and 18 will theoretically be eradicated after 33 and 50 years respectively with a vaccination coverage of 70%. This observation may be attributed to the effect of herd immunity, i.e. the likelihood of being infected decreases significantly even though not everybody has been vaccinated. A catch-up programme will accelerate this development.

If an annual vaccination of 12-year old girls is introduced with a vaccination cover of 70% without a catch-up programme a cost-effect ratio of approx. DKR 85,000 (15500 USD, 11400 Euro) is estimated per gained year of life, excluding indirect costs. A catch-up programme for the 13 to15 year age group involves a relatively large increase in the life benefit while the cost-effectiveness ratio will only increase from approx. DKR 85,000 (15500 USD, 11400 Euro) per gained year of life to approx. DKR 89,000 (16200 USD, 11900 Euro) per gained year of life. The inclusion of 12-year old boys in the vaccination programme implies a doubling of the annual vaccination costs and the additional effect is relatively modest. On the whole, the same effect is obtainable by means of a catch-up programme for the 13-19 year old girls, at a lower cost. Naturally, these analyses involve uncertainty and variability, which has been explained in the report. In order to meet part of this uncertainty scenario and sensitivity analyses have been carried out for selected parameters.

Cervical cancer strikes more than 400 women annually in Denmark, and approximately 175 of these women die from the disease. Despite the introduction of a nation wide screening programme, Denmark has one of the highest incidences and mortalities of cervical cancer in the EU.
Infection with human papillomavirus (HPV) is a prerequisite for developing cervical cancer.

Presently, two different vaccines against HPV have been tested, and this provides a potential for reducing the risk of cervical cancer by vaccination.

On the basis of this, the Danish Centre for Health Technology Assessment has carried out a health technology assessment. This report provides an evidence-based contribution to the decision-making process regarding the new possibility for vaccination.

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